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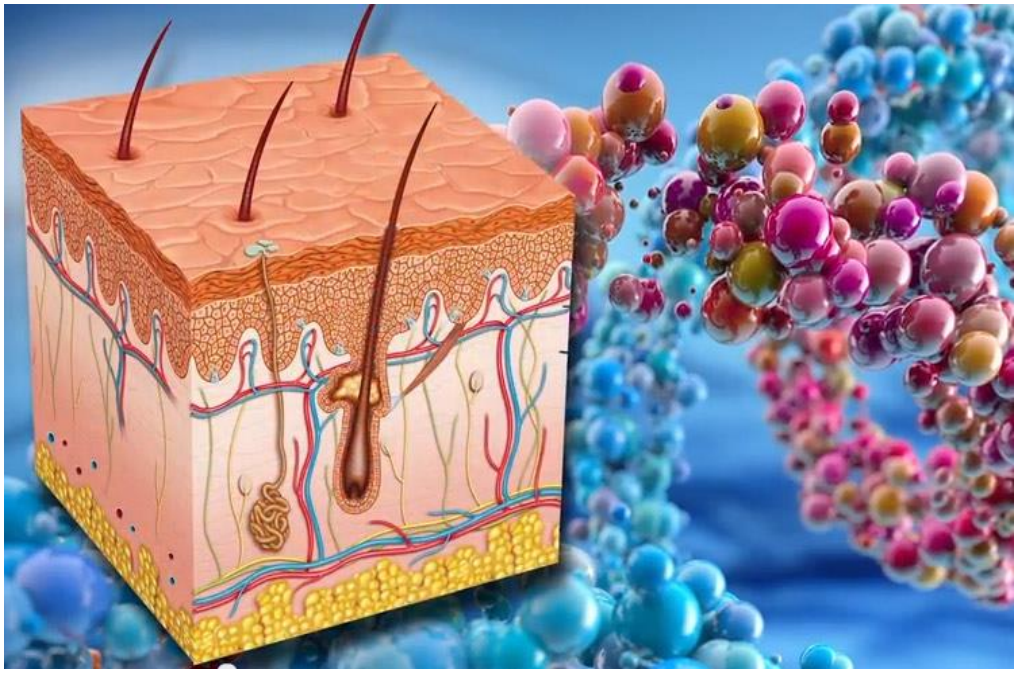
PINTA



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THE MINISTRY OF HEALTH CARE OF REPUBLIC OF UZBEKISTAN

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ANDIJAN STATE MEDICAL INSTITUTE

THE DEPARTMENT OF DERMATOLOGY AND VENEREOLOGY

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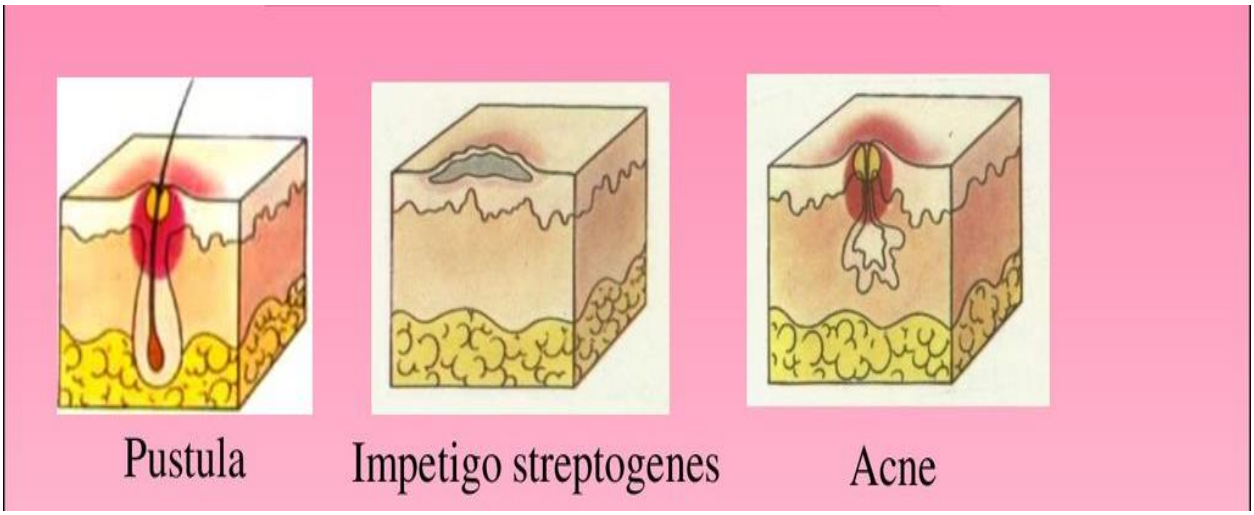
(FOR RESIDENTS, CLINICAL INTERNS, TREATMENT AND PEDIATRICS STUDENTS)



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SYPHILIS. VIRAL DERMATOSIS. PINTA.

SYPHILIS

Syphilis, also known as lues, is a contagious, sexually transmitted disease caused by the spirochete *Treponema pallidum* subspecies *pallidum.* The only known host is the human. The spirochete enters through the skin or mucous membranes, on which the primary manifestations are seen. In congenital syphilis the treponeme crosses the placenta and infects the fetus. The risk of acquiring infection from sexual contact with an infected partner in the previous 30 days is between 16% and 30%. Syphilis results in multiple patterns of skin and visceral disease and is potentially life-long.

Syphilis, yaws, pinta, and endemic syphilis are closely related. Apparently, yaws first arose with humans in Africa and spread with human migrations to Europe and Asia. Endemic syphilis evolved from yaws and became endemic in the Middle East and the Balkans at some later date. Yaws moved with human migration to the New World and became endemic in South America. Syphilis, *T. pallidum pallidum,* may have originated in the New World from *T. pallidum pertenue,* the organism causing yaws (much as human immunodeficiency virus [HIV] evolved in Africa from simian immunodeficiency virus [SIV]). A tribe in Guyana with a spirochetal infection with features of both yaws and syphilis was identified. Sequencing the genome of this spirochete suggested that it was the ancestor of *T. pallidum pallidum.* This lends support to the theory that syphilis originated more recently in the New World and was brought back to Europe by sailors who went to the New World with Christopher Columbus. Exactly how and when it became primarily a venereally transmitted disease is unclear, but apparently this happened around the end of the 15th century.

T. pallidum is a delicate spiral spirochete that is actively motile. The number of spirals varies from 4 to 14 and the entire length is 5-20 |m. It can be demonstrated in preparations from fresh primary or secondary lesions by darkfield

microscopy or by fluorescent antibody techniques. The motility is characteristic, consisting of three movements: a projection in the direction of the long axis, a rotation on its long axis, and a bending or twisting from side to side. The precise uniformity of the spiral coils is not distorted during these movements. Microscopic characteristics of *T. Pallidum* cannot be distinguished from commensal oral treponemes, so darkfield examination of oral lesions is untrustworthy. Direct fluorescent antibody testing can be used for confirmation. The electron microscope shows the organism to have an axial filament with several fibrils, a protoplasmic cylinder, and a thin membrana- ceous envelope called the periplast.

The genome of *T. pallidum* has been sequenced and contains about one-quarter of the number of genes of most bacteria. It lacks significant metabolic capacity. It is very temperature- sensitive, with some enzymes working poorly at typical body temperature (perhaps explaining why fever therapy was effective). These two factors may contribute to the inability to culture the organism in vitro. *T. pallidum* is an effective pathogen, as it disseminates widely and rapidly after infection. It is in the bloodstream within hours of intratesticular injection and in numerous organs including the brain within 18 hours after inoculation. Once the organisms reach a tissue, they are able to persist for decades. In each tissue the number of organisms is very low, perhaps below a "critical antigenic mass." In addition, *T.pallidum* expresses very few antigenic targets on its surface (only about 1% as many as *Escherichia coli).* The outer membrane proteins of *T. pallidum* also undergo rapid mutation so that during an infection the host accumulates numerous subpopulations of organisms with different surface antigens. This low infection load, widespread dissemination, poor surface antigen expression, and rapid evolution of antigeni- cally distinct subpopulations may allow the infection to persist despite the development by the host of antigen-specific antibodies and immune cells.

Syphilis remains a major health problem throughout the world. This is despite there having been a highly effective and economical treatment for more than 50 years. The story of the US and world epidemiology of syphilis illustrates a

movement of infection from one population to another due to changing social conditions and behaviors. Just as the health systems respond to one epidemic, another appears. Using serologic testing, contact tracing, and penicillin treatment, the health departments in the US reduced the incidence of syphilis dramatically from the turn of the century through the mid-1950 s. Then the incidence gradually increased through the next two decades and into the 1980 s. In the early 1980 s, half the cases of syphilis diagnosed were in men who have sex with men (MSM). Changes in sexual behavioral patterns among gay men in response to the acquired immunodeficiency syndrome (AIDS) epidemic reduced the number of these cases, but in the late 1980 s syphilis again began to increase dramatically, associated with drug usage, especially crack cocaine. The incidence of syphilis increased disproportionately among socioeconomi- cally disadvantaged minority populations, especially in major cities. Throughout the 1990 s the rate of syphilis fell in the US, so that by 1999 the national rate of 2.6 cases in 100 000 was the lowest level ever recorded. In addition, half of new cases were concentrated in 28 counties, mainly in the southeastern US and in selected urban areas. With the advent of effective antiretro- viral therapy for HIV, there was a change in sexual behavior in MSM, including those with HIV infection. Epidemics of syphilis in this group have now occurred in New York, Atlanta, Fort Lauderdale, Miami, Chicago, Houston, Los Angeles, and San Francisco. Similar epidemics have occurred in MSM in Europe. This epidemic is characterized by an older average age, anonymous sex partners (often met on the Internet), use of amphetamines and Viagra, being HIV-positive, and oral sex as the sole sexual exposure. In addition, there was a syphilis epidemic in Russia and the newly independent states starting in the late 1990 s, with rates of syphilis 34 times that of Western Europe. There have also been outbreaks of syphilis in heterosexuals associated with commercial sex workers in the UK. Worldwide it is estimated that there are about 12 million persons infected annually with syphilis, 2 million of whom are pregnant women. The Centers for Disease Control (CDC) and the World Health Organization (WHO) have undertaken campaigns to eradicate syphilis. The shifting epi-

demiology of syphilis over the last 50 years suggests it will not be an easy task without an effective vaccine. Until that time reporting of all cases to public health departments for tracing and treatment of contacts, and widespread screening of persons at risk (including all pregnant women) should be continued.

Serologic tests

Serologic testing for infection with *T. pallidum,* as in tuberculosis, is undergoing changes that incorporate newer technologies into establishing the diagnosis. Currently, most testing in the US uses older technologies, while in the UK newer technologies have been adopted. Tests are considered either "treponemal" or "nontreponemal." Treponemal tests detect specific antitreponemal antibodies, via enzyme immunoassay (EIA) or *T. pallidum* particle assay (TPPA). These new trepone- mal tests have high rates of specificity and sensitivity exceeding 95%, even in patients with primary syphilis. Nontreponemal tests are based on the fact that serum of persons with syphilis aggregates a cardiolipin-cholesterol-lecithin antigen. This aggregation can be viewed directly in tubes or on cards or slides, or can be examined in an autoanalyzer. Because these tests use lipoidal antigens rather than *T. pallidum* or components of it, they are called nontreponemal antigen tests. The most widely used nontreponemal tests are the rapid plasma reagin (RPR) and venereal disease research laboratory (VDRL) tests. These nontreponemal tests are the standard tests used in the US, and become positive, as a rule, within 5 - 6 weeks of infection, shortly before the chancre heals. Tests are generally strongly positive throughout the secondary phase, except in rare patients with AIDS, whose response is less predictable, and usually become negative during therapy, especially if therapy is begun within the first year of infection. Results may also become negative after a few decades, even without treatment. EIA tests are available that detect both IgG- and IgM- specific antibodies against *T. pallidum.* The IgM becomes detectable 2-3 weeks after infection (around the time of the appearance of the chancre). The IgG test becomes

positive at 4-5 weeks, so the IgM test is much more useful in diagnosing primary syphilis. The "treponemal" tests used in the US are the microhemagglutination assay for *T. pallidum* (MHA-TP) or the fluorescent treponemal antibody absorption (FTA-ABS) test. These specific treponemal tests are also positive earlier than the nontreponemal tests and may be used to confirm the diagnosis of primary syphilis in a patient with a negative RPR/VDRL. The EIA, TPPA, FTA-ABS and MHA-TP remain positive for life in the majority of patients, although in between 13% and 24% of patients these tests will become negative with treatment, regardless of stage and HIV status. The IgM EIA test, however, becomes negative following treatment in early syphilis, so that at 1 year, 92% of treated early syphilis patients are negative on the IgM EIA.

Since all these tests can have false-positives, although this is much less likely with the new EIA and TPPA tests, all positive results are confirmed by another test. In most US cities this involves screening the patient with a nontreponemal test, usually an RPR, and confirming all positives with a specific treponemal test, usually an MHA-TP. If a treponemal test, such as the TPPA or EIA, is used for initial screening, then the other specific treponemal test should be used to confirm the first test. A nontreponemal RPR/VDRL is also performed on all positives to determine the titer and monitor treatment success. If the initial screening treponemal specific test is positive, but the nontreponemal test is negative, then a history of prior syphilis and treatment should be sought. If prior syphilis and adequate treatment can be documented and there is no evidence on examination of either primary or late syphilis, then the patient is followed and considered serofast following treatment. If the nontreponemal test is negative, but a second treponemal test is positive, and no prior history of syphilis and its treatment can be found, then the patient is considered to have late latent syphilis (less likely, recent infection) and is treated appropriately. He/she is considered noninfectious. If the two treponemal tests are discordant, one positive and the other negative, a third treponemal specific test can be ordered, or the case can be referred to a public health department for expert consultation. Since the nontreponemal tests are falsely

negative in 25% or more of cases of primary syphilis and in up to 40% of cases of late syphilis, in these settings a specific treponemal test should also be performed as a screening test.

In resource-poor countries, serological testing for syphilis is largely unavailable since reagents require refrigeration or the tests require electrical equipment for processing. In Bangladesh and in some countries in sub-Saharan Africa and South America, more than 75% of women receive prenatal care, but only about 40% receive prenatal syphilis screening. Since syphilis is endemic in these regions, with infection rates in pregnant women exceeding 1%, millions of pregnant women with syphilis go undiagnosed, resulting in millions of cases of congenital syphilis. More than half a million babies die of congenital syphilis in sub-Saharan Africa every year. New rapid treponemal specific tests that can be used in these resource-poor countries have been developed. They cost only USS0.31-0.41 per test and await available funding to be put into use.

Nontreponemal tests are very valuable in following the efficacy of treatment in syphilis. By diluting the serum serially, the strength of the reaction can be stated in dilutions, the number given being the highest dilution giving a positive test result. In primary infection the titer may be only 1:2; in secondary syphilis it is regularly high, 1:32-1:256 or higher; in late syphilis, much lower as a rule, perhaps 1:4 or 1:8. The rise of titer in early infection is of great potential diagnostic value, as is the fall after proper treatment or the rise again if there is reinfection or relapse. Patients with very high antibody titers, as occur in secondary syphilis, may have a false-negative result when undiluted serum is tested. This "prozone" phenomenon will be overcome by diluting the serum.

Biologic false-positive test results

"Biologic false-positive" (BFP) is used to denote a positive serological test for syphilis in persons with no history or clinical evidence of syphilis. The term BFP is usually applied to the situation of a positive nontreponemal test and a negative treponemal test. Around 90% of BFP test results are of low titer (less than

1:8). Acute BFP reactions are defined as those that revert to negative in less than 6 months; those that persist for more than 6 months are categorized as chronic. Acute BFP reactions may result from vaccinations, infections (infectious mononucleosis, hepatitis, measles, typhoid, varicella, influenza, lymphogranuloma venereum, malaria), and pregnancy. Chronic BFP reactions are seen in connective tissue diseases, especially systemic lupus erythematosus (SLE) (44%), chronic liver disease, multiple blood transfusions/intravenous drug usage, and advancing age.

False-positive results to specific treponemal tests are less common but have been reported to occur in lupus erythema- tosus, drug-induced lupus, scleroderma, rheumatoid arthritis, smallpox vaccination, pregnancy, other related treponemal infections (see below), and genital herpes simplex infections.

A pattern of beaded fluorescence associated with FTA-ABS testing may be found in the sera of patients without trepone- mal disease who have SLE. The beading phenomenon, however, is not specific for SLE or even for connective tissue diseases.

CUTANEOUS SYPHILIS

Chancre (primary stage)

The chancre is usually the first cutaneous lesion, appearing 18-21 days after infection. The typical incipient chancre is a small red papule or a crusted superficial erosion. In a few days to weeks it becomes a round or oval, indurated, slightly elevated papule, with an eroded but not ulcerated surface that exudes a serous fluid (Fig. 1). On palpation it has a cartilagelike consistency. The lesion is usually, but not invariably, painless. This is the uncomplicated or classic Hunterian chancre. The regional lymph nodes on one or both sides are usually enlarged, firm, and nontender, and do not suppurate. Adenopathy begins 1 or 2 weeks after the appearance of the chancre. The Hunterian chancre leaves no scar when it heals.

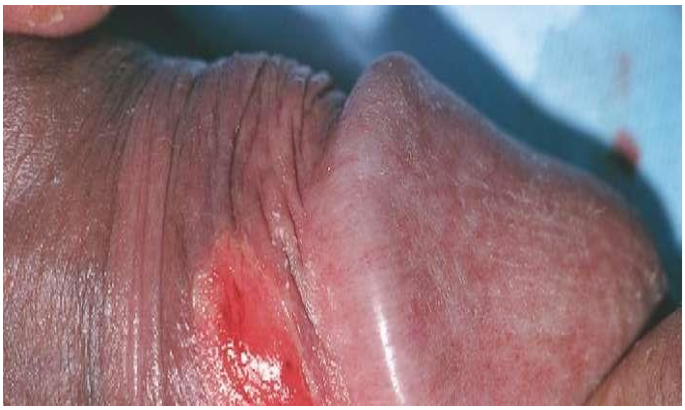


Fig. 1 Primary syphilis, chancre.

Chancres generally occur singly, although they may be multiple (Fig. 2); they vary in diameter from a few millimeters to several centimeters. In women the genital chancre is less often observed because of its location within the vagina or on the cervix. Extensive edema of the labia or cervix may occur. In men the chancre is commonly located in the coronal sulcus or on either side of the frenum. A chancre in the prepuce, being too hard to bend, will flip over all at once when the prepuce is drawn back, a phenomenon called a dory flop, from the resemblance to the movement of a broad-beamed skiff or dory as it is being turned upside down. Untreated, the chancre tends to heal spontaneously in 1-4 months. About the time of its disappearance, or usually a little before, constitutional symptoms and objective signs of generalized (secondary) syphilis occur.

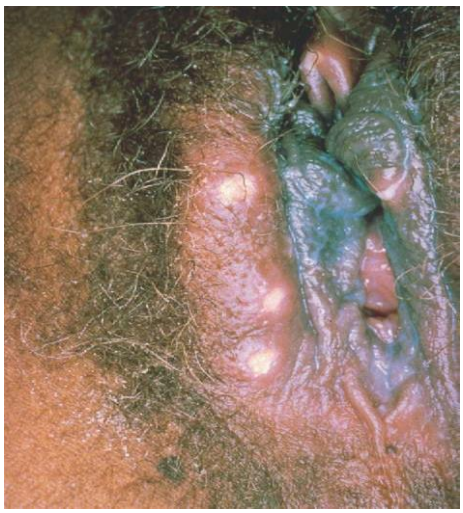


Fig. 2 Multiple chancres in a woman.

Extragenital chancres may be larger than those on the genitalia. They affect the lips, tongue, tonsil, female breast, index finger, and, especially in MSM, the anus. The presenting complaints of an anal chancre include an anal sore or fissure and irritation or bleeding on defecation. Anal chancre must be ruled out in any anal fissure not at the 6 or 12 o'clock positions. When there is a secondary eruption, no visible chancre, and the glands below Poupart's ligament are markedly enlarged, anal chancre should be suspected.

Atypical chancres are common (Fig. 3). Simultaneous infection by a spirochete and another microbial agent may produce an atypical chancre. The mixed chancre caused by infection with *Haemophilus ducreyi* and *T. pallidum* will produce a lesion that runs a course different from either chancroid or primary syphilis alone. Such a sore begins a few days after exposure, since the incubation period for chancroid is short, and later the sore may transform into an indurated syphilitic lesion. A phagedenic chancre results from the combination of a syphilitic chancre and contaminating bacteria that may cause severe tissue destruction and result in scarring. Edema indu- rativum, or penile venereal edema, is marked solid edema of the labia or the prepuce and glans penis accompanying a chancre.

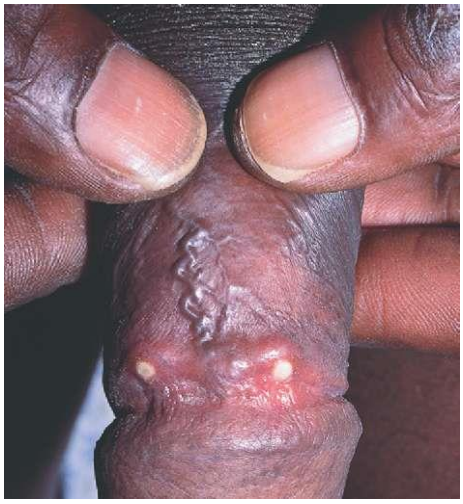


Fig. 3 Primary syphilis, atypical chancres, diagnosis confirmed by biopsy.

Chancre redux is relapse of a chancre with insufficient treatment. It is accompanied by enlarged lymph nodes. Pseudochancre redux is a gumma occurring at the site of a previous chancre. It is distinguished from relapsing chancre by the absence of lymphadenopathy and a negative darkfield examination. Syphilitic balanitis of Follmann may occur in the absence of a chancre. The lesions may be exudative, circinate, or erosive.

Histologic evaluation of a syphilitic chancre reveals an ulcer covered by neutrophils and fibrin. Subjacent there is a dense infiltrate of lymphocytes and plasma cells. Blood vessels are prominent with plump endothelial cells. Spirochetes are numerous in untreated chancres and can be demonstrated with an appropriate silver stain, such as the Warthin-Starry, Levaditi, or Steiner methods, or by immunoperoxidase staining. They are best found in the overlying epithelium or adjacent or overlying blood vessels in the upper dermis.

In a patient who presents with an acute genital ulceration, a darkfield examination should be performed if this investigation is available. The finding of typical *T. pallidum* in a sore on the cutaneous surface establishes a diagnosis of syphilis. *Treponema pertenue*, which causes yaws, and *Treponema cara- teum,* which causes pinta, are both indistinguishable morphologically from *T. pallidum,* but the diseases that they produce are usually easy to recognize. Commensal spirochetes of the oral mucosa are indistinguishable from *T. pallidum,* making oral darkfield examinations unreliable. If the darkfield examination results are negative, the examination should be repeated daily for several days, especially if the patient has been applying any topical antibacterial agents.

The lesion selected for examination is cleansed with water and dried. It is grasped firmly between the thumb and index finger and abraded sufficiently to cause clear or faintly bloodstained plasma to exude when squeezed. In the case of an eroded chancre, a few vigorous rubs with dry gauze are usually sufficient. If the lesion is made to bleed, it is necessary to wait until free bleeding has stopped to obtain satisfactory plasma. The surface of a clean coverslip is touched to the surface of the lesion so that plasma adheres. Then it is dropped on a slide and

pressed down so that the plasma spreads out in as thin a film as possible. Immersion oil forms the interface between the condenser and slide and between the coverslip and objective. The specimen must be examined quickly, before the thin film of plasma dries.

An alternative to darkfield microscopy is the direct fluorescent antibody test (DFAT-TP) for the identification of *T. palli dum* in lesions. Serous exudate from a suspected lesion is collected as described above, placed on a slide, and allowed to dry. Many health departments will examine such specimens with fluorescent antibodies specific to *T. pallidum.* The method, unlike the darkfield examination, can be used for diagnosing oral lesions. Multiplex polymerase chain reaction (PCR) is also an accurate and reproducible method for diagnosing genital ulcerations. It has the advantage of being able to diagnose multiple infectious agents simultaneously. In genital ulcer disease outbreaks it should be made available.

The results of serologic tests for syphilis are positive in 75% (nontreponemal tests) to 90% (treponemal tests) of patients with primary syphilis; both these tests should be performed in every patient with suspected primary syphilis. The likelihood of positivity depends on the duration of infection. If the chancre has been present for several weeks, test results are usually positive.

A syphilitic chancre must be differentiated from chancroid. The chancre has an incubation period of 3 weeks; is usually a painless erosion, not an ulcer; has no surrounding inflammatory zone; and is round or oval. The edge is not undermined, and the surface is smooth and at the level of the skin.

It has a dark, velvety red, lacquered appearance, is without an overlying membrane, and is cartilage-hard on palpation. Lymphadenopathy may be bilateral and is nontender and nonsuppurative. Chancroid, on the other hand, has a short incubation period of 4-7 days; the ulcer is acutely inflamed, is extremely painful, and has a surrounding inflammatory zone. The ulcer edge is undermined and extends into the dermis. It is covered by a membrane, and is soft to the touch.

Lymphadenopathy is usually unilateral and tender, and may suppurate. Chancroid lesions are usually multiple and extend into each other. Darkfield examination and cultures for chancroid confirm the diagnosis. However, since a combination of a syphilitic chancre and chancroid (mixed sores) is indistinguishable from chancroid alone, appropriate direct and sero- logic testing should be performed to investigate the presence of syphilis. Multiplex PCR allows for the simultaneous diagnosis of multiple infectious agents in genital ulcer diseases.

The primary lesion of granuloma inguinale begins as an indurated nodule that erodes to produce hypertrophic, vegetative granulation tissue. It is soft and beefy-red, and bleeds readily. A smear of clean granulation tissue from the lesion stained with Wright or Giemsa stain reveals Donovan bodies in the cytoplasm of macrophages.

The primary lesion of lymphogranuloma venereum (LGV) is usually a small, painless, transient papule or a superficial nonindurated ulcer. It most commonly occurs on the coronal sulcus, prepuce, or glans in men, or on the fourchette, vagina, or cervix in women. A primary genital lesion is noticed by about 30% of infected heterosexual men, but less frequently in women. Primary lesions are followed in 7-30 days by aden- opathy of the regional lymph nodes. LGV is confirmed by serologic tests.

Herpes simplex begins with grouped vesicles, often accompanied or preceded by burning pain. After rupture of the vesicles, irregular, tender, soft erosions form.

SECONDARY SYPHILIS

Cutaneous lesions

The skin manifestations of secondary syphilis have been called syphilids and occur in 80% or more of cases of secondary syphilis. The early eruptions are symmetrical, more or less generalized, superficial, nondestructive, exanthematic, transient, and macular; later they are maculopapular or papular eruptions, which are usually polymorphous, and less often scaly, pustular, or pigmented. The early

manifestations are apt to be distributed over the face, shoulders, flanks, palms and soles, and anal or genital regions. The severity varies widely. The presence of lesions on the palms and soles is strongly suggestive. However, a generalized syphilid can spare the palms and soles. The individual lesions are generally less than 1 cm in diameter, except in the later secondary or relapsing secondary eruptions.

Macular eruptions The earliest form of macular secondary syphilis begins with the appearance of an exanthematic erythema 6-8 weeks after the development of the chancre, which may still be present. The syphilitic exanthem extends rapidly, so that it is usually pronounced a few days after onset. It may be evanescent, lasting only a few hours or days, or it may last several months, or partially recur after having disappeared. This macular eruption appears first on the sides of the trunk, about the navel, and on the inner surfaces of the extremities.

Individual lesions of macular secondary syphilis consist of round indistinct macules that are nonconfluent and may rarely be slightly elevated or urticarial. The color varies from a light pink or rose to brownish-red. The macular eruption may not be noticed on black skin and may be so faint that it is not recognized on other skin colors also. Pain, burning, and itching are usually absent, although pruritus may be present in 1040% of cases. Simultaneous with the onset of the eruption there is a generalized shotty adenopathy most readily palpable in the posterior cervical, axillary, and epitrochlear areas. Rarely, secondary syphilis may cause livedo reticularis. The macular eruption may disappear spontaneously after a few days or weeks without any residuum, or may result in postinflamma- tory hyperpigmentation. After a varying interval, macular syphilis may be followed by other eruptions.

Papular eruptions The papular types of eruption usually arise a little later than the macular. The fully developed lesions are of a raw ham or coppery shade, and round. While most frequently lesions are from 2 to 5 mm in diameter, nodules coalescing to large plaques can occur (Figs 4 and 5). They are often only slightly raised, but a deep, firm infiltration is palpable. The surface is smooth, sometimes

shiny, and at other times covered with a thick, adherent scale. When this desquamates, it leaves a characteristic collarette of scales overhanging the border of the papule.

Papules are frequently distributed on the face and flexures of the arms and lower legs but are often distributed all over the trunk. Palmar and plantar involvement characteristically appears as indurated, yellowish-red spots (Fig. 6). Ollendorf's sign is present; the papule is exquisitely tender to the touch of a blunt probe. Healing lesions frequently leave hyperpigmented spots that, especially on the palms and soles, may persist for weeks or months. Split papules are hypertrophic, fissured papules that form in the creases of the alae nasi and at the oral commissures. These may persist for a long period. The papulosquamous syphilids, in which the adherent scales covering the lesions more or less dominate the picture, may produce a psoriasiform eruption. Follicular or lichenoid syphilids, which occur much less frequently, appear as minute scale-capped papules. If they are at the ostia of hair follicles, they are likely to be conical; elsewhere on the skin, they are domed. Often they are grouped to form scaling plaques in which the minute coalescing papules are still discernible.

Like the other syphilids, papular eruptions tend to be disseminated but may also be localized, asymmetrical, configurate, hypertrophic, or confluent. The arrangement may be corymbose or in patches, rings, or serpiginous patterns.

The annular syphilid, like sarcoidosis (which it may mimic), is more common in blacks (Fig. 7). It is often located on the cheeks, especially close to the angle of the mouth. Here it may form annular, arcuate, or gyrate patterns of delicate, slightly raised, infiltrated, finely scaling ridges. These ridges are made up of minute, flat-topped papules, and the boundaries between ridges may be difficult to discern. An old term for annular syphilids was nickels and dimes.

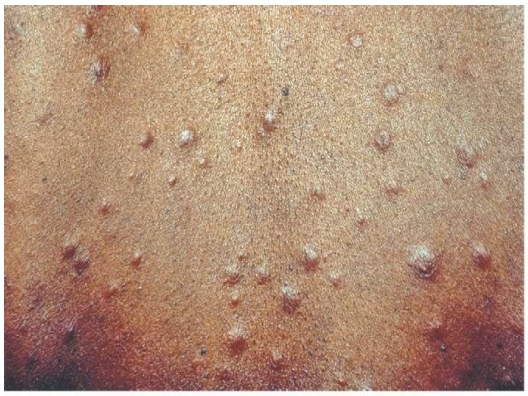


Fig. 18-4 Secondary syphilis.

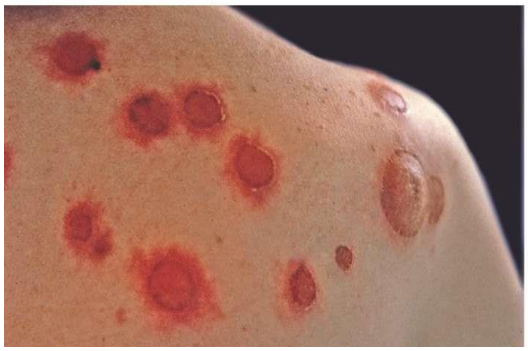


Fig. 4-5 Secondary syphilis, late, larger lesions.

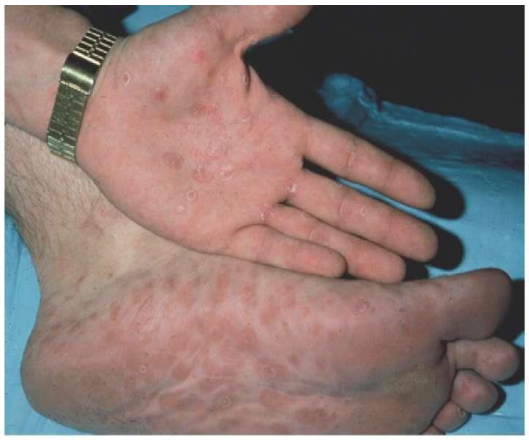


Fig. 18-6 Secondary syphilis, red flat-topped papules of the palms and soles.

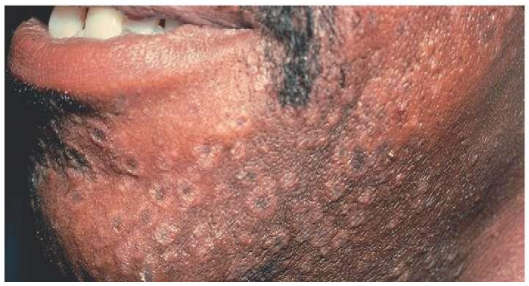


Fig. 6-7 Annular secondary syphilis.

The corymbose syphilid is another infrequent variant, usually occurring late in the secondary stage, in which a large central papule is surrounded by a group of minute satellite papules. The pustular syphilids are among the rarer manifestations of secondary syphilis. They occur widely scattered over the trunk and extremities, but they usually involve the face, especially the forehead. The pustule usually arises on a red, infiltrated base. Involution is usually slow, resulting in a small, rather persistent, crust-covered, superficial ulceration. Lesions in which the ulceration is deep are called ecthymatous. Closely related is the rupial syphilid, a lesion in which a relatively superficial ulceration is covered with a pile of terraced crusts resembling an oyster shell. Lues maligna is a rare form of secondary syphilis with severe ulcerations, pustules, or rupioid lesions, accompanied by severe constitutional symptoms.

Condylomata lata are papular lesions, relatively broad and flat, located on folds of moist skin, especially about the genitalia and anus; they may become

hypertrophic and, instead of infiltrating deeply, protrude above the surface, forming a soft, red, often mushroom-like mass 1-3 cm in diameter, usually with a smooth, moist, weeping, gray surface (Fig. 8).

Fig. 8 Condylomata of the scrotum.

Condyloma lata may be lobulated but are not covered by the digitate elevations characteristic of venereal warts (condylo- mata acuminata).

Syphilitic alopecia is irregularly distributed so that the scalp has a moth-eaten appearance. It is unusual, occurring in about 5% of patients with secondary syphilis. Smooth circular areas of alopecia mimicking alopecia areata may occur in syphilis, and an ophiasis pattern may rarely be seen.

Mucous membrane lesions are present in one-third of patients with secondary syphilis; they may be the only manifestation of the infection. The most common mucosal lesion in the early phase is the syphilitic sore throat, a diffuse pharyngitis that may be associated with tonsillitis or laryngitis. Hoarseness and sometimes complete aphonia may be present. On the tongue, smooth, small or large, well-defined patches devoid of papillae may be seen (Fig. 9), most frequently on the dorsum near the median raphe. Ulcerations may occur on the tongue and lips during the late secondary period, at times resembling aphthae or major aphthae. A rare variant of syphilis is one presenting with oral and cutaneous erosions that histologically show the features of pemphigus vulgaris with a

suprabasilar acantholytic blister and positive direct and indirect immunofluorescence finding of pemphigus as well.

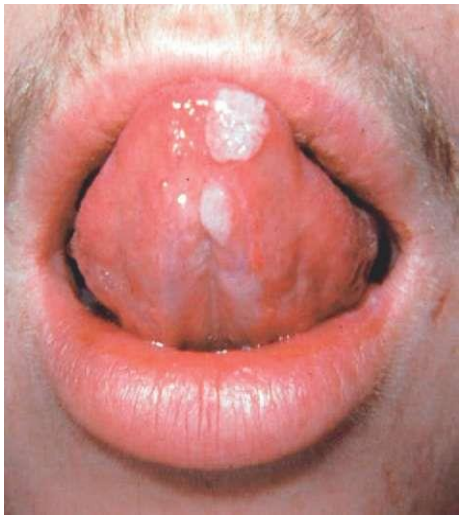


Fig. 9 Mucous patches of secondary syphilis.

Mucous patches are the most characteristic mucous membrane lesions of secondary syphilis. They are macerated, flat, grayish, rounded erosions covered by a delicate, soggy membrane. These highly infectious lesions are about 5 mm in diameter and teem with treponema. They occur on the tonsils, tongue, pharynx, gums, lips, and buccal areas, or on the geni- talia, chiefly in women. In the latter they are most common on the labia minora, vaginal mucosa, and cervix. Such mucous erosions are transitory and change from week to week, or even from day to day.

The early lesions of syphilis undergo involution either spontaneously or with treatment. Relapses occur in about 25% of untreated patients, 90% within the first year.

Such relapses may take place at the site of previous lesions, on the skin or in the viscera. Recurrent eruptions tend to be more configurate or annular, larger, and asymmetrical.

Systemic involvement

The lymphatic system in secondary syphilis is characteristically involved. The lymph nodes most frequently affected are the inguinal, posterior cervical, postauricular, and epitroch- lear. The nodes are shotty, firm, slightly enlarged, nontender, and discrete.

Acute glomerulonephritis, gastritis or gastric ulceration, proctitis, hepatitis, acute meningitis, unilateral sensorineural hearing loss, iritis, anterior uveitis, optic neuritis, Bell palsy, multiple pulmonary nodular infiltrates, periostitis, osteo-myelitis, polyarthritis, and tenosynovitis may all be seen in secondary syphilis.

Histopathology

Macules of secondary syphilis feature superficial and deep perivascular infiltrates of lymphocytes, macrophages, and plasma cells without epidermal change, or accompanied by slight vacuolar change at the dermoepidermal junction.

Papules and plaques of secondary syphilis usually show dense superficial and deep infiltrates of lymphocytes, macrophages, and plasma cells. These cells are usually distributed in a bandlike pattern in the papillary dermis and cuffed around blood vessels, accompanied by psoriasiform epidermal hyper- plasia and hyperkeratosis. Clusters of neutrophils are commonly present within the stratum corneum. The presence of numerous macrophages often gives the infiltrates a pallid appearance under scanning magnification. Vacuolar degeneration of keratinocytes is often present, giving the lesions a "psoriasiform and lichenoid" histologic pattern with slender elongated rete ridges. Plasma cells are said to be absent in 10-30% of cases. As lesions age, macrophages become more numerous, so that in late secondary lues, granulomatous foci are often present, mimicking sarcoidosis. Condylomata lata show spongiform pustules within areas of papillated epithelial hyperplasia and spirochetes are numerous. Spirochetes are most numerous within the epidermis and around superficial vessels. PCR and immunoperoxidase may identify *T. pallidum* infection when silver stains are negative.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The nontreponemal serologic tests for syphilis are almost invariably strongly reactive in secondary syphilis. An exception occurs when very high titers of antibody are present, producing a false-negative result (prozone phenomenon). The true positivity of the serum is detected on dilutional testing. Identification of spirochetes by darkfield examination or his- tologic examination of affected tissues may be used to confirm the diagnosis, especially in patients who are seronegative.

Syphilis has long been known as the "great imitator," because the various cutaneous manifestations may simulate almost any cutaneous or systemic disease. Pityriasis rosea may be mistaken for secondary syphilis, especially since both begin on the trunk. The herald patch, the oval patches with a fine scale at the edge, patterned in the lines of skin cleavage, the absence of lymphadenopathy, and infrequent mucous membrane lesions help to distinguish pityriasis rosea from secondary syphilis. Drug eruptions may produce a similar picture; however, they tend to be scarlatiniform or morbilliform. Drug eruptions are often pruritic, whereas secondary syphilis usually is not. Lichen planus may resemble papular syphilid. The characteristic papule of lichen planus is flat-topped and polygonal, has Wickham's striae, and exhibits the Koebner phenomenon. Pruritus is severe in lichen planus, and less common and less severe in syphilis. Psoriasis may be distinguished from papulosquamous secondary syphilis by the presence of adenopathy, mucous patches, and alopecia in the latter. Sarcoidosis may produce lesions morphologically identical to secondary syphilis. Histologically, multisystem involvement, adenopathy, and granulomatous inflammation are common to both diseases. Serologic testing and biopsy specimens will distinguish these two disorders.

The differential diagnosis of mucous membrane lesions of secondary syphilis is of importance. Infectious mononucleosis may cause a biologic false-positive test for syphilis but is diagnosed by a high heterophile antibody titer. Geographic tongue may be confused with the desquamative patches of syphilis or

with mucous patches. Lingua geographica occurs principally near the edges of the tongue in relatively large areas, which are often fused and have lobulated contours. It continues for several months or years and changes in extent and degree of involvement from day to day. Recurrent aphthous ulceration produces one or several painful ulcers, 1-3 mm in diameter, surrounded by hyperemic edges, with a grayish covering membrane, on nonkeratinized mucosal epithelium, especially in the gingival sulcus. A prolonged, recurrent history is characteristic. Syphilis of the lateral tongue may resemble oral hairy leukoplakia.

LATENT SYPHILIS

After the lesions of secondary syphilis have involuted, a latent period occurs. This may last for a few months or continue for the remainder of the infected person's life. Between 60% and 70% of untreated infected patients remain latently asymptomatic for life. During this latent period there are no clinical signs of syphilis, but the serologic tests for syphilis are reactive. During the early latent period infectivity persists; for at least 2 years a woman with early latent syphilis may infect her unborn child. For treatment purposes it is important to distinguish early latency (less than 1 year's duration) from late latency (of more than 1 year or unknown duration).

LATE SYPHILIS

For treatment purposes, late syphilis is defined by the CDC as infection of more than 1 year in duration, or by the WHO as more than 2 years in duration. Only about one-third of patients with late syphilis will develop complications of their infection.

Tertiary cutaneous syphilis

Tertiary syphilids most often occur 3-5 years after infection. Around 16% of untreated patients will develop tertiary lesions of the skin, mucous membrane, bone, or joints. Skin lesions tend to be localized, to occur in groups, to be

destructive, and to heal with scarring. Treponema are usually not found by silver stains or darkfield examination but may be demonstrated by PCR.

Two main types of tertiary syphilid are recognized, the nodular syphilid and the gumma, although the distinction is sometimes difficult to make. The nodular, noduloulcerative, or tubercular type consists of reddish-brown or copper-colored firm papules or nodules, 2 mm in diameter or larger. The individual lesions are usually covered with adherent scales or crusts (Fig. 10).

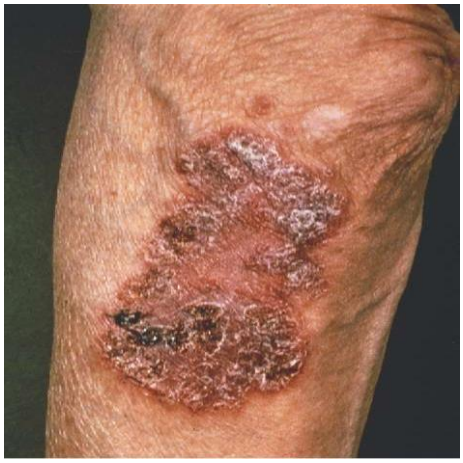


Fig. 10 Tertiary syphilis.

The lesions tend to form rings and to undergo involution as new lesions develop just beyond them, so that characteristic circular or serpiginous patterns are produced.

A distinctive and characteristic type is the kidney- shaped lesion. These frequently occur on the extensor surfaces of the arms and on the back. Individual lesions are composed of nodules in different stages of development so that it is common to find scars and pigmentation together with fresh and also ulcerated lesions. On the face the nodular eruption closely resembles lupus vulgaris. When the disease is untreated, the process may last for years, slowly marching across large areas of skin. The nodules may enlarge and eventually break down to form painless, rounded, smooth- bottomed ulcers, a few millimeters deep. These punched-out ulcers arise side by side and form serpiginous syphilitic ulcers, palm-sized in aggregate, enduring for many years (Fig. 11).

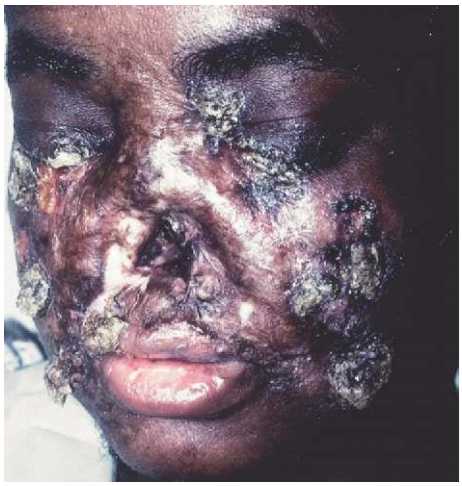


Fig. 11 Destruction of the central face in tertiary syphilis.

Gummas may occur as unilateral, isolated, single or disseminated lesions, or in serpiginous patterns resembling those of the nodular syphilid. They may be restricted to the skin or, originating in the deeper tissues, break down and secondarily involve the skin. The individual lesions, which begin as small nodules, slowly enlarge to several centimeters. Central necrosis is extensive and may lead to the formation of a deep punched-out ulcer with steep sides and a gelatinous, necrotic base. Again, progression may take place in one area while healing proceeds in another. Perhaps the most frequent site of isolated gummas is the lower legs, where deep punched-out ulcers are formed, often in large infiltrated areas. On the lower extremities gummas are frequently mistaken for erythema induratum.

Lesions may be isolated to the mucous membranes, often the tongue, on which non-indurated punched-out ulcers occur. A superficial glossitis may cause irregular ulcers, atrophy of the papillae, and smooth, shiny scarring, a condition known as smooth atrophy. In interstitial glossitis there is an underlying induration. In the advanced stages, tertiary syphilis of the tongue may lead to a diffuse enlargement (macroglossia). Perforation of the hard palate from gummatous involvement is a characteristic tertiary manifestation. It generally occurs near the center of the hard palate. Destruction of the nasal septum may also occur.

Histologically, nodular lesions of late syphilis usually have changes that resemble those of secondary lesions, with the addition of tuberculoid granulomas

containing varying numbers of multinucleate giant cells. The epidermis is often atrophic rather than hyperplastic. In gummas, there is necrosis within granulomas and fibrosis as lesions resolve. Spirochetes are scant.

For diagnosis of late syphilis clinicians rely heavily on specific treponemal tests. The nontreponemal tests, such as the VDRL and RPR, are positive in approximately 60% of cases. When there are mucous membrane lesions for which a diagnosis of carcinoma must also be considered, histologic examination is performed. Darkfield examination is not indicated, since it is always negative, but PCR of biopsy material may be positive. When not ulcerated, lesions of tertiary syphilis must be distinguished from malignant tumors, leukemids, and sarcoidosis. The ulcerated tertiary syphilids must be differentiated from other infections such as scrofuloderma, atypical mycobacterial infection, and deep fungal infections. Wegener's granulomatosis and ulcerated cutaneous malignancies must be considered Histology and appropriate cultures may be required.

LATE OSSEOUS SYPHILIS

Not infrequently, gummatous lesions involve the periosteum and the bone. Skeletal tertiary syphilis most commonly affects the head and face, and the tibia. Late manifestations of syphilis may produce periostitis, osteomyelitis, osteitis, and gumma- tous osteoarthritis. Osteocope (bone pain), most often at night, is a suggestive symptom.

Syphilitic joint lesions also occur, with the Charcot joint being the most prevalent manifestation. They are often associated with tabes dorsalis and occur most frequently in men. Although any joint may be involved, the knees and ankles are the most frequently affected. There is hydrops, then loss of the contours of the joint, hypermobility, and no pain. It is readily diagnosed by x-ray examination.

NEUROSYPHILIS

Central nervous system (CNS) infection can occur at any stage of syphilis, even the primary stage. Most persons with CNS involvement have no symptoms. Finding cerebrospinal fluid (CSF) pleocytosis or a positive CSF VDRL has been

used to confirm the diagnosis of CNS infection by *T. pallidum.* Unfortunately, a significant proportion of patients with CSF infection with *T. pallidum* will have a negative CSF-VDRL (46%) and non-diagnostic CSF pleocytosis (less than 20 white blood cells/^L) (33%). In patients with a negative CSF-VDRL but pleocytosis, an FTA can be performed on the CSF and is 100% sensitive but not specific for CNS syphilis. Combining this with flow cytometry to look for B cells in the CSF, which is 100% specific but only 40% sensitive, will allow the confirmation or exclusion of neurosyphilis in most cases with CSF pleocytosis. The likelihood of having CNS infection is ten-fold greater in persons with an RPR of greater than or equal to 1 : 32. Between 4% and 9% of persons with untreated syphilis will develop clinically symptomatic neurosyphilis, often during the first year or two of infection (while they have "early" syphilis). HIV-negative persons with negative CSF examinations have almost no risk of developing neurosyphilis; however, CSF evaluations are not routinely performed in asymptomatic persons with early syphilis, so identifying those at risk for symptomic neurosyphilis is problematic. Infection of the CNS by *T. pallidum* may also be strain-dependent, and eventually typing the infecting strain may predict those at highest risk for neurosyphilis.

Because infection of the CNS is common and the recommended treatments with benzathine penicillin do not reach treponemacidal levels in the CSF, there has been persistent concern regarding the failure to diagnose and treat asymptomatic neurosyphilis. It appears that, although treatment does not clear the spirochetes from the CSF, most non-HIV-infected persons are able to clear the CNS infection spontaneously. CSF evaluation is recommended in all patients with syphilis with any neurologic, auditory, or ophthalmic signs or symptoms, possibly resulting from syphilis, independent of stage or HIV status. In borderline cases, those with an RPR of greater than or equal to 1 : 32 should have CSF evaluation. All HIV-positive patients with RPR greater than or equal to 1 : 32 should be considered for immediate CSF evaluation, regardless of symptoms, especially if their CD4 count is 350 cells L or less. Patients with latent syphilis should have CSF evaluation if

they are HIV-positive or fail initial therapy, or if therapy other than penicillin is planned for syphilis of more than 1 year in duration. Patients with tertiary syphilis should have CSF evaluation before treatment to exclude neurosyphilis. An appropriate fall in the serum RPR after treatment for neurosyphilis predicts clearing the CNS infection, so a repeat lumbar puncture following therapy is not required in HIV- negative or HIV-positive patients adequately treated for neurosyphilis.

Early neurosyphilis

Early neurosyphilis is mainly meningeal, occurring in the first year of infection. Meningeal neurosyphilis manifests as meningitis, with fever, headache, stiff neck, nausea, vomiting, cranial nerve disorders (loss of hearing, [often unilateral], facial weakness, photophobia, blurred vision), seizures, and delirium.

Meningovascular neurosyphilis

Meningovascular neurosyphilis most frequently occurs 4-7 years after infection. It is caused by thrombosis of vessels in the CNS and presents as in other CNS ischemic events. Hemiplegia, aphasia, hemianopsia, transverse myelitis, and progressive muscular atrophy may occur. Cranial nerve palsies may also occur, such as eighth nerve deafness and eye changes. The eyes may show fixed pupils, Argyll Robertson pupils, or anisocoria.

Late (parenchymatous) neurosyphilis

Parenchymatous neurosyphilis tends to occur more than 10 years after infection. There are two classic clinical patterns: tabes dorsalis and general paresis.

Tabes dorsalis is the degeneration of the dorsal roots of the spinal nerves and of the posterior columns of the spinal cord. The symptoms and signs are numerous. Gastric crisis with severe pain and vomiting is the most frequent symptom. Other symptoms are lancinating pains, urination difficulties, paresthesias (numbness, tingling, and burning), spinal ataxia, diplopia, strabismus, vertigo, and deafness. The signs that may be present are Argyll Robertson pupils,

absent or reduced reflexes, Romberg sign, sensory loss (deep tendon tenderness, vibration, and position), atonic bladder, trophic changes, malum perforans pedis, Charcot joints, and optic atrophy.

Paresis has prodromal manifestations of headache, fatigabil- ity, and inability to concentrate. Later, personality changes occur, along with memory loss and apathy. Grandiose ideas, megalomania, delusions, hallucinations, and finally dementia may occur.

Late cardiovascular syphilis

Late cardiovascular syphilis occurs in about 10% of untreated patients. Aortitis is the basic lesion of cardiovascular syphilis, resulting in aortic insufficiency, coronary disease, and ultimately aortic aneurysm.

CONGENITAL SYPHILIS

Congenital syphilis has reappeared with heterosexual syphilis epidemics in the UK. In sub-Saharan Africa, where prenatal syphilis testing is not available, even for women with prenatal care, congenital syphilis is common. A total of 21% of all perinatal deaths in sub-Saharan Africa are due to congenital syphilis. Prenatal syphilis is acquired in utero from the mother, who usually has early syphilis. Infection through the placenta usually does not occur before the fourth month, so treatment of the mother within the first two trimesters will almost always prevent negative outcomes. If the mother has early syphilis and prenatal infection occurs soon after the fourth month, fetal death and miscarriage occur in about 40% of pregnancies. During the remainder of the pregnancy, infection is equally likely to produce characteristic developmental physical stigmata or, after the eighth month, active, infectious congenital syphilis. Forty percent of pregnancies in women with untreated early syphilis will result in a syphilitic infant. Infant mortality from congenital syphilis can be in excess of 10%. In utero infection of the fetus is rare when the pregnant mother has had syphilis for 2 or more years. Two-thirds of neonates with congenital syphilis are normal at birth,

and only detected by sero- logic testing. Lesions occurring within the first 2 years of life are called early congenital syphilis and those developing thereafter are called late congenital syphilis. The clinical manifestations of these two syndromes are different.

Early congenital syphilis

Early congenital syphilis describes those cases presenting within the first 2 years of life. Cutaneous manifestations appear most commonly during the third week of life, but sometimes occur as late as 3 months after birth. Neonates born with findings of congenital syphilis are usually severely affected. They may be premature, and are often marasmic, fretful, and dehydrated. The face is pinched and drawn, resembling that of an old man or woman. Multisystem disease is characteristic.

Snuffles, a form of rhinitis, is the most frequent and often the first specific finding. The nose is blocked, often with bloodstained mucus, and a copious discharge of mucus runs down over the lips. The nasal obstruction often interferes with the child's nursing. In persistent and progressive cases, ulcera- tions develop that may involve the bones and ultimately cause perforation of the nasal septum or development of saddle nose, which are important stigmata later in the disease.

Cutaneous lesions of congenital syphilis resemble those of acquired secondary syphilis and occur in 30-60% of infants with syphilis. The early skin eruptions are usually morbilli- form, and more rarely, purely papular. The lesions are at first a bright or violaceous red, later fading to a coppery color. The papules may become large and infiltrated; frequently scaling is pronounced. There is secondary pustule formation with crusting, especially in lesions that appear 1 or more years after birth. The eruption shows a marked predilection for the face, arms, buttocks, legs, palms, and soles.

Syphilitic pemphigus, a bullous eruption, usually on the palms and soles, is a relatively uncommon lesion. Lesions are present at birth or appear in the first week of life. They are teeming with spirochetes. The bullae quickly become purulent and rupture, leaving weeping erosions. They are found also on the eponychium,

wrists, ankles, and, infrequently, other parts of the body. Even in the absence of bullous lesions, de- squamation is common, often preceded by edema and erythema, especially on the palms and soles.

Various morphologies of cutaneous lesions occur on the face, perineum, and intertriginous areas. They are usually fissured lesions resembling mucous patches. In these sites radial scarring often results, leading to rhagades. Condylomata lata, large, moist, hypertrophic papules, are found about the anus and in other folds of the body. They are more common around the first year of life than in the newborn period. In the second or third year, recurrent secondary eruptions are likely to take the papulopustular form. Annular lesions similar to those in adults occur. Mucous patches in the mouth or on the vulva are seen infrequently.

Bone lesions occur in 70-80% of cases of early congenital syphilis. Epiphysitis is common and apparently causes pain on motion, leading to the infant's refusing to move (Parrot pseudoparalysis). Radiologic features of the bone lesions in congenital syphilis during the first 6 months after birth are quite characteristic, and x-ray films are an important part of the evaluation of a child suspected of having congenital syphilis. Bone lesions occur chiefly at the epiphyseal ends of the long bones. The changes may be classified as osteochondritis, osteomyelitis, and osteoperiostitis.

A general enlargement of the lymph nodes usually occurs, with enlargement of the spleen. Clinical evidence of involvement of the liver is common, manifested both by hepatomegaly and elevated liver function test results, and interstitial hepatitis is a frequent finding at autopsy. The nephrotic syndrome, and less commonly, acute glomerulonephritis have been reported in congenital syphilis.

Symptomatic or asymptomatic neurosyphilis, as demonstrated by a positive CSF serologic test, may be present. Eighty- six percent of infants with congenital syphilis diagnosed by clinical and laboratory findings born to mothers with untreated early syphilis will have CNS involvement, compared with only 8% of those with no clinical or laboratory findings. All infants with early congenital syphilis are treated as if they have neurosyphilis since it is very common, and

CSF-VDRL may be negative, even in documented CNS infection. Clinical manifestations may not appear until the third to sixth month of life and are meningeal or meningovascular in origin. Meningitis, obstructive hydrocephalus, cranial nerve palsies, and cerebrovascular accidents may all occur.

Late congenital syphilis

Although no sharp line can be drawn between early and late congenital syphilis, children who appear normal at birth and develop the first signs of the disease after the age of 2 years show a different clinical picture. Lesions of late congenital syphilis are of two types: malformations of tissue affected at critical growth periods (stigmata) and persistent inflammatory foci.

Inflammatory late congenital syphilis

Lesions of the cornea, bones, and CNS are the most important. Interstitial keratitis, which begins with intense pericorneal inflammation and persists to characteristic diffuse clouding of the cornea without surface ulceration, occurs in 20-50% of cases of late congenital syphilis. If persistent, it leads to permanent partial or complete opacity of the cornea. Syphilitic interstitial keratitis must be differentiated from Cogan syndrome, consisting of nonsyphilitic interstitial keratitis, usually bilateral, associated with vestibuloauditory symptoms, such as deafness, tinnitus, vertigo, nystagmus, and ataxia. It is congenital.

Perisynovitis (Clutton joints), which affects the knees, leads to symmetrical, painless swelling. Gummas may also be found in any of the long bones or in the skull. Ulcerating gummas are frequently seen. They probably begin more often in the soft parts or in the underlying bone than in the skin itself, and when they occur in the nasal septum or palate, may lead to painless perforation.

The CNS lesions in late congenital syphilis are, as in late adult neurosyphilis, usually parenchymatous (tabes dorsalis or generalized paresis). Seizures are a frequent symptom in congenital cases.

Malformations (stigmata)

The destructive effects of syphilis in young children often leave scars or developmental defects called stigmata, which persist throughout life and enable a diagnosis to be made of congenital syphilis. Hutchinson emphasized the diagnostic importance of changes in the incisor teeth, opacities of the cornea, and eighth nerve deafness, which have since become known as the Hutchinson triad. Hutchinson's teeth, corneal scars, saber shins, rhagades of the lips, saddle nose, and mulberry molars are of diagnostic importance. (Fig. 12).

Hutchinson's teeth are a malformation of the central upper incisors that appear in the second or permanent teeth. The characteristic teeth are cylindrical rather than flattened, the cutting edge is narrower than the base, and in the center of the cutting edge a notch may develop. The mulberry molar (usually the first molar, appearing about the age of 6 years) is a hyperplastic tooth, the flat occlusal surface of which is covered with a group of little knobs representing abortive cusps.

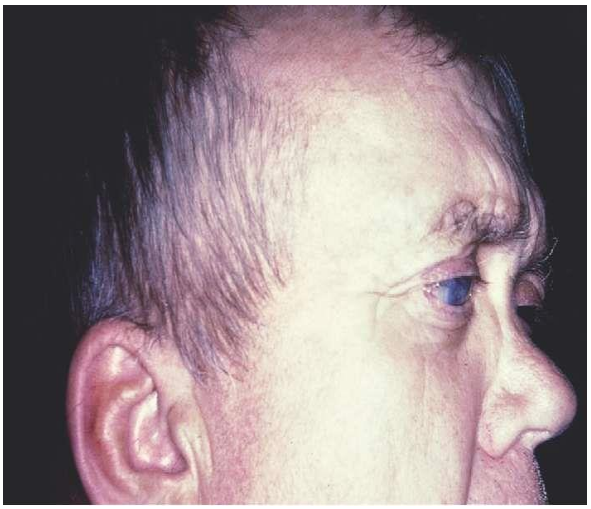


Fig. 12 Frontal bossing, interstitial keratitis and saddle nose in congenital syphilis.

Nasal chondritis in infancy results in flattening of the nasal bones, forming a so-called saddle nose. The unilateral thickening of the inner third of one clavicle (Higoumenaki's sign) is a hyperostosis resulting from syphilitic osteitis in

individuals who have had late congenital syphilis. The lesion appears typically on the right side in right- handed persons and on the left side in left-handed persons.

Diagnosis

Infants of women who meet the following criteria should be evaluated for congenital syphilis:

- maternal untreated syphilis, inadequate treatment, or no documentation of adequate treatment
- treatment of maternal syphilis with erythromycin
- treatment less than 1 month before delivery
- inadequate maternal response to treatment
- appropriate treatment before pregnancy, but insufficient serologic follow-up to document adequacy of therapy.

The results of serologic tests for syphilis for every woman delivering a baby must be known before the discharge of that baby from the hospital. Serologic testing of the mother and child at delivery are recommended. Evaluation of the children noted above might include: 1. a complete physical examination for findings of congenital syphilis nontreponemal serology of the infant's serum (not cord blood) CNS valuation pathologic evaluation of the placenta using specific antitreponemal antibody staining.

TREATMENT

Penicillin remains the drug of choice for treatment of all stages of syphilis. Erythromycin of any stage or form of syphilis. HIV testing is recommended in all patients with syphilis. Treatment for HIV-infected patients is discussed later. Patients with primary, secondary, or early latent syphilis known to be of less than 1 year in duration can be treated with a single intramuscular injection of 2.4 MU of benzathine penicillin G. In nonpregnant, penicillin- allergic, HIV-negative patients, tetracycline, 500 mg orally four times a day, or doxycycline, 100 mg orally twice a day for 2 weeks, is recommended. Ceftriaxone, 1 g intramuscularly or intravenously for 8-10 days, is an acceptable alternative if the patient cannot tolerate the above options. Azithromycin and erythromycin can no longer be

recommended as treatment for syphilis due to the widespread presence of resistance (over 75% in San Francisco). This is due to a mutation in the gene encoding a part of the ribosome responsible for the binding of macrolides. Close follow-up is recommended for all patients treated with non-penicillin-based regimens. These alternative agents are not recommended for persons with HIV infection and syphilis.

The recommended treatment of late or late latent syphilis of more than 1 year in duration in an HIV-negative patient is benzathine penicillin G 2.4 MU intramuscularly once a week for 3 weeks. In a penicillin-allergic, nonpregnant, HIV-negative patient, tetracycline, 500 mg orally four times a day, or doxy-cycline, 100 mg orally twice a day for 30 days, is recommended. CSF evaluation is recommended if neurologic or ophthalmo- logic findings are present, if there is evidence of active late (tertiary) syphilis, if treatment has previously failed, if the nontreponemal serum titer is 1 : 32 or higher, or if any regimen not based on penicillin is planned.

Recommended treatment regimens for neurosyphilis include penicillin G crystalline, 3-4 MU intravenously every 4 h for 10-14 days, or procaine penicillin, 2.4 MU/day intramuscularly, plus probenecid, 500 mg orally four times a day, both for 10-14 days. These regimens are shorter than those for treatment of late syphilis, so they may be followed by benzathine penicillin G, 2.4 MU intramuscularly, once a week for 3 weeks. Patients allergic to penicillin should have their allergy confirmed by skin testing. If allergy exists, desensitization and treatment with penicillin are recommended.

Treatment of congenital syphilis in the neonate is complex. Therapy should be undertaken in consultation with a pediatric infectious disease specialist. Management strategies can be found in the CDC *Guidelines for the Management of Sexually Transmitted Diseases.* Older children with congenital syphilis should have a CSF evaluation and be treated with aqueous crystalline penicillin G, 200 000-300 000 U/kg/day intravenously or intramuscularly (50 000 U every 4-6 h) for 10-14 days.

Pregnant women with syphilis should be treated with penicillin in doses appropriate for the stage of syphilis. A second dose of benzathine penicillin, 2.4 MU intramuscularly, may be administered 1 week after the initial dose in pregnant women with primary, secondary, or early latent syphilis. Sonographic evaluation of the fetus in the second half of pregnancy for signs of congenital infection may facilitate management and counseling. Expert consultation should be sought in cases where evidence of fetal syphilis is found, as fetal treatment failure is increased in this scenario. Follow-up quantitative serologic tests should be performed monthly until delivery. Pregnant women who are allergic to penicillin should be skin- tested and desensitized if test results are positive.

Jarisch-Herxheimer or Herxheimer reaction

A febrile reaction often occurs after the initial dose of antisyph- ilitic treatment, especially penicillin, is given. It occurs in about 60% of patients treated for seronegative primary syphilis, 90% of those with seropositive primary or secondary syphilis, and 30% of those with neurosyphilis. The reaction generally occurs 6-8 h after treatment and consists of shaking chills, fever, malaise, sore throat, myalgia, headache, tachycardia, and exacerbation of the inflammatory reaction at sites of localized spi- rochetal infection. A vesicular Herxheimer reaction can occur. A Herxheimer reaction in pregnancy may induce premature labor and fetal distress. Every effort should be made to avoid this complication. Early in pregnancy, women should rest and take acetaminophen for fever. Women treated after 20 weeks of pregnancy should seek obstetric evaluation if they experience fever, decreased fetal movement, or regular contractions within 24 h of treatment. An increase of inflammation in a vital structure may have serious consequences, as when there is an aneurysm of the aorta or iritis. When the CNS is involved, special importance is attached to avoiding the Herxheimer reaction, even though the paralyses that may result are often transitory. It is important to distinguish the Herxheimer reaction from a drug reaction to penicillin or other antibiotics. The reaction has also been described in other spirochetal diseases, such as leptospirosis and louse-borne relapsing fever.

Treatment of sex partners

Sexual partners of persons with syphilis should be identified. Persons who are exposed within 90 days of the diagnosis of primary, secondary, or early latent syphilis, even if seronega- tive, should be treated presumptively. If the exposure was longer than 90 days ago but follow-up is uncertain, presumptive treatment should be given. If the infectious source has a serologic titer of greater than 1:32, they should be presumed to have infectious early syphilis and sexual partners should be treated. At-risk partners are identified as those exposed within 3 months plus the duration of the primary lesions, for 6 months plus the duration of the secondary lesions, or 1 year for latent syphilis. Treatment of sexual partners is based on their clinical and serologic findings. If they are seronegative but had exposures as outlined above, treatment would be as for early syphilis, with benzathine penicillin, 2.4 MU intramuscularly as one dose.

Serologic testing after treatment

Before therapy and then regularly thereafter, quantitative VDRL or RPR testing should be performed on patients who are to be treated for syphilis to ensure appropriate response.

For primary and secondary syphilis in an HIV-negative non- pregnant patient, testing is repeated every 3 months in the first year, every 6 months in the second year, and yearly thereafter. At least a four-fold decrease in titer would be expected 6 months after therapy, but 15% of patients with recommended treatment will not achieve this serologic response by 1 year. Patients with prior episodes of syphilis may respond more slowly. If response is inadequate, HIV testing (if HIV status is unknown) and CSF evaluation are recommended. For HIV- negative patients who fail to respond and who have a normal CSF evaluation, optimal management is unclear. Close follow-up must be assured. If it is decided to retreat the patient, 3-weekly injections of benzathine penicillin G, 2.4 MU, are recommended. A four-fold increase in serologic titer clearly indicates treatment

failure or reinfection. These patients should have HIV testing and CSF analysis, with treatment determined by the results of these tests.

The serological response for patients with latent syphilis is slower, but a four-fold decrease in titer should be seen by 12-24 months. If no such response occurs, HIV testing and CSF evaluation are recommended. Patients treated for latent or late syphilis may be serofast, so that failure to observe a titer fall in these patients does not in itself indicate a need for retreatment. If the titer is less than 1 : 32, the possibility of a serofast state exists, and retreatment should be planned on an individual basis.

Seroreversion in specific treponemal tests can occur. By 36 months 24% of patients treated for early syphilis had a negative FTA-ABS and 13% a negative MHA-TP.

Syphilis and HIV disease

Syphilis and other genital ulcer diseases enhance the risk of transmission and acquisition of HIV. This may be due to the fact that early lesions of syphilis contain mononuclear cells with enhanced expression of CCR5, the coreceptor for HIV-1. HIV testing is recommended in all patients with syphilis.

Most HIV-infected patients with syphilis exhibit the classic clinical manifestations with appropriate serologic titers for that stage of disease. Response to treatment, both clinical and serologic in HIV-infected patients with syphilis, generally follow the clinical and serologic patterns seen in patients without coexisting HIV infection. In a large study that compared HIV-positive with HIV-negative patients with syphilis, the former were more likely to present with secondary syphilis (53% vs 33%) and were more likely to have a chancre that persisted when they had secondary syphilis (43% vs 15%). Unusual clinical manifestations of syphilis in HIV range from florid skin lesions to few atypical ones, but these are exceptions, not the rule. Since most HIV-infected patients in large urban areas in the US and Western Europe who acquire syphilis are men who

have sex with men, chancres may be in atypical locations, such as the lips, tongue, or anus.

In general, the nontreponemal tests are of higher titer in HIV-infected persons. Rarely, the serologic response to infection may be impaired or delayed, and seronegative secondary syphilis has been reported. Biopsy of the skin lesions and histopathologic evaluation with silver stains will confirm the diagnosis of syphilis in such cases. This approach, along with darkfield examination of appropriate lesions, should be considered if the clinical eruption is characteristic of syphilis and the serologic tests yield negative results.

Neurosyphilis has been frequently reported in HIV-infected persons, even after appropriate therapy for early syphilis. Manifestations have been those of early neurosyphilis or meningeal or meningovascular syphilis. These have included headache, fever, hemiplegia, and cranial nerve deficits, especially deafness (cranial nerve VIII), decreased vision (cranial nerve II), and ocular palsies (cranial nerves III and VI). Whether HIV-infected persons are at increased risk for these complications or whether they occur more quickly is unknown. It is known that spirochetes are no more likely to remain in the CSF after treatment in HIV-infected persons than in HIV-negative persons. Whether the impaired host immunity allows these residual spirochetes to cause clinical relapse more frequently or more quickly in the setting of HIV is unknown.

HIV-infected patients who have primary or secondary syphilis, who are not allergic to penicillin, and who have no neurologic or psychiatric findings should be treated with benzathine penicillin G, 2.4 MU intramuscularly. The CDC recommendations are for one injectin, but allow that some experts recommend more treatment, up to 3 consecutive weeks of therapy. Patients who are allergic to penicillin should be desensitized and treated with penicillin. Following treatment, the patient should have serologic follow-up with quantitative nontreponemal tests at 3, 6, 9, 12, and 24 months. Failure of the titer to fall is an indication for re-evaluation, including lumbar puncture.

Because of the concerns about neurologic relapse in the setting of HIV disease, more careful CNS evaluation is advocated. Lumbar puncture is recommended in HIV-infected persons with latent syphilis (of any duration), late syphilis (even with a normal neurologic examination), and HIV- infected persons with any neurologic or psychiatric signs or symptoms. If the RPR is greater than or equal to 1 : 32 and the CD4 count is less than 350, neurosyphilis is more likely and lumbar puncture could be considered. Treatment in these patients will be determined by the result of their CSF evaluation. HIV-infected persons with primary and secondary syphilis should be counseled about their possible increased risk of CNS relapse.

Benzathine penicillin, 2.4 MU intramuscularly, should be used to treat all HIV-infected contacts of persons with syphilis who are at risk of acquiring infection.

Nonvenereal treponematoses: yaws, endemic syphilis, and pinta

This group of diseases is called the endemic or nonvenereal treponematoses. They share many epidemiological and pathologic features. Like venereal syphilis, the clinical manifestations are divided into early and late stages. Early disease is considered infectious, and lasts for approximately 5 years. There are periods of latency. The histology is very similar in all the diseases, and similar to venereal syphilis. Cutaneous manifestations are prominent. The bones and mucosa may also be involved in some cases (except in pinta). The involvement of other organ systems and congenital disease is not seen. Children younger than 15 years are primarily affected. Person-to-person contact, or sharing of a drinking vessel, is the mode of transmission. The endemic treponematoses are closely related to poverty and a lack of available health services. They are described as occurring where the road ends. These diseases tend to occur in the tropics, especially yaws, and the wearing of few clothes and a hot, humid climate are associated with higher prevalence. In endemic areas, as hygiene improves, "attenuated" forms of yaws and endemic syphilis appear. A larger percentage of the population is latently infected, and secondary lesions are fewer in number, drier, and limited to moist skinfolds. Instead of several "crops" of eruptions lasting months to years, infected

persons have only a single crop. Transmission is thus reduced, although a large percentage of the population may be infected. Yaws has been eradicated from many previously endemic areas so that the number of cases currently is less than 5% of what it was 50 years ago. Unfortunately, yaws is still focally endemic in Africa (especially among the pygmies), Indonesia, Timor Leste, Papua New Guinea, the Solomon Islands, and Vanuatu. The pockets of infection in the Amazon region may be vanishing.

YAWS (PIAN, FRAMBESIA, BOUBA)

Yaws is caused by *T. pallidum* subsp *pertenue.* It is transmitted nonsexually, by contact with infectious lesions. Yaws predominantly affects children younger than 15 years of age. The disease has a disabling course, affecting the skin, bones, and joints, and is divided into early (primary and secondary) and late (tertiary) disease.

Early yaws

A primary papule or group of papules appears at the site of inoculation after an incubation period of about 3 weeks (10 days to 3 months), during which there may be headache, malaise, and other mild constitutional symptoms. The initial lesion becomes crusted and larger (2-5 cm), and is known as the mother yaw (maman pian). The crusts are amber-yellow. They may be knocked off, forming an ulcer with a red, pulpy, granulated surface, but quickly reform, so that the typical yaws lesion is crusted. The lesion is not indurated. There may be some regional adenopathy.

Exposed parts are most frequently involved — the extremities, particularly the lower legs, feet, buttocks, and face — although the mother's breasts and trunk may be infected by her child. The lesion is practically always extragenital, and when genital, is a result of accidental contact rather than intercourse. After being present for about 3-6 months, the mother yaw spontaneously disappears, leaving slight atrophy and depigmentation.

Weeks or months after the primary lesion appears, secondary yaws develops Secondary lesions resemble the mother yaw, but they are smaller and may appear around the primary lesions or in a generalized pattern. The secondary lesions may clear centrally and coalesce peripherally, forming annular lesions (ringworm yaws or tinea yaws) (Fig. 13). The palms and soles may be involved, resembling secondary syphilis. In some sites, especially around the body orifices and in the armpits, groins, and gluteal crease, condylomatous lesions may arise, resembling condyloma lata of secondary syphilis. In drier endemic regions and during drier seasons, lesions tend to be fewer, less papillomatous, and more scaly, and instead of being generalized, favor the folds of the axillae, groin, and oral cavity. Yaws in the dry seasons and regions closely resembles endemic syphilis. The palms and soles may develop thick, hyperkeratotic plaques that fissure. They are painful, resulting in a crablike gait (crab yaws).

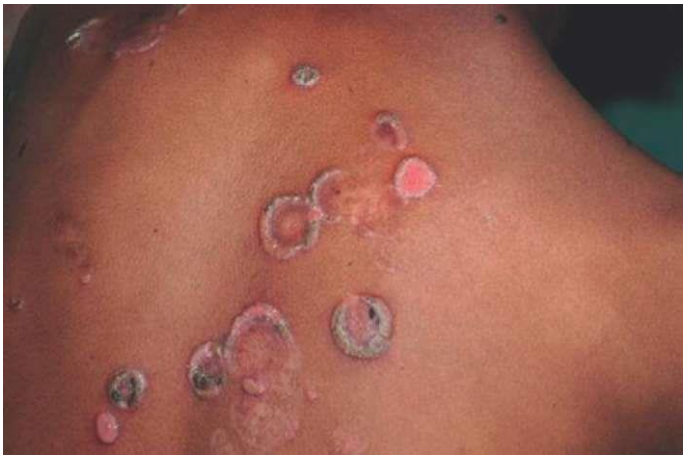


Fig. 13 Secondary lesions, yaws.

At times there is paronychia. Generalized lymphadenopathy, arthralgias, headaches, and malaise are common. With improved nutrition and hygiene, an "attenuated" form, with only scattered, flat, gray lesions in intertriginous areas, has been described.

In the course of a few weeks or months the secondary lesions may undergo spontaneous involution, leaving either no skin changes or hypopigmented macules that later become hyper- pigmented. However, the eruption may persist for many

months as a result of fresh recurrent outbreaks. The course is slower in adults than in children, in whom the secondary period rarely lasts longer than 6 months. During latency, skin lesions may relapse for as long as 5 years. Painful osteoperi-ostitis and polydactylitis may present in early yaws as fusiform swelling of the hands, feet, arms, and legs.

Late yaws

The disease usually terminates with the secondary stage, but in about 10% it progresses to the late stage, usually 5-10 years after initial infection. The typical late yaws skin lesions are gummas that present as indolent ulcers with clean-cut or undermined edges. They tend to fuse to form configurate and, occasionally, serpiginous patterns clinically indistinguishable from those of tertiary syphilis. On healing, these lesions scar, leading to contractures and deformities. Hyperkeratotic palmoplantar plaques and keratoderma frequently recur in the late stage.

Similar processes may occur in the skeletal system and other deep structures, leading to painful nodes on the bones, or destruction of the palate and nasal bone (gangosa). There may be periostitis, particularly of the tibia (saber shin, saber tibia), epiphysitis, chronic synovitis, and juxta-articular nodules. Goundou is a rare proliferative osteitis initially affecting the nasal aspects of the maxilla. Two large hard tumors form on the lateral aspects of the nose. These can significantly obstruct vision. The process may extend into other bones of the central face, affecting the palate and nose, and resulting in protrusion of the whole central face as a mass. Although yaws is classically felt to spare the eye and nervous system, abnormal CSF findings in early yaws and scattered reports of eye and neurologic findings in patients with late yaws suggest that yaws, like syphilis, has the potential to cause neurologic or ophthalmic sequelae, although very rarely.

Histopathology

Early yaws shows epidermal edema, acanthosis, papillomato- sis, neutrophilic intraepidermal microabscesses, and a moderate to dense perivascular infiltrate of lymphocytes and plasma cells. Treponema are usually demonstrable in

the primary and secondary stages with the use of the same silver stains employed in diagnosing syphilis. Tertiary yaws shows features identical to the gumma of tertiary syphilis.

Diagnosis

The diagnosis should be suspected from the typical clinical appearance in a person living in an endemic region. The presence of keratoderma palmaris et plantaris in such a person is highly suggestive of yaws. Darkfield demonstration of spiro- chetes in the early lesions and a reactive VDRL or RPR test can be used to confirm primary and secondary yaws.

Endemic syphilis (bejel)

Bejel is a Bedouin term for this nonvenereal treponematosis, which occurs primarily in the seminomadic tribes who live in the arid regions of North Africa, Southwest Asia, and the eastern Mediterranean. The etiologic agent of bejel is *T. pallidum* subsp *endemicum.* It occurs primarily in childhood and is spread by skin contact or from mouth to mouth by kissing or use of contaminated drinking vessels. The skin, oral mucosa, and skeletal system are primarily involved.

Primary lesions are rare, probably occurring undetected in the oropharyngeal mucosa. The most common presentation is with secondary oral lesions resembling mucous patches. These are shallow, relatively painless ulcerations, occasionally accompanied by laryngitis. Split papules, angular cheilitis, condylomatous lesions of the moist folds of the axillae and groin, and a nonpruritic generalized papular eruption may be seen. Generalized lymphadenopathy is common. Osteoperiostitis of the long bones may occur, causing nocturnal leg pains.

Untreated secondary bejel heals in 6-9 months. The tertiary stage can occur between 6 months and several years after the early symptoms resolve. In the tertiary stage, leg pain (peri- osteitis) and gummatous ulcerations of the skin, nasopharynx, and bone occur. Gangosa (rhinopharyngitis mutilans) can result. Rarely reported neurologic sequelae seem to be restricted to the eye, including

uveitis, choroiditis, chorioretin- itis, and optic atrophy. As with yaws, with improved nutrition, an attenuated form of endemic syphilis occurs, often presenting with leg pain from periostitis. The diagnosis of bejel is confirmed by the same means as for venereal syphilis.

PINTA

Pinta is an infectious, nonvenereal, endemic treponematosis caused by *Treponema carateum.* The mode of transmission is unknown, but repeated, direct, lesion-to-skin contact is likely. Only skin lesions occur. By contrast with yaws and bejel, pinta affects persons of all ages, favoring those between 14 and 30 years. It was once prevalent in the forests and rural areas of Central and South America, and Cuba, but it is now rarely reported. The manifestations of pinta may be divided into primary, secondary (early), and tertiary (late) stages, but historically patients may describe continuous evolution from secondary dyspigmented lesions to the characteristic achromic lesions of tertiary pinta.

Primary stage.

It is believed that the initial lesion appears 7-60 days after inoculation. The lesion begins as a tiny red papule that becomes an elevated, ill-defined, erythematous, infiltrated plaque up to 10-12.5 cm in diameter in the course of 2-3 months. Expansion of the primary lesion may occur by fusion with surrounding satellite macules or papules. Ultimately, it becomes impossible to distinguish the primary lesion from the secondary lesions. At no time is there erosion or ulceration such as occurs in the syphilitic chancre. Most initial lesions of pinta develop on the legs and other uncovered parts. The RPR and VDRL are non- reactive in the primary stage. Darkfield examination may be positive. Secondary stage

The secondary stage appears from 5 months to 1 year or more after infection. It begins with small, scaling papules that may enlarge and coalesce, simulating psoriasis, ringworm, eczema, syphilis, or Hansen's disease. They are located mostly on the extremities and face, and frequently are somewhat circi-

nate. Over time, the initially red to violaceous lesions show postinflammatory hyperpigmentation in shades of gray, blue, or brown, or hypopigmentation. Secondary lesions are classified as erythematous, desquamative, hypochromic, or hyper- chromic. Multiple different morphologies may be present simultaneously, giving a very polymorphous appearance. Nontreponemal tests for syphilis are reactive in the secondary stage in about 60% of patients. Darkfield examination may show spirochetes.

Late dyschromic stage

Until the 1940s, the late pigmentary changes were the only recognized clinical manifestations of pinta. These have an insidious onset, usually in adolescents or young adults, of widespread depigmented macules resembling vitiligo. The lesions are located chiefly on the face, waistline, wrist flexures, and trochanteric region, although at times diffuse involvement occurs, so that large areas on the trunk and extremities are affected. The lesions are symmetrical in over one-third of patients. Hemipinta is a rare variety of the disease in which the pigmentary disturbances affect only half of the body. In the late dyschromic stage of pinta, the serologic test for syphilis is positive in nearly all patients.

Histopathology

Skin lesions in early pinta show moderate acanthosis; occasionally, lichenoid changes with basal layer vacuolization; and an upper dermal perivascular infiltrate of lymphocytes and plasma cells. Melanophages are prominent in the upper dermis. Spirochetes may be demonstrated in the epidermis by special stains in primary, secondary, and hyperpigmented lesions of tertiary pinta. In tertiary pinta the depigmented skin shows a loss of basal pigment, pigmentary incontinence, and virtually no dermal inflammatory infiltrate. Spirochetes are rarely found in depigmented tertiary lesions.

Treatment

The treatment of choice is benzathine penicillin G, 1.2-2.4 MU intramuscularly (0.6-1.2 MU for children under 10 years of age). In penicillin-allergic patients, tetracycline, 500 mg four times a day for adults (or erythromycin for children, 8-10 mg/ kg four times a day for 15 days), is recommended. Penicillin- resistant yaws has been reported from New Guinea. In tertiary pinta, the blue color gradually disappears, as do the areas of partial depigmentation. The vitiliginous areas, if present for more than 5 years, are permanent. Eradication of these diseases is possible with persistent and effective treatment strategies. These include:

- screening of the whole population in endemic areas
- diagnosis of patients seen at health services and by community outreach
- health education
- improved hygiene (soap and water).

If more than 10% of the population is affected, the whole population is treated (mass treatment). If 5-10% of the population is affected, treat all active cases, all children under the age of 15, and all contacts (juvenile mass treatment). If under 5% of the population is infected, treat all active cases and all household and close personal contacts (selective mass treatment). Unfortunately, with the areas affected by the endemic treponematoses also struggling with epidemics of HIV, tuberculosis, and malaria, eradication programs have been largely discontinued.

VIRAL DISEASES

Viruses are obligatory intracellular parasites. The structural components of a viral particle (virion) consist of a central core of nucleic acid, a protective protein coat (capsid), and (in certain groups of viruses only) an outermost membrane or envelope. The capsid of the simplest viruses is made up of many identical polypeptides (structural units) that fold and interact with one another to form morphologic units (cap- someres). The number of capsomeres is believed to be

constant for each virus with cubic symmetry, and it is an important criterion in the classification of viruses. The protein coat determines serologic specificity, protects the nucleic acid from enzymatic degradation in biologic environments, controls host specificity, and increases the efficiency of infection. The outermost membrane of the enveloped viruses is essential for the attachment to, and penetration of, host cells. The envelope also contains important viral antigens.

Two main groups of viruses are distinguished: DNA and RNA. The DNA virus types are parvovirus, papovavirus, adenovirus, herpesvirus, and poxvirus. RNA viruses are picornavirus, togavirus, reovirus, coronavirus, orthomyxo- virus, retrovirus, arenavirus, rhabdovirus, and paramyxo- virus. Some viruses are distinguished by their mode of transmission: arthropod-borne viruses, respiratory viruses, fecal-oral or intestinal viruses, venereal viruses, and penetrating wound viruses.

Herpesvirus group

The herpesviruses are medium-sized viruses that contain double-stranded DNA and replicate in the cell nucleus. They are characterized by the ability to produce latent, but lifelong infection by infecting immunologically protected cells (immune cells and nerves). Intermittently, they have replica- tive episodes with amplification of the viral numbers in anatomic sites that are conducive to transmission from one host to the next (genital skin, orolabial region). The vast majority of infected persons remain asymptomatic. Viruses in this group are varicella zoster virus (VZV); herpes simplex virus (HSV)-1 and 2; cytomegalovirus (CMV); Epstein-Barr virus (EBV); human herpesviruses (HHV)-6, 7, and 8; *Herpesvirus simiae* (B virus); and other viruses of animals.

HERPES SIMPLEX

Infection with HSV is one of the most prevalent infections worldwide. HSV-1 infection, the cause of most cases of oro- labial herpes, is more common than infection with HSV-2, the cause of most cases of genital herpes. Between 30% and 95% of adults (depending on the country and group tested) are seropositive for

HSV-1. Seroprevalence for HSV-2 is lower, and it appears at the age of onset of sexual activity. In Scandinavia, the rate of infection with HSV-2 increases from 2% in 15-year-olds to 25% in 30-year-olds. About 2.4% of adults become infected annually with HSV-2 in their third decade of life. In the US about 25% of adults are infected with HSV-2. In sexually transmitted disease (STD) clinic patients, the infection rate is between 30% and 50%. In sub-Saharan Africa, infection rates are between 60% and 95%. Worldwide, the seroprevalence is higher in human immunodeficiency virus (HIV)-infected persons. Serologic data have demonstrated that many more people are infected than give a history of clinical disease. For HSV-1, about 50% of infected persons give a history of orolabial lesions. For HSV-2, 20% of infected persons are completely asymptomatic (latent infection), 20% have recurrent genital herpes they recognize, and 60% have clinical lesions that they do not recognize as genital herpes (subclinical or unrecognized infection). Most persons with HSV-2 infection are symptomatic, but the majority do not recognize that their symptoms are caused by HSV. All persons infected with HSV-1 and 2 infection are potentially infectious even if they have no clinical signs or symptoms.

HSV infections are classified as either "first episode" or "recurrent." Most patients have no lesions or findings when they are initially infected with an HSV. When the patient has his/her first clinical lesion, this is usually a recurrence. Since the initial clinical presentation is not associated with a new infection, the old terminology of "primary" infection has been abandoned. Instead, the initial clinical presentation is called a "first episode" and may represent a true primary infection or a recurrence. Persons with chronic or acute immunosuppres- sion may have prolonged and atypical clinical courses.

Infections with HSV-1 or 2 are diagnosed by specific and nonspecific methods. The most common procedure used in the office is the Tzanck smear. It is nonspecific since both HSV and VZV infections result in the formation of multinucleate epidermal giant cells. The multiple nuclei are molded or fit together like pieces of a puzzle. Although the technique is rapid, its success depends heavily

on the skill of the interpreter. The accuracy rate is between 60% and 90%, with a false-positive rate of 3-13%. The direct fluorescent antibody (DFA) test is more accurate and will identify virus type; results can be available in hours if a virology laboratory is nearby. Viral culture is very specific and relatively rapid (compared to serological tests), since HSV is stable in transport and grows readily and rapidly in culture. Results are often available in 48-72 h. However, the sensitivity may be as low as 25-50%, since nearby viral laboratories are not readily available to many practitioners. Polymerase chain reaction (PCR) is as specific as viral culture and can be performed on dried or fixed tissue, It is four times more sensitive than viral culture when compared head to head. Skin biopsies of lesions can detect viropathic changes caused by HSV, and with specific HSV antibodies, immunoperoxidase techniques can accurately diagnose infection. The accuracy of various tests is dependent on lesion morphology. Only acute, vesicular lesions are likely to be positive with Tzanck smears. Crusted, eroded, or ulcerative lesions are best diagnosed by viral culture, fluorescent antibody, his- tologic methods, or PCR.

Serologic tests are generally not used in determining whether a skin lesion is due to HSV infection. A positive serologic test indicates only that the individual is infected with that virus, not that the viral infection is the cause of the current lesion. Secondgeneration enzymelinked immunosorbent assay (ELISA) tests and G protein-specific Western blot serologic tests can detect specific infection with HSV-1 and 2 but cannot determine the duration or source of that infection. In addition to determining the infection rate in various populations, serologic tests are most useful in evaluating couples in which only one partner gives a history of genital herpes (discordant couples), in couples at risk for neonatal herpes infection, and for possible HSV vaccination when it becomes available.

Orolabial herpes

Orolabial herpes is virtually always caused by HSV-1. In 1% or less of newly infected persons, herpetic gingivostomatitis develops, chiefly in children and young adults (Fig. 14).

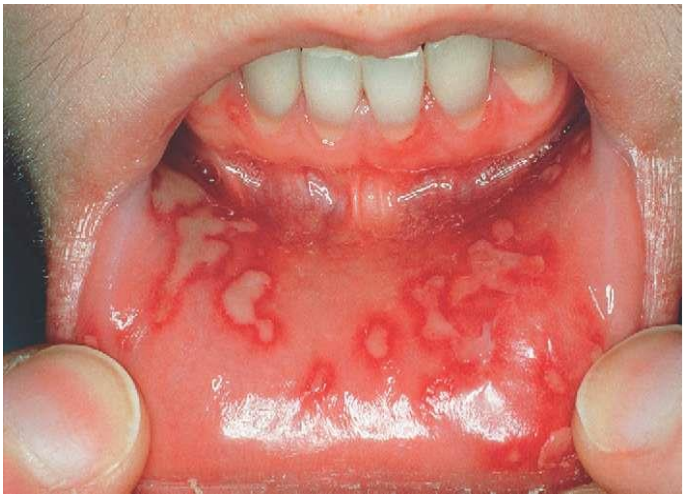


Fig. 14 Herpetic gingivostomatitis, extensive erosions of the oral mucosa.

The onset is often accompanied by high fever, regional lymphadenopathy, and malaise. The herpetic lesions in the mouth are usually broken vesicles that appear as erosions or ulcers covered with a white membrane. The erosions may become widespread on the oral mucosa, tongue, and tonsils, and the gingiva margin is commonly eroded. Herpetic gingivostomatitis produces pain, foul breath, and dysphagia. In young children, dehydration may occur. It may cause pharyngitis, with ulcerative or exudative lesions of the posterior pharynx. The duration, untreated, is 1-2 weeks. If the initial episode of herpetic gingivostomatitis or herpes labialis is so severe that an intravenous delivery is required, acyclovir, 5 mg/kg three times a day, is recommended. Oral therapeutic options include acyclovir suspension, 15 mg/kg five times daily for 7 days, valacyclovir, 1 g twice daily for 7 days, or famciclovir, 500 mg twice daily for 7 days. This therapy reduces the duration of the illness by more than 50%.

Fig. 15 HSV-1, eyelid infection from a "kiss" from an infected adult.

The most frequent clinical manifestation of orolabial herpes is the "cold sore" or "fever blister." Recurrent HSV-1 is the cause 95% or more of the time, and typically presents as grouped blisters on an erythematous base. The lips near the vermilion are most frequently involved. Lesions may, however, occur wherever the virus was inoculated or proliferated during the initial episode (Fig. 15). Recurrences may be seen on the cheeks, eyelids, and earlobes. Oral recurrent HSV usually affects the keratinized surfaces of the hard palate and attached gingiva. Outbreaks are variable in severity, partly related to the trigger of the outbreak. Some outbreaks are small and resolve rapidly, while others may be severe, involving both the upper and lower lips (Fig. 16). In severe outbreaks, lip swelling is often present. Patient symptomatology is variable. A prodrome of up to 24 h of tingling, itching, or burning may precede the outbreak. Local discomfort, as well as headache, nasal congestion, or mild flu-like symptoms, may occur.

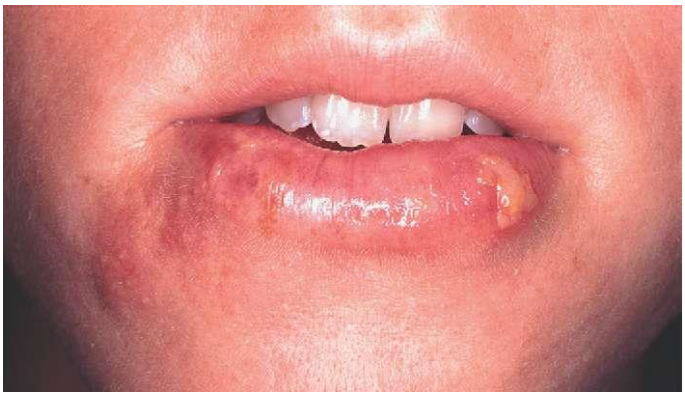


Fig. 16 Orolabial herpes simplex, severe outbreak triggered by a sunburn.

Ultraviolet (UV) exposure, especially UVB, is a frequent trigger of recurrent orolabial HSV, and the severity of the outbreak may correlate with the intensity of the sun exposure. Surgical and dental procedures of the lips (or other areas previously affected with HSV) may trigger recurrences, and a history of prior HSV should be solicited in all patients in whom such procedures are recommended (see below).

In most patients recurrent orolabial herpes represents more of a nuisance than a disease. Because UVB radiation is a common trigger, use of a sunblock daily on the lips and facial skin may reduce recurrences. All topical therapies for the acute treatment of recurrent orolabial herpes have limited efficacy, reducing disease duration and pain by 1 day or less. Tetracaine cream, penciclovir cream, and acyclovir cream (not ointment) have some limited efficacy. Topical acyclovir ointment and docosanol cream provide minimal to no reduction in healing time or discomfort. The minimal benefit from these topical agents suggests that they should not be recommended when patients present to dermatologists for significant symptomatic orolabial herpes outbreaks. If oral therapy is contemplated for patients with severely symptomatic recurrences of orolabial HSV, it must be remembered that much higher doses of oral antivirals are required than for the treatment of genital herpes. Intermittent treatment with valacyclovir, 2 g twice a day for 1 day, or famciclovir, 1.5 g as a single dose, starting at the onset of the prodrome are simple and effective oral 1 day regimens. Since the patient’s own inflammatory reaction against the virus contributes substantially to the severity of

lesions of orolabial herpes simplex, topical therapy with a high-potency topical steroid (fluocinonide gel 0.05%, three times a day) in combination with an oral antiviral leads to more rapid reduction of pain, and reduces maximum lesion area and time to healing. In non-immunosuppressed patients, if episodic treatment for orolabial HSV is recommended and an oral agent is used, the addition of a highpotency topical steroid should be considered.

Although most patients with orolabial herpes simplex do not require treatment, certain medical and dental procedures may trigger outbreaks of HSV. If the cutaneous surface has been damaged by the surgical procedure (such as a dermabrasion, chemical peel, or laser resurfacing procedure), the surgical site can be infected by the virus and may result in prolonged healing and possible scarring. Prophylaxis is regularly used before such surgeries in patients with a history of orolabial herpes simplex. Famciclovir, 250 mg twice a day, and valacy- 55lover, 500 mg twice a day, are prophylactic options, to be begun 24 h before the procedure, or the morning of the procedure and continued for 14 days. Prophylaxis could also be considered before skiing or tropical vacations and extensive dental procedures at the same dosages.

Herpetic sycosis

Recurrent or initial herpes simplex infections (usually due to HSV-1) may primarily affect the hair follicle. The clinical appearance may vary from a few eroded follicular papules (resembling acne excoriee) to extensive lesions involving the whole beard area. Close razor blade shaving immediately prior to initial exposure or in the presence of an acute orolabial lesion may be associated with a more extensive eruption. The onset may be very acute (over days), or more subacute or chronic. Diagnostic clues include the tendency for erosions, a self-limited course of 2-3 weeks, and an appropriate risk behavior Fig. 17 Herpetic sycosis.

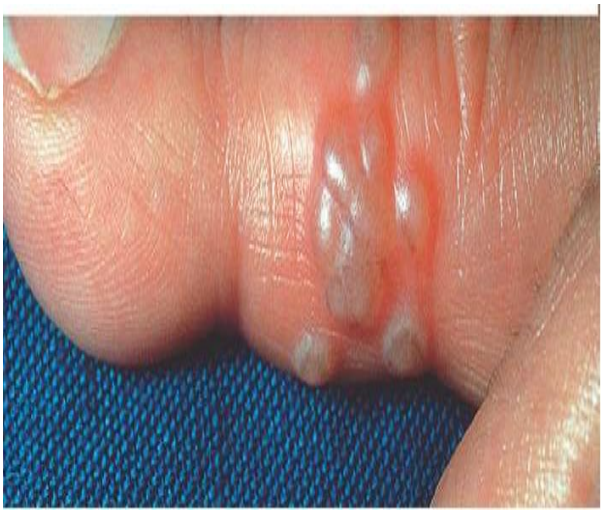


Fig. 17 Herpetic sycosis

The diagnosis may be confirmed by biopsy. Although the herpes infection is primarily in the follicle, surface cultures of eroded lesions will usually be positive in the first 5-7 days of the eruption.

Herpes gladiatorum

HSV-1 infection is highly contagious to susceptible persons who wrestle with an infected individual with an active lesion. One-third of susceptible wrestlers will become infected after a single match. In tournaments and wrestling camps, outbreaks can be epidemic, affecting up to 20% of all participants. Lesions usually occur on the lateral side of the neck, the side of the face, and the forearm, all areas in direct contact with the face of the infected wrestler. Vesicles appear 4-11 days after exposure, often preceded by 24 h of malaise, sore throat, and fever. Ocular symptoms may occur. Lesions are frequently misdiagnosed as a bacterial folliculitis. Any wrestler with a confirmed history of orolabial herpes should be on suppres- sive antiviral therapy during all periods of training and competition. Rugby players, especially forwards who participate in scrums, are also at risk.

Herpetic whitlow

HSV infection may uncommonly occur on the fingers or peri- ungually. Lesions begin with tenderness and erythema, usually of the lateral nailfold or on the palm. Deep-seated blisters develop 24-48 h after symptoms begin (Fig. 19-6).

The blisters may be very small, requiring careful inspection to detect them. Deep-seated lesions that appear unilocular may be mistaken for a paronychia or other inflammatory process. Lesions may progress to erosions, or heal without ever impairing epidermal integrity due to the thick stratum corneum in this location. Herpetic whitlow may simulate a felon. Swelling of the affected hand is not uncommon. Lymphatic streaking and swelling of the epitrochlear or axillary lymph nodes may occur, mimicking a bacterial cellulitis. Repeated episodes of herpetic lymphangitis may lead to persistent lymphedema of the affected hand. Herpetic whitlow has become much less frequent among healthcare workers since the institution of universal precautions and glove use during contact with the oral mucosa. Currently, most cases are seen in persons with herpes elsewhere. Children may be infected while thumb sucking or nail biting during their initial herpes outbreak or by touching an infectious lesion of an adult. Herpetic whitlow is bimodal in distribution, with about 20% of cases occurring in children younger than 10 years old, and 55% of cases between the ages of 20 and 40. All cases in children are caused by HSV-1, but in adults up to three-quarters of cases are caused by HSV-2. Among adults, herpetic whitlow is twice as common in females. Herpetic whitlow in healthcare workers can be transmitted to patients. In patients whose oropharynx is exposed to the ungloved hands of healthcare workers with herpetic whitlow, 37% develop herpetic pharyngitis.

Herpetic keratoconjunctivitis

Herpes simplex infection of the eye is a common cause of blindness in the US. It occurs as a punctate or marginal kera- titis, or as a dendritic corneal ulcer, which may cause disciform keratitis and leave scars that impair vision. Topical cortico- steroids in this situation may induce perforation of the cornea. Vesicles may appear on the lids, and preauricular nodes may be enlarged and tender. Recurrences are common. Ocular symptoms in any person with an initial outbreak of HSV could represent ocular HSV, and an ophthalmological evaluation should be performed to exclude this possibility.

Genital herpes

Genital herpes infection is usually due to HSV-2, which causes 85% of initial infections and up to 98% of recurrent lesions. In the mid-1980s, the prevalence of genital herpes caused by HSV-1 began to increase because of changes in sexual habits and a falling prevalence of orolabial HSV-1 infection in developed nations, so that in some developed countries HSV-1 now causes up to 50% of anogenital herpes in women. HSV-1 in the genital area is much less likely to recur (only 20-50% of patients have a recurrence, and when a recurrence does occur, the average patient experiences only about one outbreak per year.

Genital herpes is spread by skin-to-skin contact, usually during sexual activity. The incubation period averages 5 days. Active lesions of HSV-2 contain live virus and are infectious. Persons with recurrent genital herpes shed virus asympto- matically between outbreaks (asymptomatic shedding).

Even persons who are HSV-2-infected but have never had any clinical lesions or symptoms shed virus, so everyone who is HSV-2-infected is potentially infectious to a sexual partner. Asymptomatic shedding occurs simultaneously from several anatomic sites (penis, vagina, cervix, and rectum) and can occur through normally appearing intact skin and mucosae. In addition, persons with HSV-2 infection may have lesions they do not recognize as being caused by HSV (unrecognized outbreak) or have recurrent lesions that do not cause symptoms (subclinical outbreak). Most transmission of genital herpes occurs during subclinical or unrecognized outbreaks, or while the infected person is shedding asymptomatically.

The risk of transmission in monogamous couples, in which only one partner is infected, is about 5-10% annually, with women being at much greater risk than men for acquiring HSV-2 from their infected partner. Prior HSV-1 infection does not reduce the risk of being infected with HSV-2 but does make it more likely that initial infection will be asymptomatic. There is no strategy that absolutely prevents herpes transmission. All prevention strategies are more effective in reducing the

risk of male-to-female transmission than female-to-male transmission. Condom use for all sexual exposures and avoiding sexual exposure when active lesions are present have been shown to be effective strategies, as has chronic suppressive therapy of the infected partner with valacyclovir, 500 mg/day.

The symptomatology during acquisition of infection with HSV-2 has a broad clinical spectrum from totally asymptomatic to severe genital ulcer disease (erosive vulvovaginitis or proctitis). Only 57% of new HSV-2 infections are symptomatic. Clinically, the majority of symptomatic initial herpes lesions are classic grouped blisters on an erythematous base. At times, the initial clinical episode is that of typical grouped blisters, but with a longer duration of 10-14 days. While uncommon and representing 1% or fewer of new infections, severe first- episode genital herpes can be a significant systemic illness. Grouped blisters and erosions appear in the vagina, in the rectum, or on the penis, with continued development of new blisters over 7-14 days. Lesions are bilaterally symmetrical and often extensive, and the inguinal lymph nodes can be enlarged bilaterally. Fever and flu-like symptoms may be present, but in women the major complaint is vaginal pain and dysuria (herpetic vulvovaginitis). The whole illness may last 3 weeks or more. If the inoculation occurs in the rectal area, severe proctitis may occur from extensive erosions in the anal canal and on the rectal mucosa. The initial clinical episode of genital herpes is treated with oral acyclovir, 200 mg five times a day or 400 mg three times a day; famciclovir, 250 mg three times a day; or valacyclovir, 1000 mg twice a day, all for 7-10 days. Since it is very difficult on clinical grounds to distinguish true initial (or primary) HSV-2 infection from a recurrence, all patients with their initial clinical episode receive the same therapy. Only serology can determine whether the person is totally HSV-nai've and suffering a true primary episode, is partially immune due to prior HSV-1 infection, or is already HSV-2-infected and their first clinical presentation is actually a recurrence. In fact, 25% of "initial" clinical episodes of genital herpes are actually recurrences.

Virtually all persons infected with HSV-2 will have recurrences, even if the initial infection was subclinical or asymptomatic. HSV-2 infection results in recurrences in the genital area six times more frequently than HSV-1. Twenty percent of persons with HSV-2 infection are truly asymptomatic, never having had either an initial lesion or recurrences. Twenty percent of patients have lesions they recognize as recurrent genital herpes and 60% have clinical lesions that are culture-positive for HSV-2, but are unrecognized by the patient as being caused by genital herpes. This large group of persons with subclinical or unrecognized genital herpes is infectious, at least intermittently, and represents one factor in the increasing number of new HSV-2 infections.

Typical recurrent genital herpes begins with a prodrome of burning, itching, or tingling. Usually within 24 h, red papules appear at the site, progress to blisters filled with clear fluid over 24 h, form erosions over the next 24-36 h, and heal in another 2-3 days (Fig. 19-7). The average total duration of a typical outbreak of genital herpes is 7 days. Lesions are usually grouped blisters, and the coalescent grouped erosions they evolve into characteristically have a scalloped border Fig. 18 Recurrent genital herpes. Erosions or ulcerations from genital herpes are usually very tender and not indurated (as opposed to the chancre of primary syphilis).

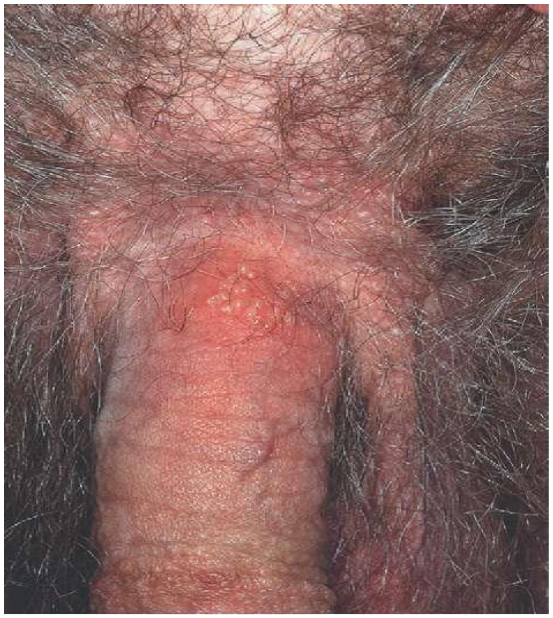


Fig. 18 Recurrent genital herpes.

Lesions tend to recur in the same anatomic region, although not at exactly the same site (as opposed to a fixed drug eruption). Less classic clinical manifestations are tiny erosions or linear fissures on the genital skin. Lesions occur on the vulva, vagina, and cervical mucosa, as well as the penile and vulval skin. The upper buttock is a common site for recurrent genital herpes in both men and women. Intraurethral genital herpes may present with dysuria and a clear penile discharge, and is usually misdiagnosed as a more common, nongonococcal urethritis such as *Chlamydia* or *Ureaplasma.* Inguinal adenopa- thy may be present. Looking into the urethra and culturing any erosions will establish the diagnosis. Recurrent genital herpes heals without scarring unless the lesion is secondarily infected.

The natural history of untreated recurrent genital herpes is not well studied. Over the first several years of infection, the frequency of recurrences usually stays the same. Over longer periods (more than 3-5 years) the frequency of outbreaks decreases in at least two-thirds of patients treated with sup- pressive antiviral therapy.

Recurrent genital herpes is a problematic disease due to the social stigma associated with it. Because it is not curable, patients frequently demonstrate a significant emotional response when they are first diagnosed. These include anger (at the presumed source of the infection), depression, guilt, and the feeling they are not worthy. During the visit the healthcare worker should ask about a patient's feelings surrounding the diagnosis and any psychological complications that have occurred. This psychological component of genital herpes must be recognized, addressed directly with the patient, and managed for the therapy of recurrent genital herpes to be successful.

Management of recurrent genital herpes should be individualized. A careful history, including a sexual history, should be obtained. Examination should include seeing the patient during an active recurrence, so that the infection can be con- firmed. The diagnosis of recurrent genital herpes should not be made on clinical appearance alone because of the psychological impact of the diagnosis. The

diagnosis is best confirmed by a viral culture or DFA examination, allowing for typing of the causative virus. If clinical lesions are not present, serology can determine if the patient is infected with HSV-2. If the patient is HSV-1-seropositive, but HSV-2-seronegative, the possibility of genital HSV-1 disease cannot be excluded.

Treatment depends on several factors, including the frequency of recurrences, severity of recurrences, infection status of the sexual partner, and psychological impact of the infection on the patient. For patients with few or mildly symptomatic recurrences, treatment is often not necessary. Counseling regarding transmission risk is required. In patients with severe but infrequent recurrences or in those who have severe psychological complications, intermittent therapy may be useful. To be effective, intermittent therapy must be initiated at the earliest sign of an outbreak. The patient must be given the medication before the recurrence, so treatment can be started by the patient when the first symptoms appear. Intermittent therapy only reduces the duration of the average recurrence by about 1 day. However, it is a powerful tool in the patient who is totally overwhelmed by each outbreak. The treatment of recurrent genital herpes is acyclovir, 200 mg five times a day or 800 mg twice a day, or famciclovir, 125 mg twice a day, all for 5 days. Shorter regimens that are equally effective include valacyclovir, 500 mg twice a day for 3 days; acyclovir, 800 mg three times a day for 2 days; or famciclovir, 1 g twice a day for one day.

For patients with frequent recurrences (more than 6-12 per year), suppressive therapy is more reasonable. Acyclovir, 400 mg twice a day, 200 mg three times a day, or 800 mg once a day, will suppress 85% of recurrences, and 20% of patients will be recurrence-free during suppressive therapy. Valacyclovir, 500 mg/day (or 1000 mg/day for persons with more than 10 recurrences per year), or famciclovir, 250 mg twice a day, are equally effective alternatives. Up to 5% of immunocompetent patients will have significant recurrences on these doses, and the dose of the antiviral may need to be increased. Chronic suppressive therapy reduces asymptomatic shedding by almost 95%. After 10 years of suppressive

therapy a large number of patients can stop treatment with a substantial reduction in frequency of recurrences. Chronic suppressive therapy is very safe and laboratory monitoring is not required.

Intrauterine and neonatal herpes simplex

Neonatal herpes infection occurs in between 1 in 3000 and 1 in 20 000 live births, resulting in 1500-2200 cases of neonatal herpes annually in the US. Eighty-five percent of cases of neonatal herpes simplex infections occur at the time of delivery, 5% occur in utero with intact membranes, and 10-15% occur from nonmaternal sources after delivery. In utero infection may result in fetal anomalies, including skin lesions and scars, limb hypoplasia, microcephaly, microphthalmos, encephalitis, chorioretinitis, and intracerebral calcifications. It is either fatal or complicated by permanent neurologic sequelae.

Seventy percent of cases of neonatal herpes simplex are caused by HSV-2. Neonatal HSV-1 infections are usually acquired postnatally through contact with a person with oro- labial disease, but can also occur intrapartum if the mother is genitally infected with HSV-1. The clinical spectrum of perinatally acquired neonatal herpes can be divided into three forms:

- localized infection of the skin, eyes and/or mouth (SEM)
- central nervous system (CNS) disease
- disseminated disease (encephalitis, hepatitis, pneumonia, and coagulopathy).

The pattern of involvement at presentation is important prog- nostically. With treatment, localized disease (skin, eyes, or mouth) is rarely fatal, whereas brain or disseminated disease is fatal in 15-50% of neonates so affected. In treated neonates, long-term sequelae occur in 10% of neonates with localized disease. More than 50% of cases of CNS or disseminated neonatal herpes suffer neurologic disability.

In 68% of infected babies, skin vesicles are the presenting sign, and are a good source for virus recovery. However, 39% of neonates with disseminated disease, 32% with CNS disease, and 17% with SEM disease never develop

vesicular skin lesions. Because the incubation period may be as long as 3 weeks, and averages about 1 week, skin lesions and symptoms may not appear until the child has been discharged from hospital.

The diagnosis of neonatal herpes is confirmed by viral culture or preferably immediate DFA staining of material from skin or ocular lesions. CNS involvement is detected by PCR of the cerebrospinal fluid (CSF). PCR of the CSF is negative in 24% of cases of neonatal CNS herpes infection, so empiric therapy pending other testing may be required. Neonatal herpes infections are treated with intravenous acyclovir, 60 mg/kg/day for 14 days for SEM disease, and 21 days for CNS and disseminated disease.

Seventy percent of mothers of infants with neonatal herpes simplex are asymptomatic at the time of delivery and have no history of genital herpes. Thus, extended history-taking is of no value in predicting which pregnancies may be complicated by neonatal herpes. The most important predictors of infection appear to be the nature of the mother's infection at delivery (first episode versus recurrent), and the presence of active lesions on the cervix, vagina, or vulvar area. The risk of infection for an infant delivered vaginally when the mother has active recurrent genital herpes infection is between 2% and 5%, whereas it is 26-56% if the maternal infection at delivery is a first episode. One strategy to prevent neonatal HSV would be to prevent transmission of HSV to at-risk women during pregnancy, eliminating initial HSV episodes during pregnancy. To accomplish this, pregnant women and their partners would be tested to identify discordant couples for HSV-1 and 2. If the woman is HSV-1-negative and the man is HSV-1-positive, orogenital contact during pregnancy should be avoided, and a condom should be used for all episodes of sexual contact. Valacyclovir suppression of the infected male could also be considered, but might have limited efficacy. If the woman is HSV-2-seronegative and her partner is HSV-2- seropositive, barrier protection for sexual contact during gestation is recommended, and valacyclovir suppression of the man could be considered. Abstinence from intercourse during the third trimester would also reduce the chances of an at-risk mother acquiring

genital herpes that might first present peri- natally. These strategies have not been tested and could not be guaranteed to prevent all cases of neonatal HSV. At a minimum, discordant couples should be made aware of the increased risk to the fetus that acquisition of HSV by the mother during pregnancy presents.

The appropriate management of pregnancies complicated by genital herpes is complex and there are still areas of controversy. Routine prenatal cultures are not recommended for women with recurrent genital herpes, as they do not predict shedding at the time of delivery. Such cultures may be of value in women with primary genital herpes during pregnancy. Scalp electrodes should be avoided in deliveries where cervical shedding of HSV is possible, as they have been documented to increase the risk of infection of the newborn by up to seven-fold (Fig. 19). Vacuum-assisted delivery also increases the relative risk of neonatal transmission of HSV by between 2 and 27 times. Genital HSV-1 infection appears to be much more frequently transmitted intrapartum than HSV-2. The current recommendation is still to perform cesarean section in the setting of active genital lesions or prodromal symptoms. This will reduce the risk of transmission of HSV to the infant from 8% to 1% for women who are culture-positive from the cervix at time of delivery. However, this approach will not prevent all cases of neonatal herpes, is expensive, and has a high maternal morbidity (US$2.5 million to prevent each case of neonatal herpes, 1580 excess cesarian sections for every poor-outcome case of neonatal HSV prevented, and 0.57 maternal deaths for every neonatal death prevented.) Because the risk of neonatal herpes is much greater in mothers who experience their initial episode during pregnancy, antiviral treatment of all initial episodes of genital HSV in pregnancy is recommended (except in the first month of gestation where there may be an increased risk of spontaneous abortion).

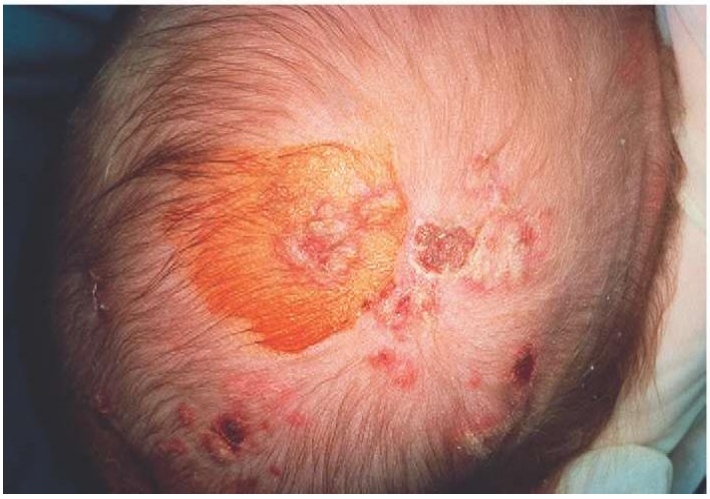


Fig. 19. Neonatal herpes, a scalp monitor was associated with infection of this neonate.

Standard acyclovir doses for initial episodes (acyclovir, 400 mg three times a day for 10 days) are recommended. This is especially true for all initial episodes in the third trimester. Chronic suppressive therapy with acyclovir has been used from 36 weeks' gestation to delivery in women with an initial episode of genital HSV during pregnancy to reduce outbreaks and prevent the need for cesarean section. This approach has been recommended by the American College of Obstetrics and Gynecology, and may also be considered for women with recurrent genital herpes.

The condition of extensive congenital erosions and vesicles healing with reticulate scarring may represent intrauterine neonatal herpes simplex (Fig. 20). The condition is rare since intrauterine HSV infection is rare and usually fatal. Probably only a few children survive to present later in life with the characteristic widespread reticulate scarring of the whole body. This may explain the associated CNS manifestations seen in many affected children. One of the authors (TB) has seen a child with this condition who developed infrequent widespread cutaneous blisters from which HSV could be cultured. Modern obstetric practices which screen for herpes in pregnant women and prophylactic treatment with acyclovir in the third trimester may prevent the condition, explaining the lack of recent cases.

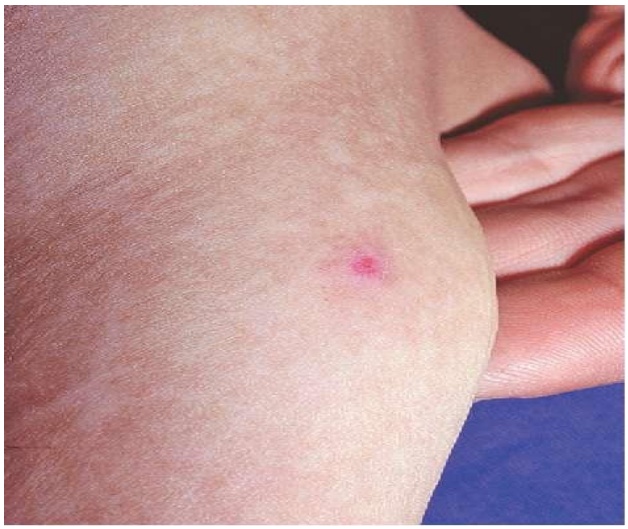


Fig. 20. Extensive congenital erosions and vesicles healing with reticulate scarring

Eczema herpeticum (Kaposi varicelliform eruption)

Infection with herpesvirus in patients with atopic dermatitis (AD) may result in spread of herpes simplex throughout the eczematous areas. This is called eczema herpeticum or Kaposi varicelliform eruption (KVE). In a large series the development of eczema herpeticum was associated with more severe atopic dermatitis, higher IgE levels, elevated eosinophil count, food and environmental allergies as defined by radioaller- gosorbent-testing (RAST), and onset of AD before age 5. Eczema herpeticum patients are also more likely to have *Staphylococcus aureus* and molluscum contagiosum infections. All these features identify AD patients who have significant Th2 shift of their immune system. The use of topical calcineurin inhibitors (TCIs) has been repeatedly associated with the development of eczema herpeticum. Bath or hot tub exposure has been reported as a risk factor for development of KVE. The Th2 shift of the immune system and the use of TCIs are both associated with a decrease in antimicrobial peptides in the epidermis, an important defense against cutaneous HSV infection. In addition, in Japan, polymorphisms in the *IL-18* gene are associated with eczema herpeticum complicating TCI treatment. The repair of the epidermal lipid barrier with physi-ologic lipid mixtures reverses some of the negative effects of the TCIs and may reduce the risk of eczema herpeticum.

In general, the term Kaposi varicelliform eruption is used for cases of disseminated cutaneous HSV associated with skin diseases other than atopic dermatitis. Cutaneous dissemination of HSV-1 or 2 may also occur in severe seborrheic dermatitis, scabies, Darier's disease, benign familial pemphigus, pemphigus (foliaceus or vulgaris), pemphigoid, cutaneous T-cell lymphoma, Wiskott-Aldrich syndrome, allergic and photoallergic contact dermatitis, and burns. In its severest form, hundreds of umbilicated vesicles may be present at the onset, with fever and regional adenopathy. Although the cutaneous eruption is alarming, the disease is often self-limited in healthy individuals. Much milder cases are considerably more common and probably go unrecognized and untreated. They present as a few superficial erosions or even small papules (Fig. 21). In patients with systemic immunosuppression in addition to an impaired barrier, such as patients with pemphigus and cutaneous T-cell lymphoma, KVE can be fatal, usually from *S. aureus* septicemia, but also from visceral dissemination of herpes simplex.

Psoriasis patients treated with immunosuppressives may suffer KVE as well, although this is less common. It usually occurs in the setting of worsening disease or erythroderma. Patients present with erosive lesions in the axilla and erosions of the psoriatic plaques. Lesions extend cephalad to caudad, and the development of large, ulcerated painful plaques can occur. The lesions are commonly co-infected with bacteria and yeast. Cultures positive for other pathogens do NOT exclude the diagnosis of KVE, and specific viral cultures, DFAs, and biopsies should be taken if the diagnosis of KVE is suspected.

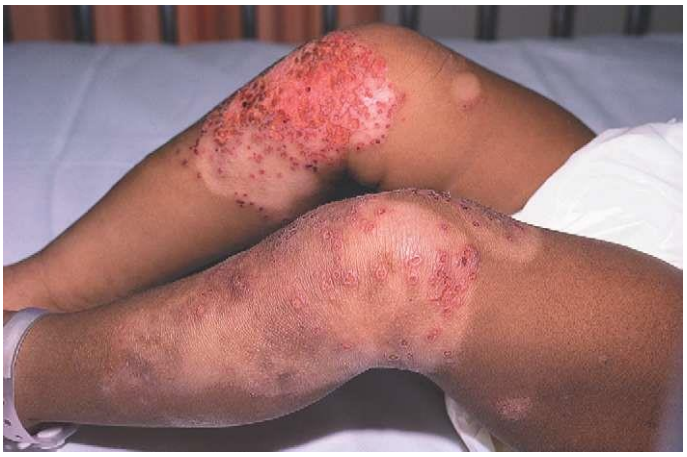


Fig. 20 Eczema herpeticum, sudden appearance of uniform erosions, accentuated in areas of active dermatitis.

Given the limited toxicity of systemic antiviral therapy, treatment should be started immediately pending the return of laboratory confirmation. Depending on the severity of the disease, either intravenous or oral antiviral therapy should be given for KVE.

Immunocompromised patients

In patients with immunosuppression of the cell-mediated immune system by cytotoxic agents, corticosteroids, or congenital or acquired immunodeficiency, primary and recurrent cases of herpes simplex are more severe, more persistent, more symptomatic, and more resistant to therapy. In some settings (such as in bone marrow transplant recipients), the risk of severe reactivation is so high that prophylactic systemic anti- virals are administered. In immunosuppressed patients, any erosive mucocutaneous lesion should be considered to be herpes simplex until proved otherwise, especially lesions in the genital and orolabial regions. Atypical morphologies are also seen.

Typically, lesions appear as erosions or crusts (Fig. 21). The early vesicular lesions may be transient or never seen. The three clinical hallmarks of herpes simplex infection are pain, an active vesicular border, and a scalloped periphery. Untreated erosive lesions may gradually expand, but they may also remain fixed and even become papular or vegetative, mimicking a wart or granulation tissue. In the oral mucosa numerous erosions may be seen, involving all surfaces (as

opposed to only the hard, keratinized surfaces usually involved by recurrent oral herpes simplex in the immunocompetent host). The tongue may be affected with geometric fissures on the central dorsal surface (Fig. 22). Symptomatic stomatitis associated with cancer chemotherapy is at times caused or exacerbated by HSV infection. Herpetic whitlow presents as a painful paronychia that is initially vesicular and involves the lateral or proximal nailfolds. Untreated, it may lead to loss of the nail plate and ulceration of a large portion of the digit.

Despite the frequent and severe skin infections caused by HSV in the immunosuppressed, visceral dissemination is unusual. Extension of oral HSV into the esophagus or trachea may develop spontaneously or as a complication of intubation through an infected oropharynx. Ocular involvement can occur from direct inoculation, and if lesions are present around the eye, careful ophthalmologic evaluation is required.

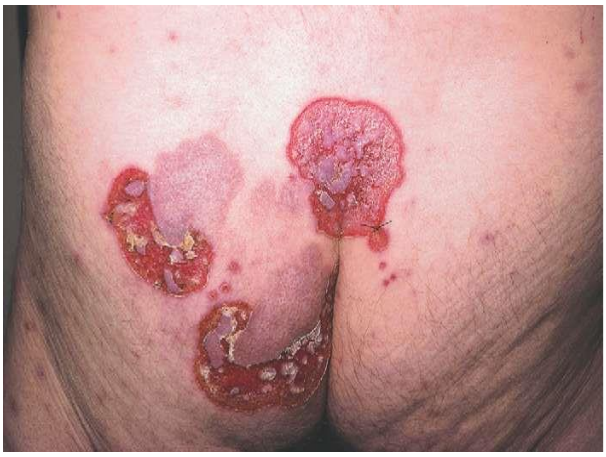


Fig. 21 Herpes simplex, HSV-2, infected areas spontaneously heal while new erosions appear.

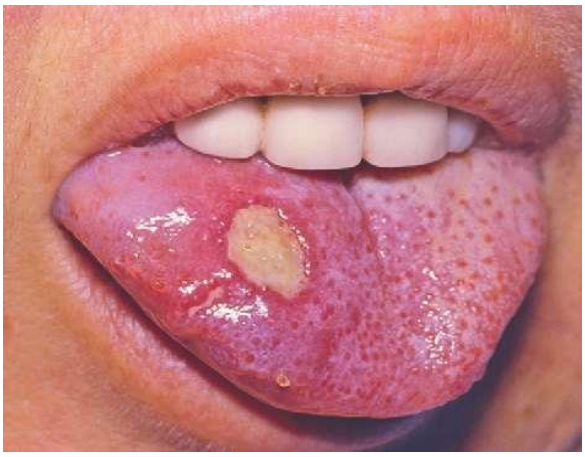


Fig. 22 Immunocompromised patient with tongue ulcer an fissures secondary to HSV.

In an immunosuppressed host, since most lesions are ulcera- tive and not vesicular, Tzanck smears are of less value. Viral cultures taken from the ulcer margin are positive. DFA testing is specific and rapid, and is very useful in immunosuppressed hosts in whom therapeutic decisions need to be made expeditiously. At times, these tests are negative, but a skin biopsy will show typical herpetic changes in the epithelium adjacent to the ulceration. If an ulceration does

not respond to treatment in 48 h and cultures are negative, a biopsy is recommended, as it may be the only technique that demonstrates the associated herpesvirus infection.

Therapy often can be instituted on clinical grounds pending confirmatory tests. Acyclovir, 400 mg orally three times a day; famciclovir, 500 mg twice a day; or valacyclovir, 1 g twice a day, all for a minimum of 5-10 days, is used. Therapy should continue until lesions are essentially healed. In severe infection, or in the hospitalized patient with moderate disease, intravenous acyclovir (5 mg/kg) can be given initially to control the disease. In patients with acquired immune deficiency syndrome (AIDS) and those with persistent immuno- suppression, consideration should be given to chronic suppressive therapy with acyclovir, 400-800 mg twice or three times a day, or valacyclovir or famciclovir, both at a dose of 500 mg twice a day.

In the immunosuppressed host (but not in the immunocom- petent host), long-duration treatment with acyclovir and its analogs, or treatment of large herpetic ulcerations, may be complicated by the development of acyclovir resistance. This resistance may be due to selection of acyclovir-resistant wild- type virus, which is present in large numbers on the surface of such large herpes lesions. In the immunocompetent host, these acyclovir-resistant mutants are few in number and eradicated by the host's immune system. The immunosuppressed host has much more HSV in their lesions, and in addition their own immune system is ineffective in killing the virus. These acyclovir-resistant viral strains may be difficult to culture and at times may only be identified by skin biopsy or PCR of the ulceration. Antiviral resistance is suspected if maximum oral doses of acyclovir, valacyclovir, or famciclovir do not lead to improvement. Intravenous acyclovir, except if given by constant infusion, will also invariably fail in such cases. Resistance to one drug is associated with resistance to all three of these drugs and is usually due to loss of the viral thymidine kinase. HSV isolates can be tested for sensitivity to acyclovir and some other antivirals. The standard treatment of acyclovir-resistant herpes simplex is intravenous foscarnet. In cases intolerant

of or resistant to foscarnet, intravenous cidofovir may be used. Smaller lesions can sometimes be treated with topical trifluoro- thymidine (Viroptic) with or without topical or intralesional interferon (IFN)-a. Imiquimod may be of benefit in healing these lesions. Destruction of small lesions by desiccation followed by the above therapies may also be curative. If lesions recur, they may be acyclovir-sensitive or resistant, depending on the status of the virus in the dorsal root ganglion.

Histopathology

The vesicles of herpes simplex are intraepidermal. The affected epidermis and adjacent inflamed dermis are infiltrated with leukocytes and a serous exudate containing dissociated cells collects to form the vesicle. There is ballooning degeneration of the epidermal cells to produce acantholysis. The most char- acteristic feature is the presence of multinucleated giant cells which tend to mold together, forming a crude jigsaw puzzle appearance. The steel-gray color of the nucleus and peripheral condensation of the nucleoplasm may be clues to HSV infection, even if multinucleate cells are not seen. Immunoperoxidase stains can detect herpes simplex infection even in paraffin- fixed tissue, allowing the diagnosis to be absolutely confirmed from histologic material.

Differential diagnosis

Herpes labialis must most frequently be differentiated from impetigo. Herpetic lesions are composed of groups of tense, small vesicles, whereas in bullous impetigo the blisters are unilocular, occur at the periphery of a crust, and are flaccid. A mixed infection is not unusual and should especially be suspected in immunosuppressed hosts and when lesions are present in the typical herpetic regions around the mouth. Herpes zoster presents with clusters of lesions along a der- matome, but early on, if the number of zoster lesions is limited, it can be relatively indistinguishable from herpes simplex. In general, herpes zoster will be more painful and over 24 h will progress to involve more of the affected dermatome. DFA testing can rapidly make this distinction.

A genital herpes lesion, especially on the glans or corona, is easily mistaken for a syphilitic chancre or chancroid. Darkfield examination, multiplex PCR, and cultures for *Haemophilus ducreyi* on selective media will aid in making the diagnosis, as will diagnostic tests for HSV (Tzanck, culture, or DFA). Combined infections occur in up to 20% of cases, so finding a single pathogen may not complete the diagnostic evaluation.

Herpetic gingivostomatitis is often difficult to differentiate from aphthosis, streptococcal infections, diphtheria, coxsackie - virus infections, and oral erythema multiforme. Aphthae have a tendency to occur mostly on the buccal and labial mucosae. They usually form shallow, grayish erosions, generally surrounded by a prominent ring of hyperemia. Aphthae commonly occur on nonattached mucosa while recurrent herpes of the oral cavity primarily affects the attached gingiva and palate.

Varicella

Varicella, commonly known as chickenpox, is the primary infection with the VZV. In temperate regions, 90% of cases occur in children younger than 10 years of age, with the highest age-specific incidence in children aged 1-4 years in unvacci- nated children. More than 90% of adults in temperate countries have evidence of prior infection and are "immune" to varicella. In tropical countries, however, varicella tends to be a disease of teenagers, and only 60% of adults are "immune" serologically. The incubation period is 10-21 days (usually 14-15 days). Transmission is via the respiratory route and less commonly by direct contact with the lesions. A susceptible person may develop varicella following exposure to the lesions of herpes zoster. Infected persons are most infectious from 5 days before the appearance of the eruption, and most infectious 1-2 days prior to the appearance of the rash. Infectivity ceases 5-6 days after the eruption appears in most cases. There is an initial viral replication in the nasopharynx and conjunctiva, followed by infection of the reticuloendothelial system (liver spleen) between days 4 and 6. A secondary viremia occurs at days 11-20, resulting in infection of the epidermis and the appearance of the characteristic skin lesions. Low- grade fever,

malaise, and headache are usually present but slight. The severity of the disease is age-dependent, with adults having more severe disease and a greater risk of visceral disease. In healthy children the death rate from varicella is 1.4 in 100 000 cases; in adults, 30.9 in 100 000 cases. Pregnant women have five times greater risk of an adverse outcome. As with most viral infections, immunosuppression may worsen the course of the disease. Lifelong immunity follows varicella and second episodes of "varicella" indicate either immunosuppression or another viral infection such as coxsackievirus.

Varicella is characterized by a vesicular eruption consisting of delicate "teardrop" vesicles on an erythematous base (Fig. 23). The eruption starts with faint macules that develop rapidly into vesicles within 24 h. Successive fresh crops of vesicles appear for a few days, mainly on the trunk, face, and oral mucosa. Initially, the exanthem may be limited to sun- exposed areas, the diaper area of infants, or sites of inflammation. The vesicles quickly become pustular and umbilicated, then crusted. Since the lesions appear in crops, lesions of various stages are present at the same time, a useful clue to the diagnosis. Lesions tend not to scar, but larger ones and those that become secondarily infected may heal with a characteristic round, depressed scar.

Secondary bacterial infection with *S. aureus* or a streptococ- cal organism is the most common complication of varicella (Fig. 24). Rarely, it may be complicated by osteomyelitis, other deep-seated infections, or septicemia. Other complications are rare.

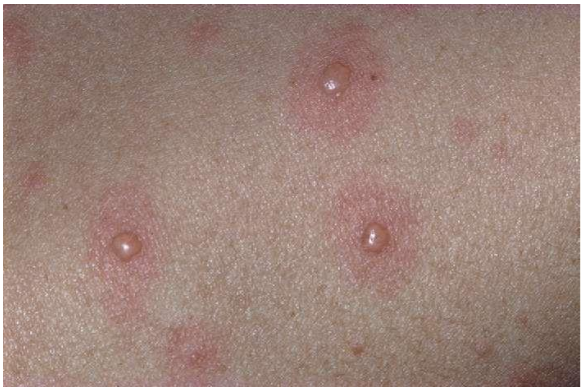


Fig. 23 Varicella.

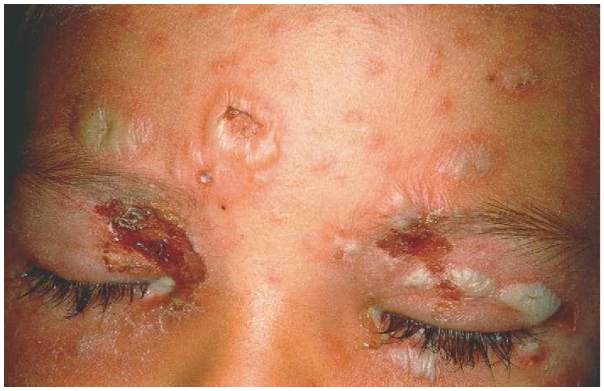


Fig. 24 Varicella with bullous impetigo as a complication.

Pneumonia is uncommon in normal children but is seen in 1 in 400 adults with varicella. It may be bacterial or caused by the varicella, a difficult differential diagnosis.Cerebellar ataxia and encephalitis are the most common neurologic complications. Asymptomatic myocarditis and hepati tis are not uncommon in children with varicella, but these conditions are rarely significant and resolve spontaneously with no treatment. Reye syndrome, a syndrome of hepatitis and acute encephalopathy, is associated with the use of aspirin to treat the symptoms of varicella. Aspirin is absolutely con- traindicated in patients with varicella. Any child with varicella and severe vomiting should be referred immediately to exclude Reye syndrome. Symptomatic thrombocytopenia is a rare manifestation of varicella, which can occur either with the exanthem or several weeks after. Purpura fulminans, a form of disseminated intravascular coagulation associated with low levels of protein C and S, may complicate varicella.

The diagnosis of varicella is easily made clinically. A Tzanck smear from a vesicle will usually show characteristic multi- nucleate giant cells. If needed, the most useful clinical test is a DFA test, which is rapid and will both confirm the infection and type the virus. Since the VZV grows poorly and slowly in the laboratory, viral culture is rarely indicated.

Treatment

Both immunocompetent children and adults with varicella benefit from acyclovir therapy if started early (within 24 h of the appearance of the eruption). Therapy does not appear to alter the development of adequate immunity to reinfection. Because the complications of varicella are infrequent in children, routine treatment is not recommended; therapeutic decisions are made on a case-by-case basis. Acyclovir therapy seems to benefit most secondary cases within a household, which tend to be more severe than the index case. In this setting, therapy can be instituted earlier. Therapy does not, however, return children to school sooner and the impact on parental work days missed is not known. The dose is 20 mg/kg (maximum 800 mg per dose) four times a day for 5 days. Aspirin and other salicylates should not be used as antipyretics in varicella because their

use increases the risk of Reye syndrome. Topical antipruritic lotions, oatmeal baths, dressing the patient in light, cool clothing, and keeping the environment cool may all relieve some of the symptomatology. Children living in warm homes and kept very warm with clothing have anecdotally been observed to have more numerous skin lesions. Children with atopic dermatitis, Darier's disease, congenital ichthyosiform erythroderma, diabetes, cystic fibrosis, conditions requiring chronic salicylate or steroid therapy, and inborn errors of metabolism should be treated with acyclovir since they may suffer more complications or exacerbations of their underlying illness with varicella.

Varicella is more severe and complications are more common in adults. Between 5% and 14% of adults will have pulmonary involvement. Smokers and those with preexisting lung disease (but not asthma) are at increased risk. The pneumonitis can progress rapidly and be fatal. Adults with varicella and at least one other risk factor should be evaluated with physical examination, pulse oximetry, and chest radiography. Antiviral treatment is recommended in all adolescents and adults (13 and older) with varicella. The dose is 800 mg four or five times a day for 5 days. Severe, fulminant cutaneous disease and visceral complications are treated with intravenous acyclovir, 10 mg/kg every 8 h, adjusted for creatinine clearance. If the patient is hospitalized for therapy, strict isolation is required. Patients with varicella should not be admitted to wards with immunocompromised hosts or on to pediatric wards, but rather are best placed on wards with healthy patients recovering from acute trauma.

Pregnant women and neonates

Maternal infection with the VZV during the first 20 weeks of gestation may result in a syndrome of congenital malformations (congenital varicella syndrome), as well as severe illness in the mother. In one study, 4 of 31 women with varicella in pregnancy developed varicella pneumonia. The risk for spontaneous abortion by 20 weeks is 3%; in an additional 0.7% of pregnancies, fetal death occurs after 20 weeks. The risk of preterm labor, as reported in various studies, has varied from no increase to a three-fold increase. Severe varicella and varicella pneumonia or

disseminated disease in pregnancy should be treated with intravenous acyclovir. All varicella in pregnancy should be treated with oral acyclovir, 800 mg five times a day for 7 days (except perhaps during the first month, when a specialist should be consulted). In all women past 35 weeks of gestation or with increased risk of premature labor, admission and intravenous acyclovir, 10 mg/kg three times daily, should be recommended. The patient should be evaluated for pneumonia, renal function should be carefully monitored, and the patient should be switched to oral therapy once lesions stop appearing (usually in 48-72 hours).

Varicella zoster immune globulin (VZIG) should not be given once the pregnant woman has developed varicella. VZIG should be given for significant exposures (see below) within the first 72-96 h to ameliorate maternal varicella and prevent complications. Its use should be limited to seronega- tive women because of its cost and the high rate of asymptomatic infection in the US. The lack of a history of prior varicella is associated with seronegativity in only 20% or fewer of the US population.

Congenital varicella syndrome is characterized by a series of anomalies, including hypoplastic limbs (usually unilateral and lower extremity), cutaneous scars, and ocular and CNS disease. Female fetuses are affected more commonly than males. The overall risk for this syndrome is between 1% and 2% (the former figure from the largest series). The highest risk is from maternal varicella between weeks 13 and 20 when the risk is 2%. Infection of the fetus in utero may result in zoster occurring postnatally, often in the first 2 years of life. This occurs in about 1% of varicella-complicated pregnancies and the risk for this complication is greatest in varicella occurring in weeks 25-36 of gestation. The value of VZIG in preventing or modifying fetal complications of maternal varicella is unknown. In one study, however, of 97 patients with varicella in pregnancy who were treated with VZIG, none had complications of congenital varicella syndrome or infantile zoster, suggesting some efficacy for VZIG. Although apparently safe in pregnancy, acyclovir's efficacy in preventing fetal complications of maternal varicella is unknown.

If the mother develops varicella between 5 days before and 2 days after delivery, neonatal varicella can occur and be severe, as transplacental delivery of antivaricella antibody has been inadequate. These neonates develop varicella at 5-10 days of age. In such cases the administration of VZIG is warranted and acyclovir therapy intravenously should be considered.

Varicella vaccine

Live attenuated viral vaccine for varicella is a currently recommended childhood immunization. Two doses are now recommended, one between age 12 and 15 months and the second at 4-6 years. This double vaccination schedule is recommended since epidemics of varicella still occurred in children ages 9-11 in well-immunized communities, suggesting a waning of immunity by this age. Complications of varicella vaccination are uncommon. A mild skin eruption from which virus can usually not be isolated, occurring locally at the injection site within 2 days or generalized 1-3 weeks after immunization, occurs in 6% of children. Many of the breakthrough cases in vaccinated children are mild and many of the skin lesions were not vesicular (see modified varicella-like syndrome below). Prevention of severe varicella is virtually 100%, even when the vaccine is given within 36 h of exposure. Immunized children with no detectable antibody also have reduced severity of varicella after exposure. Secondary complications of varicella, including scarring, are virtually eliminated by vaccination.

Household exposure of immunosuppressed children to recently immunized siblings does not appear to pose a great risk. Children whose leukemia is in remission are also protected by the vaccine but may require three doses. Leukemic children still receiving chemotherapy have a complication rate from vaccination (usually a varicella-like eruption) approaching 50%. They may require acyclovir therapy. Unprotected close contacts developed varicella 15% of the time. In leukemic children, adequate immunization results in complete immunity in some and partial immunity in the rest, protecting them from severe varicella. Immunization also reduces the attack rate for zoster in leukemic children.

Modified varicella-like syndrome

Children immunized with live attenuated varicella vaccine may develop varicella of reduced severity on exposure to natural varicella. This has been called modified varicella-like syndrome (MVLS). The frequency of MVLS is between 0% and 2.7% per year and children with lower antibody titers are more likely to develop MVLS. The illness occurs an average of 15 days after exposure to varicella and consists primarily of macules and papules with relatively few vesicles. The average number of lesions is about 35-50, compared with natural varicella, which usually has about 300 lesions. The majority of patients are afebrile and the illness is mild, lasting fewer than 5 days on average.

Immunocompromised patients

Varicella cases can be extremely severe and even fatal in immunosuppressed patients, especially in individuals with impaired cell-mediated immunity. Before effective antiviral therapy nearly one-third of children with cancer developed complications of varicella and 7% died. In this setting, varicella pneumonia, hepatitis, and encephalitis are frequent. Prior varicella does not always protect the immunosuppressed host from multiple episodes. The skin lesions in the immunosup- pressed host are usually identical to varicella in the healthy host; however, the number of lesions may be numerous (Fig. 25). In an immunosuppressed patient, the lesions more frequently become necrotic and ulceration may occur. Even if the lesions are few, the size of the lesion may be large (up to several centimeters) and necrosis of the full thickness of the dermis may occur. In HIV infection, varicella may be severe and fatal. Atypical cases of a few scattered lesions without a dermatomal distribution usually represent reactivation disease with dissemination. Chronic varicella may complicate HIV infection, resulting in ulcerative (ecthymatous) or hyperkera- totic (verrucous) lesions. These patterns of infection may be associated with acyclovir resistance.

The degree of immunosuppression likely to result in severe varicella has been a matter of debate. There are case reports of severe and even fatal varicella in otherwise healthy children given short courses of oral steroids or even using only

inhaled steroids. In a case-control study, however, corticosteroid use did not appear to be a risk factor for the development of severe varicella. In the UK, any patient receiving or having received systemic steroids in the prior 3 months, regardless of dose, is considered at increased risk for severe varicella. Inhaled steroids are not considered an indication for prophylactic VZIG or antiviral treatment. A "high-risk" or significant exposure has been defined as:

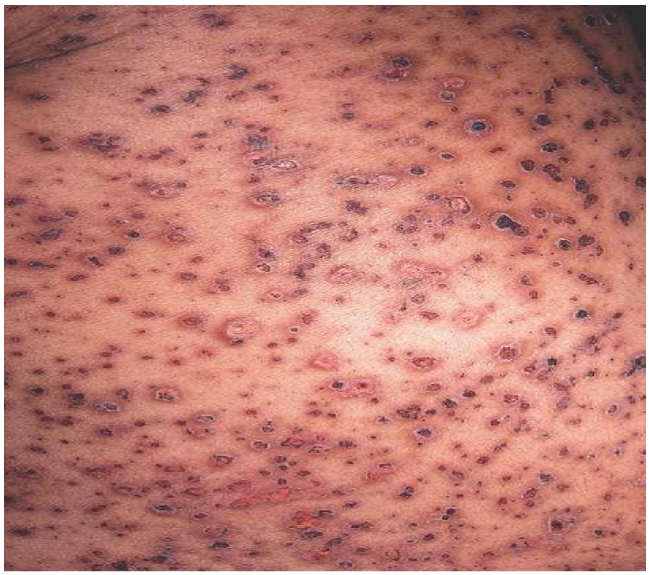


Fig. 25 Varicella in a patient with advanced Hodgkin disease.

- household contact, i.e. living in the same house as a case of chickenpox or zoster
- face-to-face contact with a case of chickenpox for at least 5 min
- contact indoors with a case of chickenpox or herpes zoster for more than 1 h or, within a hospital setting, a case of chickenpox or herpes zoster in an adjacent bed or the same open ward.

Immunosuppressed children with no prior history of varicella and a high-risk exposure should be treated with VZIG as soon as possible after exposure (within 96 h). Pre-engraftment bone marrow transplant patients should be treated the same. VZIG treatment does not reduce the frequency of infection, but it does reduce the severity of infection and complications. The value of prophylactic antivirals is unknown. Parents of immunosuppressed children and their doctors

should be aware that severe disease can occur and the parents counseled to return immediately after significant exposure or if varicella develops.

An unusual variant of recurrent varicella is seen in elderly patients with a history of varicella in childhood, who have a malignancy of the bone marrow and are on chemotherapy. They develop a mild illness with 10-40 widespread lesions and usually no systemic findings. This type of recurrent varicella tends to relapse. It is different from typical varicella, as all the lesions are in a single stage of development and for this reason could be easily confused with smallpox.

Ideally, management of varicella in the immunocompro- mised patient would involve prevention through the use of varicella vaccination before immunosuppression. Vaccination is safe if the person is more than 1 year from induction chemotherapy, chemotherapy is halted around the time of vaccination, and the lymphocyte count is higher than 700/mm^3. Intravenous acyclovir at a dose of 10 mg/kg three times a day (or 500 mg/m^2 in children) is given as soon as the diagnosis of varicella is suspected. Intravenous therapy is continued until 2 days after all new vesicles have stopped. Oral antivirals are continued for a minimum of 10 days of treatment. VZIG is of no proven benefit once clinical disease has developed, but may be given if the patient has severe life-threatening disease and is not responding to intravenous acyclovir.

In HIV-infected adults, treatment is individualized. Persons with typical varicella should be evaluated for the presence of pneumonia or hepatitis. Valacyclovir, 1 g three times a day; famciclovir, 500 mg three times a day; or acyclovir, 800 mg every 4 h, may be used if no visceral complications are present. The former two agents may be preferable to acyclovir because of their enhanced oral bioavailability. Visceral disease mandates intravenous therapy. If the response to oral antiviral agents is not rapid, intravenous acyclovir therapy should be instituted. Antiviral treatment must be continued until all lesions are completely healed. Most cases of chronic or acyclovir-resistant VZV infection are associated with initial inadequate oral doses of acyclovir (either too short in duration, too low a dose, or in patients with gastrointestinal disease, in whom reduced

gastrointestinal absorption may be associated with inadequate blood levels of acyclovir). Atypical disseminated cases must be treated aggressively until all lesions resolve. The diagnosis of acyclovir-resistant VZV infection may be difficult. Acyclovir-resistant VZV strains may be hard to culture and sensitivity testing is still not standardized or readily available for VZV. Acyclovir-resistant varicella is treated with foscarnet, and in cases failing that agent, cidofovir.

Zoster (shingles, herpes zoster)

Zoster is caused by reactivation of VZV. Following primary infection or vaccination, VZV remains latent in the sensory dorsal root ganglion cells. The virus begins to replicate at some later time, traveling down the sensory nerve into the skin. Other than immunosuppression and age-related deficiency of cell-mediated immunity, the factors involved in reactivation are unknown.

The incidence of zoster increases with age. Below the age of 45, the annual incidence is less than 1 in 1000 persons. Among patients older than 75 years of age, the rate is more than four times greater. For white persons older than 80 years of age, the lifetime risk of developing zoster is 10-30%. Overall, about 1 in 3 unvaccinated persons will develop herpes zoster. For unknown reasons, being nonwhite reduces the risk for herpes zoster, with African Americans being four times less likely to develop zoster. Immunosuppression, especially hematologic malignancy and HIV infection, dramatically increases the risk for zoster. In HIV-infected persons the annual incidence is 30 in 1000 persons, or an annual risk of 3%. With the universal use of varicella vaccination and decrease in pediatric and adolescent varicella cases, older persons will no longer have periodic boosts of the anti-VZV immune activity. This could result in an increase in the incidence of zoster.

Herpes zoster classically occurs unilaterally within the distribution of a cranial or spinal sensory nerve, often with some overflow into the dermatomes above and below. The dermatomes most frequently affected are the thoracic (55%), cranial (20%, with the trigeminal nerve being the most common single nerve involved), lumbar (15%), and sacral (5%). The cutaneous eruption is frequently

preceded by one to several days of pain in the affected area, although the pain may appear simultaneously or even following the skin eruption, or the eruption may be painless. The eruption initially presents as papules and plaques of erythema in the dermatome. Within hours the plaques develop blisters (Fig. 26). Lesions continue to appear for several days. The eruption may have few lesions or reach total confluence in the dermatome. Lesions may become hemorrhagic, necrotic, or bullous. Rarely, the patient may have pain, but no skin lesions (zoster sine herpete).

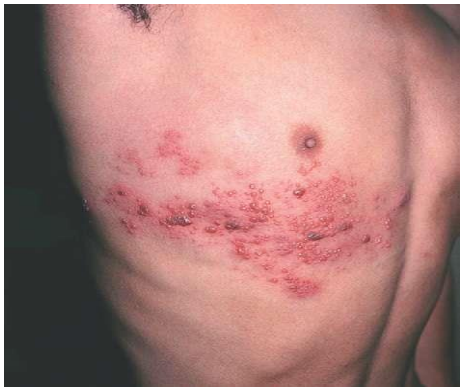


Fig. 26 Herpes zoster, classic dermatomal distribution.

There is a correlation with the pain severity and extent of the skin lesions, and elderly persons tend to have more severe pain. In patients under 30 years of age, the pain may be minimal. It is not uncommon for there to be scattered lesions outside the dermatome, usually fewer than 20. In the typical case, new vesicles appear for 1-5 days, become pustular, crust, and heal. The total duration of the eruption depends on three factors: patient age, severity of eruption, and presence of underlying immunosuppression. In younger patients, the total duration is 23 weeks, whereas in elderly patients, the cutaneous lesions of zoster may require 6 weeks or more to heal. Scarring is more common in elderly and immunosuppressed patients. Scarring also correlates with the severity of the initial eruption. Lesions may develop on the mucous membranes within the mouth in zoster of the maxillary (Fig. 27) or mandibular division of the facial nerve, or in the vagina in zoster in the S2 or S3 dermatome. Zoster may appear in recent surgical scars.

Zoster may rarely be seen in children under the age of 1 year. This can occur due to intrauterine exposure to VZV or due to exposure to VZV during the first few months of life. The maternal antibodies still present result in muted expression of varicella—subclinical or very mild disease. The immaturity of the infant's immune system results in poor immune response to the infection, allowing for early relapse in the form of zoster.

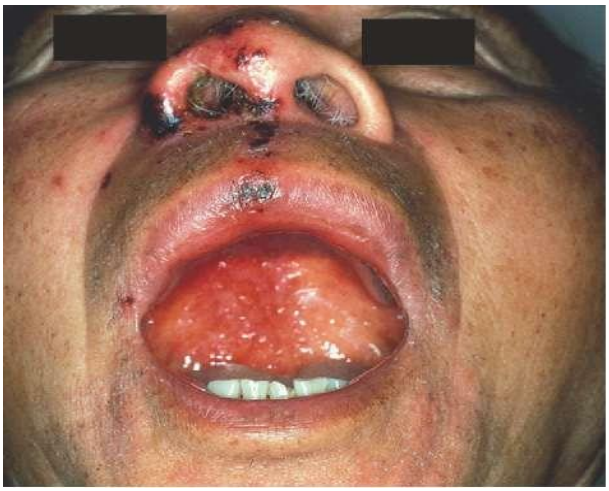


Fig. 27 Oral zoster.

Disseminated herpes zoster

Disseminated herpes zoster is defined as more than 20 lesions outside the affected dermatome. It occurs chiefly in old or debilitated individuals, especially in patients with lympho- reticular malignancy or AIDS. Low levels of serum antibody against VZV are a highly significant risk factor in predicting dissemination of disease. The dermatomal lesions are sometimes hemorrhagic or gangrenous. The outlying vesicles or bullae, which are usually not grouped, resemble varicella and are often umbilicated and may be hemorrhagic. Visceral dissemination to the lungs and CNS may occur in the setting of disseminated zoster. Disseminated zoster requires careful evaluation and systemic antiviral therapy. This would initially be intravenous acyclovir, which may be changed to an oral antiviral agent once visceral involvement has been excluded and the patient has received at least 2-3 days of intravenous therapy.

Ophthalmic zoster

In herpes zoster ophthalmicus, the ophthalmic division of the fifth cranial nerve is involved. If the external division of the nasociliary branch is affected, with vesicles on the side and tip of the nose (Hutchinson's sign), the eye is involved 76% of the time, as compared with 34% when it is not involved (Fig. 28). Vesicles on the lid margin are virtually always associated with ocular involvement. In any case, the patient with ophthalmic zoster should be seen by an ophthalmologist. Systemic antiviral therapy should be started immediately, pending ophthalmologic evaluation. Ocular involvement is most commonly in the form of uveitis (92%) and keratitis (50%). Less common but more severe complications include glaucoma, optic neuritis, encephalitis, hemiplegia, and acute retinal necrosis. These complications are reduced from 50% of patients with herpes zoster ophthalmicus to 20-30% with effective antiviral therapy. Unlike the cutaneous lesions, ocular lesions of zoster and their complications tend to recur, sometimes as long as 10 years after the zoster episode.

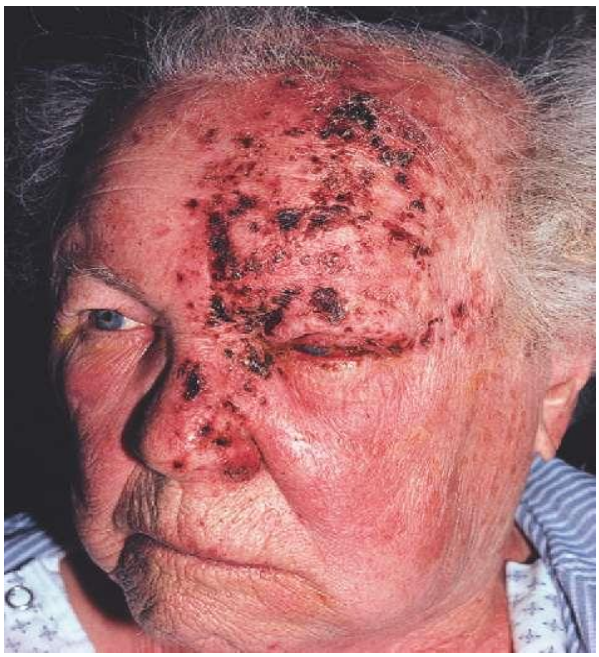


Fig. 28 Herpes zoster, involvement of the V1 dermatome.

Other complications

Motor nerve neuropathy occurs in about 3% of patients with zoster and is three times more common if zoster is associated with underlying malignancy. Seventy-five percent of cases slowly recover, leaving 25% with some residual motor deficit. If the sacral dermatome S3, or less often S2 or S4, is involved, urinary hesitancy or actual urinary retention may occur. Hematuria and pyuria may also be present. The prognosis is good for complete recovery. Similarly pseudo-obstruction, colonic spasm, dilatation, obstipation, constipation, and reduced anal sphincter tone can occur with thoracic (T6-T12), lumbar, or sacral zoster. Recovery is complete. Maxillary and mandibular alveolar bone necrosis may occur an average of 30 days after zoster of the maxillary or mandibular branches of the trigeminal nerve. Limited or widespread loss of teeth may result.

Ramsay Hunt syndrome results from involvement of the facial and auditory nerves by VSV. Herpetic inflammation of the geniculate ganglion is felt to be the cause of this syndrome. The presenting features include zoster of the external ear or tympanic membrane; herpes auricularis with ipsilateral facial paralysis; or herpes auricularis, facial paralysis, and auditory symptoms. Auditory symptoms include mild to severe tinnitus, deafness, vertigo, nausea and vomiting, and nystagmus.

Herpes zoster can be associated with delayed complications. Many of these are due to vasculopathies affecting the CNS or even peripheral arteries. Delayed contralateral hemiparesis, simulating stroke, is a rare but serious complication of herpes zoster that occurs weeks to months (mean 7 weeks) after an episode of zoster affecting the first branch of the trigeminal nerve. By direct extension along the intracranial branches of the trigeminal nerve, VZV gains access to the CNS and infects the cerebral arteries. Patients present with headache and hemi- plegia. Arteriography is diagnostic, demonstrating thrombosis of the anterior or middle cerebral artery. This form of vascu- lopathy can also occur following varicella and may be the cause of up to one-third of ischemic strokes in children. The recognized vasculopathic complications of VZV have been expanded to include

changes in mental status, aphasia, ataxia, hemisensory loss, and both hemianopia and monocular visual loss. Monocular vision loss can occur up to 6 months following zoster. Aneurysm, subarachnoid or cerebral hemorrhage, carotid dissection, and even peripheral vascular disease are other recognized forms of VZV vasculopathy. The vasculopa- thy may be multifocal and involve both large and small arteries. In more than one-third of cases VZV vasculopathy occurs without a rash. MRI is virtually always abnormal. The diagnosis is confirmed by VZV PCR and anti-VZV IgG antibody testing of the CSF. Since this is due to active viral replication in the vessels, the treatment is intravenous acyclovir, 1015 mg/kg three times daily for a minimum of 14 days. In some patients, months of oral antivirals are given if symptoms are slow to resolve. A short burst of systemic steroids is sometimes also given.

Treatment

Middle-aged and elderly patients are urged to restrict their physical activities or even stay home in bed for a few days. Bed rest may be of paramount importance in the prevention of neuralgia. Younger patients may usually continue with their customary activities.

Local applications of heat, as with an electric heating pad or a hot-water bottle, are recommended. Simple local application of gentle pressure with the hand or with an abdominal binder often gives great relief.

Antiviral therapy is the cornerstone in the management of herpes zoster. Since antiviral therapy does not reduce the rate of zoster-associated pain, clinicians may under-appreciate the tremendous benefit these antiviral drugs provide. The main benefit of therapy is in reduction of the duration and severity of zoster-associated pain. Therefore, treatment in immunocompetent patients is indicated for those at highest risk for persistent pain—those over 50 years of age. It is also recommended to treat all patients with painful or severe zoster, ophthalmic zoster, Ramsay Hunt syndrome, immuno- suppression, cutaneous or visceral dissemination, and motor nerve involvement. In the most severe cases, especially in ophthalmic zoster and disseminated zoster, initial intravenous therapy

may be considered. Therapy should be started as soon as the diagnosis is suspected, pending laboratory confirmation. It is preferable for treatment to be instituted within the first 3 or 4 days. In immunocompetent patients, the efficacy of starting treatment beyond this time is unknown. Treatment leads to more rapid resolution of the skin lesions and, most importantly, substantially decreases the duration of zoster- associated pain. Valacyclovir, 1000 mg, and famciclovir, 500 mg, may be given three times a day. These agents are as effective as or superior to acyclovir, 800 mg five times a day, probably because of better absorption and the fact that higher blood levels are achieved. They are as safe as acyclovir. If not contraindicated, they are preferred.

In the immunocompetent host, a total of 7 days of treatment has been shown to be as effective as 21 days of treatment. Valacyclovir and famciclovir must be dose-adjusted in patients with renal impairment. In an elderly patient, if the renal status is unknown, the newer agents may be started at twice-a-day dosing (which is almost as effective), pending evaluation of renal function, or acyclovir can be used. For patients with renal failure (creatinine clearance of less than 25 mL/min), acyclovir is preferable. In the setting of known or acquired renal failure, acyclovir neurotoxicity can occur from intravenous acyclovir or oral valacyclovir therapy. This can present in the acute setting as hallucinations, or with prolonged elevated blood levels, disorientation, dizziness, loss of decorum, incoherence, photophobia, difficulty speaking, delirium, confusion, agitation, and death delusion. Since acyclovir can reduce renal function, the patient's baseline renal function may have been normal, but high doses of acyclovir may have reduced renal function, leading to neurotoxic acyclovir levels.

In the immunosuppressed patient, an antiviral agent should always be given because of the increased risk of dissemination and zoster-associated complications. The doses are identical to those used in immunocompetent hosts. In immunosuppressed patients with ophthalmic zoster, disseminated zoster, or Ramsay Hunt syndrome, and in patients failing oral therapy, intravenous acyclovir should be used at a dose of 10 mg/kg three times a day, adjusted for renal function.

Since some of the pain during acute zoster (acute zoster neuritis) may have an inflammatory component, corticoster- oids have been used during the acute episode. The use of corticosteroids in this setting is controversial. In selected older individuals, corticosteroid use is associated with better quality- of-life measures, reduction in time to uninterrupted sleep, quicker return to usual activities, and reduced analgesic use. A tapering dose of systemic steroids, starting at about 1 mg/ kg and lasting 10-14 days, is adequate to achieve these benefits. Systemic steroids should not be used in immunosup- pressed patients or when there is a contraindication to systemic steroid use. All factors being considered, the benefits of cortico- steroid therapy during acute zoster appear to outweigh the risks in treatment-eligible patients. Reduction in postherpetic neuralgia by corticosteroids has never been documented despite multiple studies, but this is also true of antiviral therapy which reduces the severity and duration but not the prevalence of postherpetic neuralgia.

Zoster-associated pain (postherpetic neuralgia, PHN)

Pain is the most troublesome symptom of zoster. Eighty-four percent of patients over the age of 50 will have pain preceding the eruption and 89% will have pain with the eruption. Various terminologies are used to classify the pain. The simplest approach is to term all pain occurring immediately preceding or after zoster "zoster-associated pain" (ZAP). Another classification system separates acute pain (within the first 30 days), subacute pain (between 30 and 120 days), and chronic pain (lasting more than 120 days).

Two different mechanisms are proposed to cause ZAP: sen- sitization and deafferentation. Nociceptors (sensory nerves mediating pain) become sensitized following injury, resulting in ongoing discharge and hyperexcitability (peripheral sensi- tization). Prolonged discharge of the nociceptor enhances the dorsal horn neurons to afferent stimuli and expands the dorsal horn neuron's receptive field (central sensitization), leading to allodynia and hyperalgesia. In addition, neural destruction causes spontaneous activity in deafferented central neurons, generating constant pain. The spinal terminals of mechano- receptors may contact receptors

formerly occupied by C-fibers, leading to hyperalgesia and allodynia. The loss of function or death of dorsal horn neurons, which have an inhibitory effect on adjacent neurons, contributes to an increase in activity being transmitted up the spinal cord. The central sensitization is initially temporary (self-limited), but may become permanent.

The quality of the pain associated with herpes zoster varies, but three basic types have been described. There is the constant, monotonous, usually burning or deep, aching pain; the shooting, lancinating (neuritic) pain; and triggered pain. The latter is usually allodynia (pain with normal nonpainful stimuli such as light touch) or hyperalgesia (severe pain produced by a stimulus normally producing mild pain). The character and quality of acute zoster pain are identical to the pain that persists after the skin lesions have healed, although they be mediated by different mechanisms.

The rate of resolution of pain following herpes zoster is reported over a wide range. The following data are from a prospective study and do not represent selected patients, as are recruited in drug trials for herpes zoster. The tendency to have persistent pain is age-dependent, occurring for longer than 1 month in only 2% of persons under 40 years of age. Fifty percent of persons over 60 years of age and 75% of those over 70 years of age continue to have pain beyond 1 month. Although the natural history is for gradual improvement in persons over 70 years, 25% have some pain at 3 months and 10% have pain at 1 year. Severe pain lasting longer than 1 year is uncommon, but 8% of persons over 60 have mild pain and 2% still have moderate pain at 1 year.

ZAP, especially that of long duration, is very difficult to manage. Adequate medication should be provided to control the pain from the first visit. Once established, neuropathic pain is very difficult to control. Every effort should be made to prevent neuronal damage. In addition, chronic pain may lead to depression, complicating management of the pain. Patients with persistent moderate to severe pain may benefit from referral to a pain clinic. With this

background, the importance of early and adequate antiviral therapy and pain control cannot be overemphasized.

Oral antiviral agents are recommended in all patients over 50 with pain in whom blisters are still present, even if they are not given within the first 96 h of the eruption. Oral analgesia should be maximized using acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opiate analgesia as required. Capsaicin applied topically every few hours may reduce pain, but the application itself may cause burning and the benefits are modest. Local anesthetics, such as 10% lido- caine in gel form, 5% lidocaine-prilocaine, or lidocaine patches (Lidoderm), may acutely reduce pain. These topical measures may provide some short-term analgesic effect, but do not appear to have any long-term benefit in reducing the severity or prevalence of ZAP. Sublesional anesthesia, epidural blocks, and sympathetic blocks with and without corticosteroids have been reported in large series, but rarely studied in a controlled manner. They provide acute relief of pain. Although the benefit of nerve blocks in preventing or treating persistent ZAP remains to be proven, they are a reasonable consideration in the acute setting if the patient is having very severe pain (unable to eat or sleep) and oral therapy has yet to be effective. They may also be used in patients who have failed the standard therapies listed below. A transcutaneous electrical nerve stimulation (TENS) unit may be beneficial for persistent neuralgia. Botulinum toxin, 100 U, spread out over the affected area in a checkerboard or fan-like pattern with 5 U per route, has dramatically improved PHN in four reported patients with thoracic zoster.

Despite this vast array of medication options, PHN is commonly difficult to treat for two reasons. The recommended medications are simply often not effective. Second, in the elderly who are most severely affected by PHN, these medications have significant and often intolerable side effects, limiting the dose one can prescribe. If multiple agents are combined to reduce the toxicity of any one agent, the side effects of these agents overlap (sedation, depression,

constipation) and there may be drug-drug interactions, limiting combination treatment options.

Three classes of medication are used as standards to manage ZAP and PHN - tricyclic antidepressants, anti-seizure medications, and longacting opiates. If opiate analgesia is required, it should be provided by a long-acting agent, and the duration of treatment should be limited and the patient transitioned to another class of agent. Constipation is a major side effect in the elderly. During painful zoster these patients ingest less fluid and fiber, enhancing the constipating effects of the opiates. Bulk laxatives should be recommended. Tramadol is an option for acute pain control, but drug interactions with the tricyclics must be monitored. The tricyclic antidepressants, such as amitriptyline (or nortriptyline) and desipramine, are well tested and documented as effective for the management of PHN. They are considered first-line agents in this condition. They are dosed at 25 mg/night (or 10 mg for those over the age of 65-70 years). The dose is increased by the same amount nightly until pain control is achieved or the maximum dose is reached. The ultimate dose is somewhere between 25 and 100 mg in a single nightly dose. The early use of amitriptyline was able to reduce the pain prevalence at 6 months, suggesting that early intervention is optimal. Venlafaxine (Effexor) may be used in patients who do not tolerate tricyclics. The starting dose is 25 mg/night and the dose is gradually titrated up as required. Gabapentin (Neurontin) and pregabalin (Lyrica) have been documented as aiding in the reduction of zoster- associated pain. The starting dose of gabapentin is usually 300 mg three times daily, escalating up to 3600 mg per day. Pregabalin has improved pharmacokinetics and is dosed at 300 mg or 600 mg daily, depending on renal function. There is better absorption and steadier blood levels. The anticonvulsants diphenylhydantoin, carbamazepine, and valproate; neuroleptics, such as chlorprothixene, and phenothiazines; and H_2-blockers, such as cimetidine, cannot be recommended, as they have been not been studied critically, many are poorly tolerated by the elderly, and some are associated with significant side effects. If the patient fails to respond to

local measures, oral analgesics, including opiates, tricyclics, gabapentin, and venlafaxine, referral to a pain center is recommended.

Immunosuppressed patients

Patients with malignancy (especially Hodgkin disease and leukemia) are five times more likely to develop zoster than are their age-matched counterparts. Patients who also have a higher incidence of zoster include those with deficient immune systems, such as individuals who are immunosuppressed for organ transplantation or by connective tissue disease, or by the agents used to treat these conditions (especially cortico- steroids, chemotherapeutic agents, cyclosporine, sirolimus and tacrolimus). Following stem cell transplantation for leukemia, up to 68% of patients will develop herpes zoster in the first 12 months (median 5 months). The cumulative incidence of VZV reactivation in this group may exceed 80% in the first 3 years. Although persons who are immunosuppressed have increased rates of zoster, screening for underlying malignancy, beyond a good history and physical examination, is not indicated in those with zoster. However, since zoster is 30 times more common in HIV-infected persons, the zoster patient under 50 years of age should be questioned about HIV risk factors. In pediatric patients with HIV infection and in other immunosuppressed children, zoster may rapidly follow primary varicella.

The clinical appearance of zoster in the immunosuppressed is usually identical to typical zoster, but the lesions may be more ulcerative and necrotic, and may scar more severely. Dermatomal zoster may appear, progress to involve the der- matome, and persist without resolution. Multidermatomal zoster is more common in the immunosuppressed. Visceral dissemination and fatal outcome are extremely rare in immunosuppressed patients (about 0.3%), but cutaneous dissemination is not uncommon, occurring in 12% of cancer patients, especially those with hematologic malignancies. Bone marrow transplant patients with zoster develop disseminated zoster 25% of the time, and visceral dissemination 10-15% of the time. Disseminated zoster may be associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and present with

hyponatremia, abdominal pain, and ileus. This later presentation has been reported in stem cell transplant patients. Despite treatment with intravenous acyclovir, the SIADH can be fatal. In this setting the number of skin lesions may be small and the lesions resemble "papules" rather than vesicles. Mortality in patients with zoster who have undergone bone marrow transplantation is 5%. VZV IgG serostatus is determined before transplant and all seropositive patients receive prophylaxis with either acy- clovir, 800 mg twice daily, or valacyclovir, 500 mg twice daily for 1 year or longer if the patient is on immunosuppressive therapy. In AIDS patients, ocular and neurologic complications of herpes zoster are increased. Immunosuppressed patients often have recurrences of zoster, up to 25% in patients with AIDS (Fig. 29).

Two atypical patterns of zoster have been described in AIDS patients: ecthymatous lesions, which are punched-out ulcera- tions with a central crust, and verrucous lesions (Fig. 30). These patterns were not reported before the AIDS epidemic. Atypical clinical patterns, especially the verrucous pattern, may correlate with acyclovir resistance.

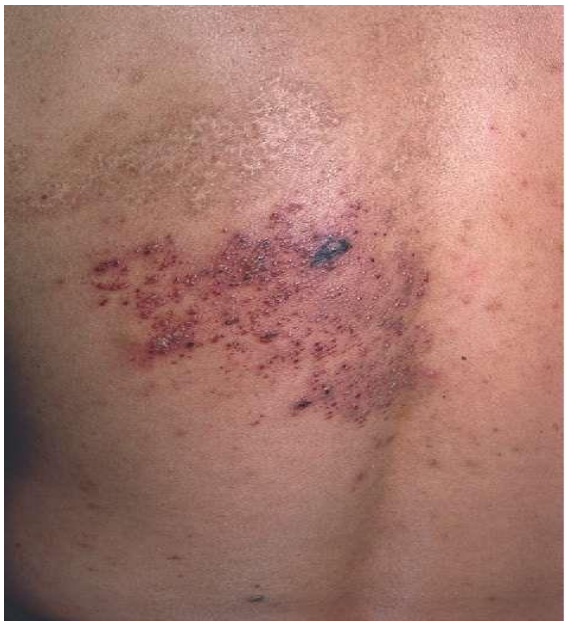


Fig. 29 Recurrent zoster in AIDS.

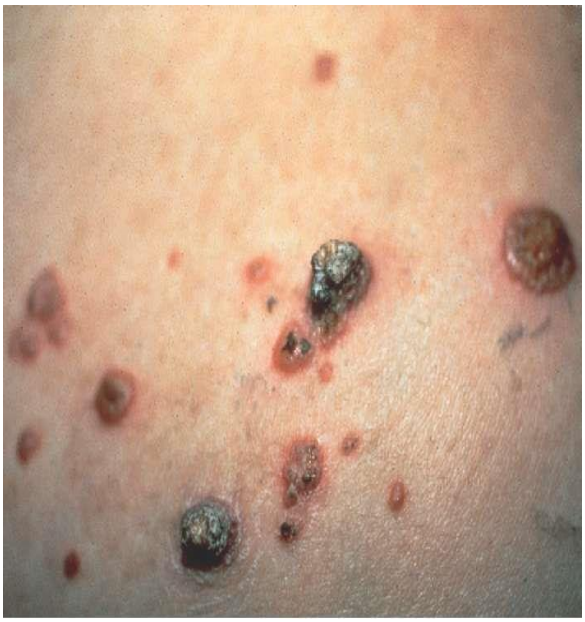


Fig. 30 Verrucous zoster in AIDS.

Diagnosis

The same techniques used for the diagnosis of varicella are used to diagnose herpes zoster. The clinical appearance is often adequate to lead to suspicion of the diagnosis, and an in-office Tzanck smear can rapidly confirm the clinical suspicion. Zosteriform herpes simplex could also produce a positive result to a Tzanck smear, but the number of lesions is usually more limited and the degree of pain substantially less. Beyond Tzanck preparation, DFA testing is preferred to a viral culture, since it is rapid, types the virus, and has a higher yield than a culture will produce. When compared in documented VZV infections, Tzanck smear was 75% positive (with up to 10% false-positives and high variability, depending on the skill of the examiner), and culture only 44% positive. PCR testing is 97% positive. In atypical lesions, biopsy may be necessary to demonstrate the typical herpesvirus cytopathic effects. Immunoperoxidase stain tests can then be performed on paraffin-fixed tissue to identify the VZV specifically. In cases in which acyclovir fails clinically, viral culture may be attempted and acyclovir sensitivity testing performed. It is not as standardized for VZV as it is for HSV and its availability is limited.

Histopathology

As in the case of herpes simplex, the vesicles in zoster are intraepidermal. Within and at the sides of the vesicle are found large, swollen cells called balloon cells, which are degenerated cells of the spinous layer. Acidophilic inclusion bodies similar to those seen in herpes simplex are present in the nuclei of the cells of the vesicle epithelium. Multinucleated keratinocytes, nuclear molding, and peripheral condensation of the nucleo- plasm are characteristic and confirmatory of an infection with either HSV or VZV. In the vicinity of the vesicle there is marked intercellular and intracellular edema. In the upper part of the dermis, vascular dilatation, edema, and a perivas- cular infiltration of lymphocytes and polymorphonuclear leukocytes are present. Atypical lymphocytes may also be found. An underlying leukocytoclastic vasculitis is suggestive of VZV infection

over HSV. Inflammatory and degenerative changes are also noted in the posterior root ganglia and in the dorsal nerve roots of the affected nerve. The lesions correspond to the areas of innervation of the affected nerve ganglion, with necrosis of the nerve cells.

Differential diagnosis

The distinctive clinical picture permits a diagnosis with little difficulty. A unilateral, painful eruption of grouped vesicles along a dermatome, with hyperesthesia and on occasion regional lymph node enlargement, is typical. Occasionally, segmental cutaneous paresthesias or pain may precede the eruption by 4 or 5 days. In such patients, prodromal symptoms are easily confused with the pain of angina pectoris, duodenal ulcer, biliary or renal colic, appendicitis, pleurodynia, or early glaucoma. The diagnosis becomes obvious once the cutaneous eruption appears. Herpes simplex and herpes zoster are confused if the lesions of HSV are linear (zosteriform HSV), or if the number of zoster lesions is small and localized to one site (not involving the whole dermatome). DFA testing or viral culture will distinguish them. DFA is generally preferred because it is rapid and sensitive.

Prevention of zoster

A vaccine using the same attenuated virus as in the varicella vaccination, but at much higher titers, has been licensed for the prevention of herpes zoster (Zostavax). It is recommended in all persons aged 60 years or older. This vaccination reduces the incidence of zoster by 50%. In addition, PHN was 67% lower in the vaccine recipients and the duration of ZAP was shortened. Burden of illness was also reduced. Those vaccinated between the ages of 60 and 69 had a greater reduction in zoster incidence than those over 70, but in both groups PHN and burden of illness were reduced similarly. Since it is a live virus vaccine, persons on antiviral medications must stop them 24 hours before immunization and not take them for 14 days following immunization. Immunosuppressed patients can be safely immunized following specific guidelines.

Inflammatory skin lesions following a zoster infection (isotopic response)

Following zoster, inflammatory skin lesions may rarely occur within the affected dermatome. Lesions usually appear within a month, or rarely, longer than 3 months, after the zoster. Clinically, the lesions are usually flat-topped or annular papules in the dermatome. Histologically, such papules most frequently demonstrate various patterns of granulomatous inflammation from typical granuloma annulare to sarcoidal reactions, or even granulomatous vasculitis (Fig. 31). Persistent viral genome has not been detected in these lesions, suggesting that continued antiviral therapy is not indicated. Persistent VZV glycoproteins may be the triggering antigens. Topical and intralesional therapy with corticosteroid medications is beneficial, but the natural history of these lesions is generally spontaneous resolution. Less commonly, other inflammatory skin diseases have been reported in areas of prior zoster, including lichen planus, lichen sclerosus, Kaposi sarcoma, graft versus host disease, morphea, and benign or even atypical lymphoid infiltrates. Leukemic infiltrates and lymphomas may affect zoster scars, as can metastatic carcinomas (inflammatory oncotaxis) or nonmelanoma skin cancers.

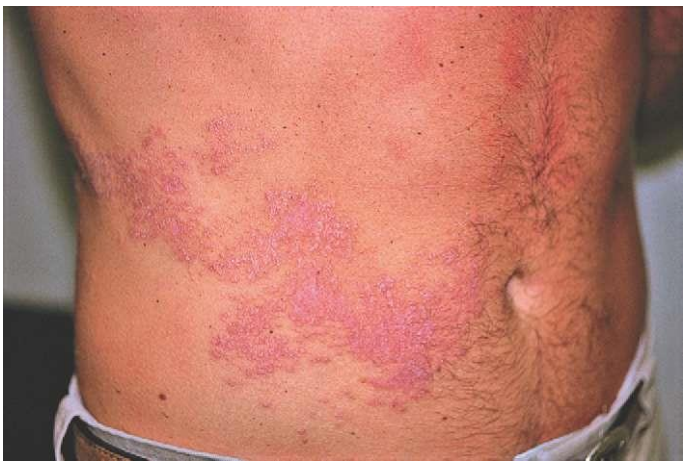


Fig. 31 Granulomatous vasculitis

Epstein-Barr virus

Epstein-Barr virus (EBV) is a y-herpesvirus. It infects human mucosal epithelial cells and B lymphocytes, and infection persists for the life of the host. EBV infection may be latent-not producing virions, but simply spread from mother cell to both daughter cells by copying the viral DNA with each host cell

replication. Intermittently, infection may be productive, resulting in production and release of infectious virions. EBV infection may transit between latent and productive infection many times. The ability of EBV to maintain persistent infection is aided by the expression of the EBV nuclear antigen (EBNA)-1 viral gene product, which prevents cytotoxic T-lymphocyte response to the virus.

Initial infection with EBV occurs in childhood or early adulthood, so that by the early twenties, 95% of the population has been infected. The virus is shed into the saliva, so contact with oral secretions is the most common route of transmission. Primary infection may be asymptomatic or produce only a mild, nonspecific febrile illness, especially in younger children. In young adults, primary infection is more likely to be symptomatic and in 50% of cases produces a syndrome termed infectious mononucleosis. The incubation period is 3-7 weeks. Infectious mononucleosis is characterized by a constellation of findings: fever (up to 40°C), headache, lymphadenopathy, splenomegaly, and pharyngitis (sore throat).

Cutaneous and mucous membrane lesions are present in about 10% of patients with infectious mononucleosis; up to 70% of patients require hospitalization. Exanthems occur in 3-15% of children with infectious mononucleosis. Edema of the eyelids and a macular or morbilliform eruption are most common. The latter is usually on the trunk and upper extremities. Other less common eruptions are urticarial, vesicular, bullous, petechial, and purpuric types. The mucous membrane lesions consist of distinctive pinhead-sized petechiae, 5-20 in number, at the junction of the soft and hard palate (Forchheimer spots). Gianotti-Crosti syndrome (GCS) and the papular- purpuric glove and stocking syndrome are two specific viral exanthem patterns which may occur in the setting of asymptomatic primary EBV infection. EBV is now the leading cause of GCS worldwide. EBV reactivation has been uncommonly associated with drug-induced hypersensitivity syndrome (DRESS). EBV is also associated with enhanced insect bite reactions.

Painful genital ulcerations may precede the symptomatic phase of infectious mononucleosis, especially in premenarcheal girls. The ulcerations are up to 2 cm in diameter, single or multiple, and may be accompanied by marked swelling of the labia. Lesions last several weeks and heal spontaneously, often as the patient is developing symptoms of infectious mononu- cleosis. Transmission to patients via orogenital sex has been proposed, but the virus may also reach the vulvar mucosa hematogenously. EBV has been recovered by culture from these genital ulcerations. The lesions closely resemble herpetic ulcerations and fixed drug eruption, which must be considered in the differential diagnosis.

Laboratory evaluation in patients with infectious mono- nucleosis frequently shows an absolute lymphocytosis of greater than 50% and monocytosis with abnormally large lymphocytes. Atypical lymphocytes (Downey cells) usually represent at least 10% of the total leukocyte count. The white blood cell count ranges from 10 000 to 40 000/mm^3. Liver function tests may be elevated. Heterophile antibodies will be present in 95% or more of cases. In acute primary EBV infection the IgM antibodies to early antigen (EA) and viral capsid antigen (VCA) are found in high titer and fall during recovery. Antibodies to VCA and EBNA appear in the recovering phase and persist for years after primary infection. There is no specific therapy and in most cases no treatment is required. Acyclovir is not effective in altering the length or severity of infectious mononucleosis, although it is active against EBV in doses used for VZV. If patients have severe pharyngeal involvement with encroachment on the airway, 4 days of oral corticosteroid therapy (40-60 mg/day prednisone) is useful to induce a prompt reduction in pharyngeal swelling. Most patients recover completely.

Patients with mononucleosis treated with ampicillin, amoxi- cillin, or other semisynthetic penicillins commonly develop a generalized, pruritic, erythematous to copper-colored macular exanthem on the 7th-10th day of therapy. The eruption starts on the pressure points and extensor surfaces, generalizes, and becomes confluent. The eruption lasts about 1 week and resolves with desquamation. The

eruption often does not recur when these medications are given after the acute mononucle- osis has resolved.

Oral hairy leukoplakia (OHL) is a distinctive condition strongly associated with HIV. It appears as poorly demarcated, corrugated white plaques seen on the lateral aspects of the tongue (Fig. 32). Lesions on the other areas of the oral mucosa are simply white plaques without the typical corrugations. OHL can be distinguished from thrush by the fact that OHL cannot be removed by firm scraping with a tongue blade.

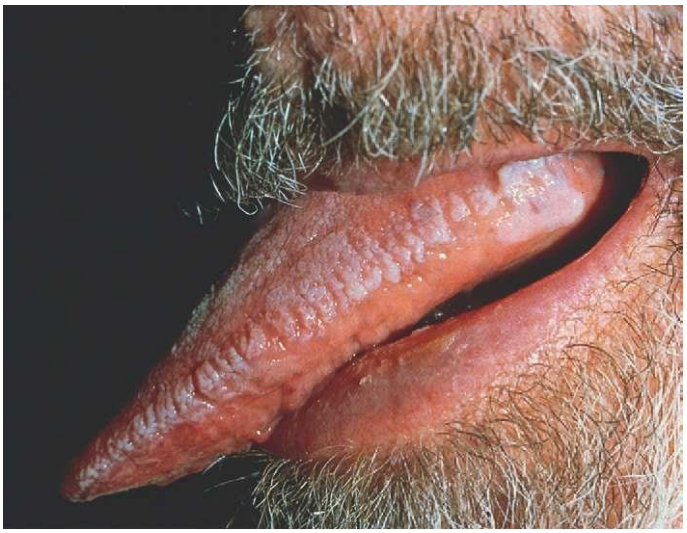


Fig. 32 Oral hairy leukoplakia.

More than one-third of patients with AIDS have OHL, but is not restricted to patients with HIV infection; it also occurs in other immunosuppressed hosts, especially renal and bone marrow transplant recipients, and those using inhaled steroids for chronic obstructive pulmonary disease. OHL can be a part of the immune reconstitution inflammatory syndrome (IRIS). EBV does not establish infection in the basal cell layer of the oral epithelium but is maintained by repeated direct infection of the epithelium by EBV in the oral cavity; it is not reactivation of EBV at the site. Only chronically immunosuppressed patients continuously shed EBV in their oral secretions; hence the restriction of OHL to immunosuppressed hosts. In normal persons a similar morphologic and histologic picture can be seen

(pseudo-OHL), but EBV is not found in these patients' lesions. Thus, the finding of OHL warrants HIV testing. If results are negative, special histologic studies searching for EBV in the OHL biopsy should be performed. If EBV is found, a work-up for immunosuppression is recommended.

OHL is usually asymptomatic and requires no treatment. If treatment is requested in immunosuppressed hosts, podo- phyllin, applied for 30 s-1 min to the lesions once each month, is easiest. Tretinoin gel, applied topically twice a day, or oral acyclovir, 400 mg five times a day, is also effective. Lesions recur when treatment is discontinued.

In immunosuppressed and immunocompetent hosts, EBV may be responsible for benign and malignant disorders, some of which can be fatal. These include Kikuchi's histocytic necro- tizing lymphadenitis, hydroa vacciniforme of the severe type, plasmablastic lymphoma, post-transplant lymphoprolifera- tive disorder, Burkitt lymphoma, and nasopharyngeal carcinoma.

Cytomegalic inclusion disease

Congenital cytomegalovirus (CMV) infection, as documented by CMV excretion, is found in 1% of newborns. Ninety percent of these babies are asymptomatic. Clinical manifestations in infants may include jaundice, hepatosplenomegaly, cerebral calcifications, chorioretinitis, microcephaly, mental retardation, and deafness. Cutaneous manifestations may result from thrombocytopenia, with resultant petechiae, purpura, and ecchymoses. Purpuric lesions, which may be macular, papular, or nodular, may show extramedullary hematopoiesis (dermal erythropoiesis), producing the "blueberry muffin baby." A generalized vesicular eruption may very rarely occur. Most symptomatic cases occur within the first 2 months of life. Neonatal disease is more severe and sequelae are more frequent in neonates born of mothers with primary rather than recurrent CMV disease in pregnancy.

Between 50 and 80% of immunocompetent adults and up to 100% of HIV-infected men who have sex with men (MSM) are infected with CMV. Infection in

adults may be acquired by exposure to infected children, sexual transmission, and transfusion of CMV-infected blood. Symptomatic primary infection in adults is unusual and is identical to infectious mononucle- osis caused by EBV. An urticarial or morbilliform eruption or erythema nodosum may occur in primary CMV infection in immunocompetent adults. Ampicillin and amoxicillin admin- istration will often result in a morbilliform eruption in acute CMV infection, similar to that seen in acute EBV infection.

CMV infection is very common in AIDS patients, most frequently causing retinitis (20% of patients), colitis (15%), cholangitis, encephalitis, polyradiculomyopathy, and adrenalitis. It occurs in the setting of very advanced HIV infection (usually with CD4 counts below 50) and has become much less common in the era of highly active antiretroviral therapy (HAART).

CMV infection in tissues is usually identified by the histo- logic finding of a typical CMV cytopathic effect. In a very small percentage of AIDS patients with CMV infection, skin lesions may occur that contain such cytopathic changes. In most cases CMV is found in association with another infectious process and the treatment of that other infection will lead to resolution of the CMV in the skin without treatment of the CMV. This is especially true of perianal HSV ulcerations. CMV may even be found in totally normal skin in CMV-viremic AIDS patients, suggesting that finding the CMV cytopathic effect is alone insufficient to imply a causal relationship of the CMV to any cutaneous lesion. Only in the case of perianal and oral ulcera- tions has the pathogenic role of CMV been documented. In unusual cases of very painful perianal ulcerations, only CMV infection is found histologically. The CMV cytopathic changes may be noted in the nerves at the base of these ulcerations, suggesting that CMV neuritis may be producing the severe pain that characterizes these cases. The diagnosis of CMV ulceration is one of exclusion. CMV cytopathic changes must be seen in the lesion and cultures, and histologic evidence of any other infectious agent must be negative. In these cases, clinically suggested by their location (perianal or oral)

and painful nature, specific treatment with ganciclovir, foscarnet, or cidofovir will lead to healing of the ulceration and dramatic resolution of the pain.

Human herpesviruses-6 and 7

Infection with HHV-6 is almost universal in adults, with sero- positivity in the 80-85% range in the US, and seroprevalence almost 100% in children. There are intermittent periods of viral reactivation throughout life; persistent infection occurs in several organs, particularly in the CNS. Acute seroconversion to HHV-6 and to HHV-7 each appears to be responsible for about one-third of roseola cases, and in the remaining third neither is found. HHV-6 infection occurs earlier than HHV-7, and second episodes of roseola in HHV-6-seropositive children may be caused by HHV-7. Primary infection with HHV-6 is associated with roseola only 9% of the time, and 18% of children with seroconversion have a rash. Primary infection may occur with only fever and no rash, or rash without fever. Other common findings include otitis media, diarrhea, and bulging fontanelles, sometimes with findings of meningo- encephalitis. Uncommonly, hepatitis, intussusception, and even fatal multisystem disease may occur. In adults, acute HHV-6 infection resembles acute mononucleosis. Viral recovery is reduced in patients receiving acyclovir therapy, but ganciclovir is the recommended agent for treatment of severe disease associated with HHV-6. HHV-6 and 7 may be the etiologic agents responsible for pityriasis rosea.

As with other herpesviruses, the pattern of disease in HHV-6 may be different in immunosuppressed hosts. Chronic macular or papular generalized exanthems have been reported in two patients, one following bone marrow transplantation for severe combined immunodeficiency and one with acute leuke-mia who was undergoing chemotherapy. In the latter patient, the eruption cleared with recovery of the bone marrow.

Roseola infantum (exanthem subitum, sixth disease)

Roseola infantum is a common cause of sudden, unexplained high fever in young children between 6 and 36 months of age. Prodromal fever is usually high and convulsions and lymph- adenopathy may accompany it. Suddenly, on about

the fourth day, the fever drops. Coincident with the drop in temperature, a morbilliform erythema consisting of rose-colored discrete macules appears on the neck, trunk, and buttocks, and sometimes on the face and extremities. Often there is a blanched halo around the lesions. The eruption may also be papular or, rarely, even vesicular. The mucous membranes are spared. Complete resolution of the eruption occurs in 1-2 days. A case of spontaneously healing, generalized eruptive histiocytosis has been reported following exanthem subitum.

Human herpesvirus-8

HHV-8, a y-herpesvirus, is most closely related to EBV and *Herpesvirus saimiri.* It has been found in virtually all patients with Kaposi sarcoma, including those who have AIDS, in African cases; in elderly men from the Mediterranean basin; and in transplant patients. In addition, the seropositiv- ity rate (infection rate) for this virus correlates with the prevalence of Kaposi sarcoma in a given population.

The background seroprevalence rate in North America and Northern Europe is near zero. Seroprevalence is highest in Kaposi sarcoma-endemic areas in sub-Saharan Africa (50100%). In the general population in Italy, the seroprevalence is 10-15%, being 6-10% in children under age 16 and 22% after age 50. In south central Italy and Sardinia, seroprevalence rates are higher, being in the 20-25% range for the general population. In Italy, high rates of HHV-8 seropositivity are also seen in HIV-infected gay men (up to 60%), in female prostitutes (40%), and in heterosexual men who have had sex with prostitutes (40%). Infection with HHV-8 precedes and predicts subsequent development of Kaposi sarcoma in HIV- infected men. In addition to Kaposi sarcoma lesions, HHV-8 can be found in saliva and in circulating blood cells in HHV- 8-infected patients. HHV-8 is also found in the semen of up to 20% of patients with Kaposi sarcoma. Heterosexual partners of patients with classic Kaposi sarcoma have high rates of HHV-8 seropositivity (over 40%). These epidemiologic features all strongly support sexual transmission as an important mechanism of the spread of HHV-8. The finding of a significant number of infections in prepubertal children, however, suggests that nonsexual

methods of transmission also exist. HHV-8 seroprevalence rates in heterosexual intravenous drug users and persons with HIV infection acquired via blood transfusion are not increased above the general population, suggesting that HHV-8 is poorly transmitted by blood and blood products.

HHV-8 is present in a rare type of B-cell lymphoma called body cavity-based B-cell lymphoma or primary effusion lym- phoma (PEL), which presents with pleural, pericardial, and peritoneal malignant effusions. Rarely, this form of lymphoma may be associated with skin lesions, which histologically are CD30+ anaplastic large cell lymphoma. HHV-8 is also found in all cases of Castleman's disease associated with HIV infection and 10-50% of cases in HIV-negative persons. Exanthems and cutaneous nodules may accompany multicentric Castleman's disease, and HHV-8 has been identified in the skin lesions of one such patient.

B virus

Rare cases of respiratory or human-to-human contact spread have been reported. Within a few days of the bite, vesicles, erythema, necrosis, or edema appear at the site of inoculation. Regional lymph nodes are enlarged and tender. Fever is typically present. In a substantial number of human infections, rapid progression to neurologic disease occurs. This is initially manifested by peripheral nerve involvement (dysesthesia, paresthesia), then progresses to spinal cord involvement (myelitis and ascending paralysis with hyporeflexia), and finally to brain disease (decreased consciousness, seizures, and respiratory depression). Fifteen of 22 reported cases have died, and all survivors of encephalitis suffered severe neurologic sequelae. Treatment with acyclovir or ganciclovir has been successful in some cases, but other patients similarly treated have died. Because *H. simiae* infection may recur after a period of latency, lifetime surveillance is required. The Centers for Disease Control (CDC) have issued guidelines to protect workers from B virus infection.

Infectious hepatitis Hepatitis B virus

Hepatitis B virus (HBV) is a double-stranded DNA virus that is spread by blood and blood products, and sexually in Europe and the Western Hemisphere. In Africa and Asia, infection often occurs perinatally. HBV is the primary cause of hepato- cellular carcinoma and may also cause liver failure and cirrhosis. Acute infection with HBV is associated with anorexia, nausea, right upper quadrant pain, and malaise. Between 20 and 30% of persons with acute HBV infection have a serum sickness-like illness with urticaria, arthralgias, and, occasionally, arthritis, glomerulonephritis, or vasculitis. These symptoms appear 1-6 weeks before the onset of clinically apparent liver disease. Immune complexes containing hepatitis B surface antigen and hypocomplementemia occur in the serum and in joint fluid. The process spontaneously resolves as antigen is cleared from the blood.

B virus *(Herpesvirus simiae)* is endemic in Asiatic Old World monkeys (macaques) and may infect other monkeys housed in close quarters with infected monkeys. In macaques the disease is a recurrent vesicular eruption analogous to HSV in humans, with virus shed from conjunctiva, oral mucosa, and the urogenital area. Humans become infected after being bitten, scratched, or contaminated.

Hepatitis B is also associated with polyarteritis nodosa (PAN) in 7-8% of cases. This usually occurs within the first 6 months of infection, even during the acute phase, but may occur as long as 12 years after infection. Unlike the urticarial reaction, which is usually associated eventually with the development of clinical hepatitis, HBV infection associated with PAN may be silent.

A highly effective vaccine is available to prevent HBV infection. It is recommended as a part of standard childhood immunizations and all healthcare workers should be immunized. IFN-a and lamivudine may be used to treat active HBV infection, although following therapy, HBV viremia may by an animal shedding B virus. Usually, patients are animal handlers or researchers.

Hepatitis C virus

Hepatitis C virus (HCV) is a single-stranded RNA virus that causes most cases of non-A, non-B viral hepatitis. Now that a serologic test is available to

screen blood products for HCV infection, the vast majority of new cases of HCV infection are parenterally transmitted via intravenous drug usage. Sexual transmission, as compared to HBV, is uncommon (less than 1% transmission/year of exposure). Maternal to infant spread occurs in 5% of cases. Only about one-third of patients are symptomatic during acute infection. Between 55% and 85% of patients will have chronic infections. Although in most cases patients have minimal symptoms for the first one to two decades of infection, cirrhosis and liver failure, as well as hepatocellular carcinoma, are common sequelae. Chronic HCV infection is associated with various skin disorders, either by direct effect or as a consequence of the associated hepatic damage.

Cutaneous necrotizing vasculitis, which is usually associated with a circulating mixed cryoglobulin, occurs in approximately 1% of patients with chronic HCV infection. In 84% of cases of type II cryoglobulinemia, HCV infection is present. The most common clinical presentation is palpable purpura of the lower extremities (90% of cases). Livedo reticularis, urticaria, and subcutaneous nodules showing a granulomatous vasculitis may also occur. Arthropathy, glomerulonephritis, and neuropathy frequently accompany the skin eruption. Leg ulcers can occur in 10-20%. Histologically, in all cases a leuko-cytoclastic vasculitis is seen. In some cases, the vasculitis may involve small arteries, giving a histologic pattern similar to that seen in PAN. In various studies 5-20% of patients with PAN were HCV-positive, suggesting that both HBV and HCV can cause PAN. The presence of anti-HCV antibodies should not be used as the sole diagnostic test in persons with PAN, as PAN may cause a false-positive ELISA test for HCV. Rheumatoid factor, a type II cryoglobulin, and hypocomple-mentemia are found in up to 80% of cases. HCV-infected patients with mixed cryoglobulinemia are 35 times more likely to develop non-Hodgkin lymphoma, usually of the B-cell type.

Patients with porphyria cutanea tarda (PCT) often have hepatocellular abnormalities. Depending on the prevalence of HCV infection in the population studied, between 10 and 95% of sporadic (not familial) PCT cases are HCV-

associated. Treatment of the HCV infection with IFN may lead to improvement of the PCT.

HCV infection has been associated with lichen planus. The likelihood of identifying HCV infection in a patient with lichen planus is greatest in geographic regions with high rates of HCV infection. Patients with mucosal ulcerative lichen planus are also more likely to be HCV-infected. Serologic testing in a patient should be considered if the patient has HCV risk factors or abnormal liver function tests, or is from a geographic region or population in which HCV infection is common. HCV may also be associated with cutaneous B-cell lymphoma, xerostomia (but not typical Sjogren syndrome), possibly erythema multiforme, and autoimmune thyroid disease. Approximately 15% of patients with HCV infection have pruritus. Pruritus virtually always is associated with advanced liver disease and abnormal liver function tests. Patients with pruritus and normal liver function tests and no history of hepatitis will rarely be found to be infected with HCV.

Necrolytic acral erythema is an uncommon condition uniquely associated with HCV infection. It resembles the "deficiency" dermatoses, except that it has an acral distribution. The clinical lesions are painful or pruritic, keratotic, well-defined plaques with raised red scaly borders, or diffuse hyperkeratosis (Fig. 33). Erosion and flaccid blisters may occur, contributing to the discomfort. The dorsal feet (less commonly, the dorsal hands), as well as the lower extremities, may be involved. Histologically, there is necrosis of the superficial portion of the epidermis, along with hyperkeratosis, loss of the granular cell layer, and parakeratosis. Intraepidermal spongiotic foci are present, which may be macroscopic at times, the cleavage plane being between the necrotic and viable epidermis.

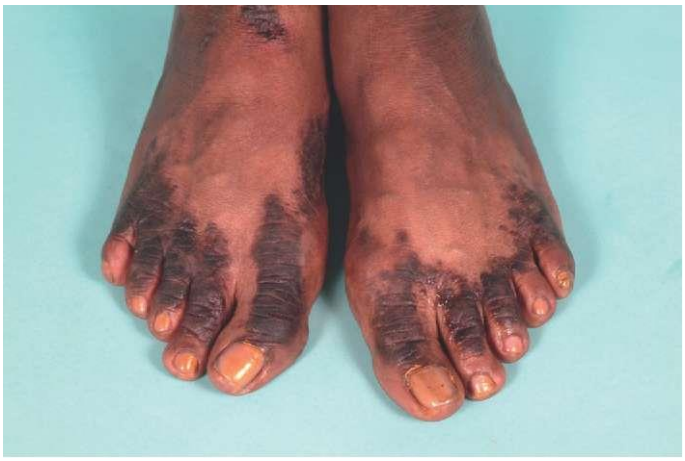


Fig. 33 Necrolytic acral erythema.

Zinc, essential fatty acid, and glucagon levels are normal, but the patients may be hypoalbuminemic and have low serum amino acids due to their liver disease. Treatment of the associated HCV infection with IFN and riba- virin, or IFN plus zinc, has resulted in resolution. Hyperalimentation was also partially effective in some patients, as was amino acid supplementation with zinc.

A combination of IFN-a and ribavirin is used to treat patients with chronic HCV infection, with sustained responses (negative HCV in the blood at 12 months) in slightly over 50% of patients. Complications caused by the presence of the virus in the blood, such as vasculitis, improve with such treatment. The response of other associated conditions, such as lichen planus and PCT, is variable. Combined IFN and ribavirin therapy may be complicated by an eczematous eruption with pruritus in about 8% of patients and severe pruritus in about 1%. Eczema typically affects the distal extremities, dorsal hands, face, neck, and less commonly the trunk, axillae, and buttocks. The eruption may be photodistributed and photo- exacerbated. These eczematous eruptions typically begin 2-4 months after treatment is begun. In affected patients, prior treatment with IFN alone was usually not associated with an eczematous eruption. Histologically, the eruptions show a spongiotic dermatitis. The eruption resolves completely if treatment is stopped for 2-3 weeks, but will recur when treatment is restarted. Aggressive therapy with antihistamines, emollients, and potent topical steroids will usually control the eczema, allowing uninterrupted continuation of

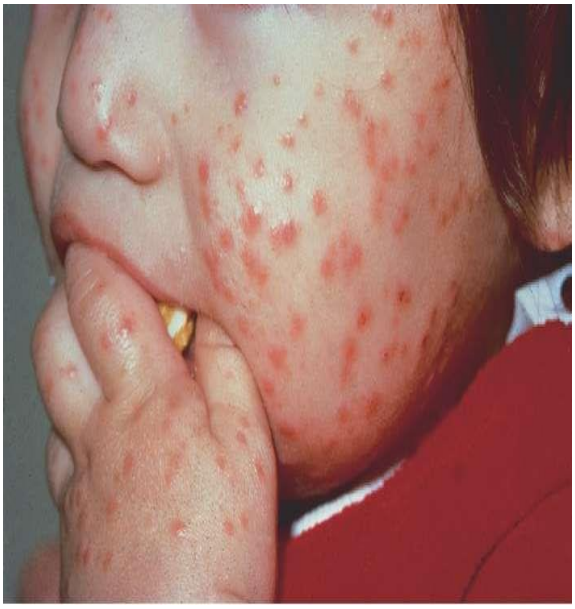
treatment. The severity of the pruritus in these cases may relate to the tendency of liver disease to cause itch and the frequent psychiatric side effects of HCV and IFN (depression, anxiety), which may reduce itch threshold. Patients receiving IFN-a for HCV infection may develop cosmetically unsightly granulo- matous nodules at filler injection sites.

Gianotti-Crosti syndrome (papular acrodermatitis of childhood, papulovesicular acrolocated syndrome)

Gianotti-Crosti syndrome (GCS) is a characteristic viral exan- them. It was initially associated with the early anicteric phase of HBV infection. With universal HBV immunization, HBV is now a rare cause of GCS. EBV is now the most common cause of GCS worldwide. Other implicated infectious agents have included adenovirus, CMV, enteroviruses (coxsackie A16, B4, and B5), vaccinia virus, rotavirus, hepatitis A and C, respiratory syncytial virus, parainfluenza virus, parvovirus B19, rubella virus, HHV-6, streptococcus, and *Mycobacterium avium* infection. Immunizations against poliovirus, diphtheria, pertussis, Japanese encephalitis, influenza, and hepatitis B and measles (together) have also caused this syndrome. The clinical features of GCS are identical, independent of the cause:

- The condition typically affects children between 6 months and 14 years of age (median age 2 years, 90% of cases occurring before the age of 4), and may rarely be seen in adults (women only). Chuh proposed diagnostic criteria involving the following positive clinical features: monomorphous flat-topped, pink-brown, papules or papulovesicles of 1-10 mm in diameter (Figs 34 and 35)
- any three or all four sites involved—face, buttocks, forearms, and extensor legs
- symmetry
- duration of at least 10 days.
- Negative clinical features:
- extensive truncal lesions
- scaly lesions.

The lesions develop over a few days but last longer than most viral exanthems (more than 10 days and up to many weeks). Lesion numbers may vary from a few to a generalized eruption coalescing to form plaques covering the face, trunk, and upper extremities. Early in the course of the eruption, the lesions will demonstrate a Koebner phenomenon. Pruritus is variable and the mucous membranes are spared, except when inflamed by the associated infectious agent. Depending on the cause, the lymph nodes, mainly inguinal and axillary, are moderately enlarged for 2-3 months. No treatment appears to shorten the course of the disease, which is self-limited.



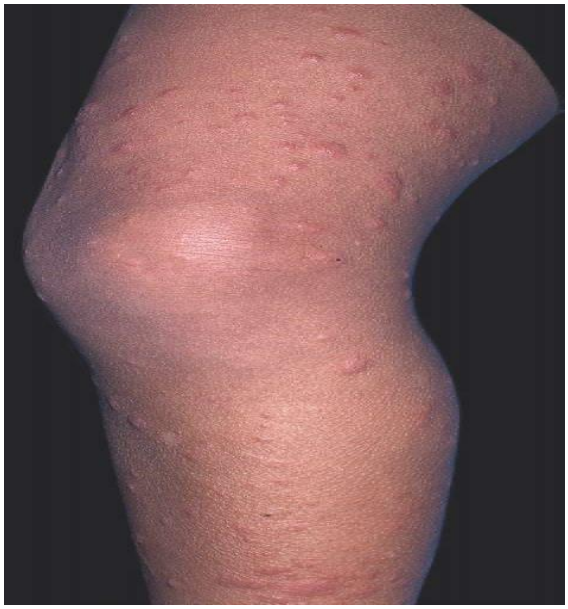


Fig. 34 Gianotti-Crosti syndrome. **Fig. 35** Papules on the leg, Gianottiti syndrome.

Poxvirus group

The poxviruses are DNA viruses of a high molecular weight. The viruses are 200-300 nm in diameter, and hence can be seen in routine histologic material. The orthopoxviruses include variola, vaccinia, monkeypox, cowpox, buffalopox, and Cantagalo and Aracatuba. The parapoxviruses are primarily zoonotic, and include orf, paravaccinia, bovine papular stomatitis, deerpox, and sealpox. Tanapox is the sole yatapoxvirus to cause human disease.

Variola major (smallpox)

Smallpox was eradicated worldwide in 1977. It continues to be of interest to dermatologists as it is a potential biologic warfare agent. Variola is spread via the respiratory route, with 37-88% of unvaccinated contacts becoming infected. The incubation period for smallpox is 7-17 days (average 10-12 days). The prodromal phase consists of 2-3 days of high fever (over 40°C), severe headache, and backache. The fever subsides and an exanthem covers the tongue, mouth, and oropharynx. This is followed in 1 day by the appearance of skin lesions. The skin lesions are distributed in a centrifugal pattern, the face, arms, and legs being more heavily involved than the trunk. Lesions appear first on the palms and soles, and feel like firm "BBs" under the skin. Beginning as erythematous macules (days 1-2), the lesions all in synchrony become 2-3 mm papules (days 2-4) and evolve to 2-5 mm vesicles (days 4-7) and 4-6 mm pustules (days 5-15). The pustules umbilicate, collapse, and form crusts beginning in the second week. The total evolution averages 2 weeks. Lesions on the palms and soles persist the longest. The crusts separate after about 1 more week, leaving scars (Fig. 36), which are permanent in 6580% of the survivors. Patients are infectious from the onset of the exanthem through the first 7-10 days of the eruption. A variety of complications occur, including pneumonitis, blindness due to viral keratitis or secondary infection (1% of patients), encephalitis (less than 1% of patients), arthritis (2% of children), and osteitis. Immunity is lifelong. The mortality rate was 5-40% in undeveloped countries (and at a time prior to current intensive care and antiviral management). Six clinical patterns of smallpox have been described. Variola major, or "ordinary smallpox," had a case fatality rate of 30%.

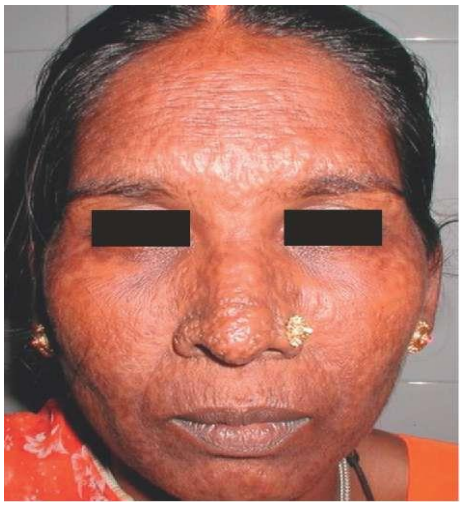


Fig. 36 Smallpox scars.

Fatalities were rare. Flat lesions occur in about 7% of persons, and evolve slowly and coalesce. Ninety-seven percent of unvaccinated persons with flat variola died. Hemorrhagic smallpox occurred in a small percentage of patients, resembles a purpuric eruption or vasculitis, and was universally fatal within a week. This variant is very hard to diagnose without a biopsy, but is highly infectious. Variola sine eruption describes infection in patients who develop flu-like symptoms but no skin lesions. They do not appear to be infectious. Variola minor appears to be a subtype of variola that is milder and resulted in death in less than 1% of patients.

Diagnosis is made by electron microscopy, viral culture, and PCR. Special laboratories, usually associated with the City and State Health Departments in the US, have the capacity to process these specimens and confirm the diagnosis. The differential diagnosis is primarily varicella, especially of the more severe form seen in adults. In varicella the prodrome lasts for 1-2 days; fever begins with the onset of the eruption (not preceding it by 1-3 days, as in variola); the eruption is concentrated on the torso (not centrifugally); individual lesions of different stages are present; and individual lesions evolve from vesicles to crust within 24 h. The diagnostic test of choice in this setting would be a Tzanck smear or DFA, which can rapidly confirm the diagnosis of varicella.

Treatment of smallpox includes strict isolation and protection of healthcare workers. Only vaccinated persons should treat the patient, and any of those

exposed should immediately be vaccinated, as this modifies the disease. Cidofovir may be indicated, as it modifies infections by other orthopox viruses.

Vaccinia

The vaccinia virus has been propagated in laboratories for immunization against smallpox. There are multiple strains used in vaccines and the rates of complications vary somewhat, depending on the strain used. New vaccines have been developed, but were not used during the mass immunizations that took place between 2002 and 2004, so their adverse reaction profiles are poorly understood. The available antiviral agents with activity against vaccinia are limited. If a case of vaccinia is encountered, the State Health Department or CDC should be contacted immediately for optimal management.

Vaccination

Vaccination is inoculation of live vaccinia virus into the epidermis and upper dermis by the multiple puncture technique. Between 3 and 5 days after inoculation, a papule forms, which becomes vesicular at days 5-8, then pustular, reaching a maximum size at days 8-10. The pustule dries from the center outward, revealing the pathognomonic umbilicated pustule, and forms a scab that separates 14-21 days after vaccination, resulting in a pitted scar. Formation by days 6-8 of a papule, vesicle, ulcer, or crusted lesion, surrounded by a rim of erythema and induration, is termed a "major reaction" or "take." The rim of erythema averages 3.5-4 cm in diameter in new vaccinees and peaks on days 9-11. Repeat vaccinees have reactions of a similar time course, but the maximum diameter of the erythema is only 1-2 cm. Reactions that do not match this description are considered equivocal and such persons cannot be considered immune. Revaccination should be considered. A large vaccination reaction, or "robust take," is the development of a plaque of erythema and induration of greater than 10 cm at the site of inoculation. This occurs in 10% of initial vaccines. It peaks at days 8-10 and resolves without treatment within 72 h. Cellulitis secondary to vaccination occurs in days 1-5 after vaccination or after several weeks, and progresses without treatment. Management should be expectant, but a bacterial

culture may be taken. Since vaccinated patients may have fever at days 8-10 following vaccination, this is not helpful in separating cellulitis from a "robust take." Rarely, patients will develop lesions at the site of vaccination an average of 2 months following vaccination. The nature of these lesions is unknown, but they have not been identified as containing live virus and are self-limited.

Vaccination involves the inoculation of a live virus. Complications result from an abnormal response to the vaccination by the host or from inadvertent transmission to another person. Persons with defective cutaneous or systemic immunity are at particular risk for adverse outcomes from vaccination. Since some complications may be fatal, extremely careful steps must be taken to avoid complications.

Inadvertent inoculation and autoinoculation

Inadvertent inoculation of vaccinia may occur by transmission of virus via hands or fomites from the vaccination site to another skin area or the eye, or to another person. Accidental autoinoculation occurs in about 1 in 1000 vaccinees. Autoinoculation most commonly occurs around the eyes and elsewhere on the face, but the groin and other sites may be involved (Fig. 37). These lesions evolve in parallel with the primary vaccination site and, except for ocular lesions, cause no sequelae, except scarring at times. Any evidence of ocular inflammation in a recently vaccinated individual could represent ocular vaccinia infection and requires immediate ophthal- mologic evaluation. Transmission to others (secondary transfer) is rare if the vaccination site is kept covered until it heals (7.4 in 100 000 primary vaccinees). It usually occurs within a household or through intimate contact. Serial transmission can occur among male sports partners. Correct bandaging of the vaccination site using foam or occlusive dressings and not gauze bandages, and treating the inoculation site with povidone iodine ointment beginning at 7 days after immuniza tion both can reduce viral shedding and might reduce autoin- oculation and secondary cases.

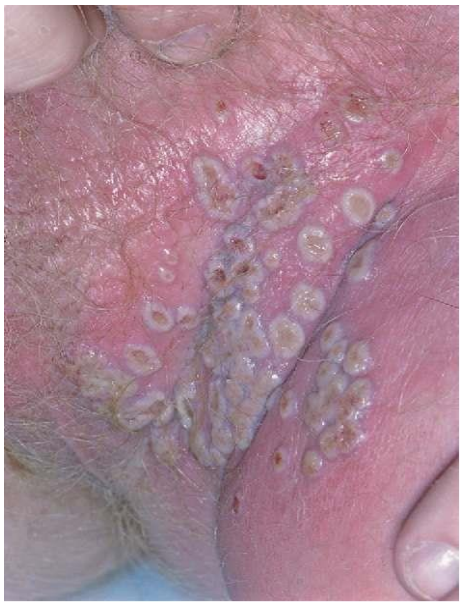


Fig. 37 Vaccinia, typical reaction at about 1 week.

Generalized vaccinia

Between 6 and 9 days after vaccination, a generalized vaccinia eruption may occur, in about 81 per 1 million new vaccinees or 32 per 1 million repeat vaccinees. The lesions are papulovesicles that become pustules and involute in 3 weeks, although successive crops may occur within that time. Generalized vaccinia may be accompanied by fever, but patients do not appear ill. Lesions may be generalized or limited to one anatomic region, and can number from a few to hundreds. They can be confused with multiple site autoinoculation, as well as erythema multiforme. The diagnosis is confirmed by biopsy, viral culture, or PCR. Generalized vaccinia is self-limited and does not require treatment in the immuno-competent host. In the setting of underlying immunodeficiency, early intervention with vaccinia immune globulin (VIG) may be beneficial.

ECZEMA VACCINATUM

Eczema vaccinatum is analogous to eczema herpeticum, representing vaccinia virus infection superimposed on a chronic dermatitis, especially atopic dermatitis. Patients with Darier's disease, Netherton, and other disorders of cornification may also be at risk. Since patients with atopic dermatitis or any past history of atopic dermatitis should not be vaccinated, most cases of eczema vaccinatum represent secondary transfer to an at-risk individual from a recent

vaccinee, usually a family member. The vesicles appear suddenly, mostly in areas of active dermatitis. The lesions are sometimes umbilicated and appear in crops, resembling smallpox or chickenpox. The onset is sudden and fresh vesicles appear for several days. Scarring is common. Often there is cervical adenopathy and fever, and affected persons are systemically ill (as opposed to those with generalized vaccinia). Secondary bacterial infection can complicate eczema vaccinatum. The mortality rate for eczema vaccinatum is 30-40% if untreated. VIG reduces mortality to 7%. Multiple doses of VIG and perhaps treatment with effective antivirals may be required. One case occurred during the recent mass vaccination of the US military.

Progressive vaccinia (vaccinia necrosum, vaccinia gangrenosum)

Progressive vaccinia is a rare, severe and often fatal complication of vaccination that occurs in persons who are immuno- deficient. Most cases occur when infants with undiagnosed immunodeficiency are immunized. The initial vaccination site continues to progress and fails to heal after more than 15 days. The vaccination site is characterized by a painless but progressive necrosis and ulceration (Fig. 38), with or without meta- static lesions to distant sites (skin, bones, viscera). No inflammation is present at the sites of infection, even histologi- cally. Inflammation may indicate secondary bacterial infection. Untreated progressive vaccinia is virtually always fatal. Progressive vaccinia is diagnosed by skin biopsy, viral culture, or PCR. VIG should be given, and antiviral antibiotics should be considered.

Cutaneous immunologic complications

A spectrum of erythematous eruptions occurs following vaccination. These eruptions are more common than generalized vaccinia, with which they are often confused. Cases of Stevens- Johnson syndrome following vaccination have been seen in the past, primarily in children, but apparently are rare in adult vaccinees (no cases among more than 30 000 civilian adult vaccinees).

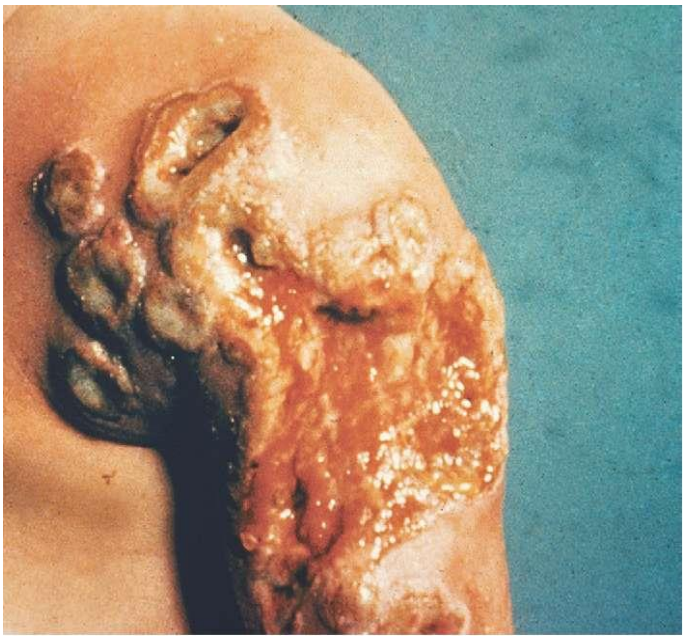


Fig. 38 Vaccinia, disseminated.

Benign hypersensitivity reactions to vaccinia

About 0.08% of vaccinees will develop a diffuse cutaneous eruption during the second week after vaccination, around the peak of the immunization site reaction. These have been classified as exanthematous (by far the most common), urticarial, and erythema multiforme-like (the most rare). A follicular eruption has also been reported (see below). All these reaction patterns evolve over 1-2 days, and resolve over days. Patients may have mild symptoms but are afebrile. At times, the eruption may evolve from around the inoculation site and generalize. This had been called "roseola vaccinia" in the past. Primary vaccinees are more likely to develop these reactions. Histology is nonspecific, showing features of a viral exanthem (a mild spongiotic dermatitis). These reactions are distinguished from generalized vaccinia by a later onset (end of second week as opposed to days 6-9 after vaccination), prominent erythema, lack of vesicles and pustules, and negative laboratory testing for vaccinia virus. The eruptions described as erythema multiforme-like lack mucosal involvement and blistering, and more closely resemble urticaria multiforme (see Chapter 7). They are distinguished from erythema multiforme/ Stevens-Johnson syndrome by the absence of atypical

purpu- ric or typical targetoid lesions, lack of mucosal involvement, and histologic evaluation.

Post-vaccination follicular eruption

A generalized variant of this eruption occurred in 2.7% of new vaccinees and a localized variant in 7.4% during a trial of Aventis Pasteur smallpox vaccine. In the second week, 9-11 days following vaccination, multiple follicular, erythematous papules appeared, primarily on the face, trunk, and proximal extremities. Lesions were mildly pruritic. Over several days the lesions evolved to pustules, which resolved without scarring. Lesions were simultaneously at different stages of development. The number of lesions was usually limited and rarely exceeded 50. Lesions spontaneously resolved over a few days. Histologic evaluation revealed a suppurative folliculitis. No virus was detected in the lesions by PCR or viral culture.

Other skin lesions at vaccination scars

Melanomas, basal cell carcinomas, and squamous cell carcinomas have all occurred in vaccination scars. Benign lesions with a tendency to occur in scars, such as dermatofibromas, sarcoidosis, and granuloma annulare, also can occur in vaccination scars.

Human monkeypox

Human monkeypox is a rare, sporadic zoonosis that occurs in remote areas of the tropical rainforests in central and western Africa. Monkeypox virus is an orthopoxvirus. The main vector for monkeypox is wild African rodents and monkeys. Humans and anteaters are accidental hosts. Direct contact with an infected animal or person appears to be required to acquire the infection. In Africa, more than 90% of cases occur in children under 15 years of age, in whom the fatality rate is 11%. The secondary attack rate in African households is 10%. A recent outbreak of 81 cases of monkeypox occurred in the US. Prairie dogs became infected when housed with infected African rodents. Persons who purchased the prairie dogs become infected, most commonly via bites or

scratches, or through areas of damaged skin. The pattern of monkeypox seen in the US cases was different from that of African cases, since transmission was felt to be by inoculation, and many of the affected persons were previously immunized with vaccinia. Primary skin lesions occurred at sites of inoculation and limited spread occurred thereafter, with the appearance of 1-50 additional satellite and disseminated lesions over several days. Patients often had fever, respiratory symptoms, and characteristic lymphadenopathy (67%). About one-quarter required hospitalization, and only two children had serious clinical illness, one with encephalitis and one with severe oropharyngeal lesions.

In Africa, the disease is clinically similar to smallpox, with an incubation period of 10-14 days. Patients develop headache (100%); fever, sweats, and chills (82%); and lymphadenopathy (90%). Lymphadenopathy is not a feature of smallpox. The prodrome lasts 2 days, followed by the appearance of 2-5 mm papules. The lesions spread centrifugally and progress from papules to vesicles, then pustules all in a 14-21-day period. In 80% of cases, the lesions are largely monomorphic, but are more pleomorphic than smallpox. The distribution is generalized and the buccal mucosa can be affected. Lesions resolve with hemorrhagic crusts. The disease is self-limited. It is less severe in persons previously vaccinated against smallpox.

Buffalopoxvirus

Buffalopoxvirus is a subspecies of vaccinia virus and is endemic in buffalo herders in India. Lesions occur on the hands and arms of animal handlers and resemble a milder form of cowpox. Family members may be affected and children have developed lesions resembling eczema vaccinatum.

Zoonotic poxvirus infections

While these infections are uncommon, increasing numbers are being reported due to the popularity of exotic pets and travel to endemic areas. They continue to represent, in the case of orf, an important disease in animal husbandry. The diagnosis of zoonotic poxvirus infection is usually by epidemiologic history,

clinical features, and electron microscopy, which can separate the various poxvirus genera. Laboratory culture is slow and PCR analysis of the viral DNA allows for speciation. Rarely is antiviral therapy indicated, as most diseases are self- limited. Cidofovir, and in some cases ribavirin and adefovir dipivoxil, would be anticipated to have activity against this group of viruses.

Cowpox

Cowpox is an orthopoxvirus related to smallpox and vaccinia, which is geographically restricted to the UK, Europe, Russia, and adjacent states. It is largely a zoonosis that rarely affects cattle. The domestic cat is the usual source of human infection, but the animal reservoirs are apparently small wild rodents (mice and voles) and human infection from contact with such rodents has been confirmed. Most cases occur in the late summer and in fall.

The incubation period is about 7 days. There is then an abrupt onset of fever, malaise, headache, and muscle pain. Lesions are usually solitary (72%), with co-primaries in 25%. Lesions occur on the hands and fingers in half the cases and the face in another third. Secondary lesions are uncommon and generalized disease is rare, usually occurring in patients with atopic dermatitis. The lesion progresses from a macule through a vesicular stage, then a pustule that becomes blue- purple and hemorrhagic. A hard, painful, 1-3 cm indurated eschar develops after 2-3 weeks and may resemble cutaneous anthrax. In anthrax, however, the eschar forms by day 6. Lesions are always painful and there is local lymphadenopa- thy, which is usually tender. The amount of surrounding edema and induration is much more marked than in orf. Patients are systemically ill until the eschar stage. Healing usually takes 6-8 weeks. Scarring is common.

Farmyard pox

Because closely related parapoxviruses of sheep and cattle cause similar disease in humans, orf and milker's nodules have been collectively called farmyard pox. The epidemiologic features are discussed separately, but the clinical and histo- logic features, which are identical, are discussed jointly. The diagnosis of

these infections is based on taking an accurate history, and can virtually always be confirmed by routine his tologic evaluation. The presence of a homologue gene of vascular endothelial growth factor (VEGF) may explain the vascular nature of lesions produced by parapoxviruses.

Milker's nodules/bovine papular stomatitis/pseudocowpox

These infections cause worldwide occupational disease of milkers or veterinarians, most commonly transmitted directly from the udders (milker's nodules) or muzzles (bovine papular stomatitis) of infected cows. Lesions are usually solitary or only a few in number, and are confined to the hands or forearms (Fig. 39). Numerous lesions have been reported in healing first- and second-degree burns in milker's nodules. These cases occurred on farms with infected cattle, but the patients had not had direct contact with the cattle, suggesting indirect viral transmission. It is unclear whether milker's nodules and bovine papular stomatitis are caused by one or two species of parapoxvirus.

Also known as ecthyma contagiosum, contagious pustular dermatosis, sheep pox, and infectious labial dermatitis, orf is a common disease in goat- and sheep-farming regions throughout the world (Fig. 40).

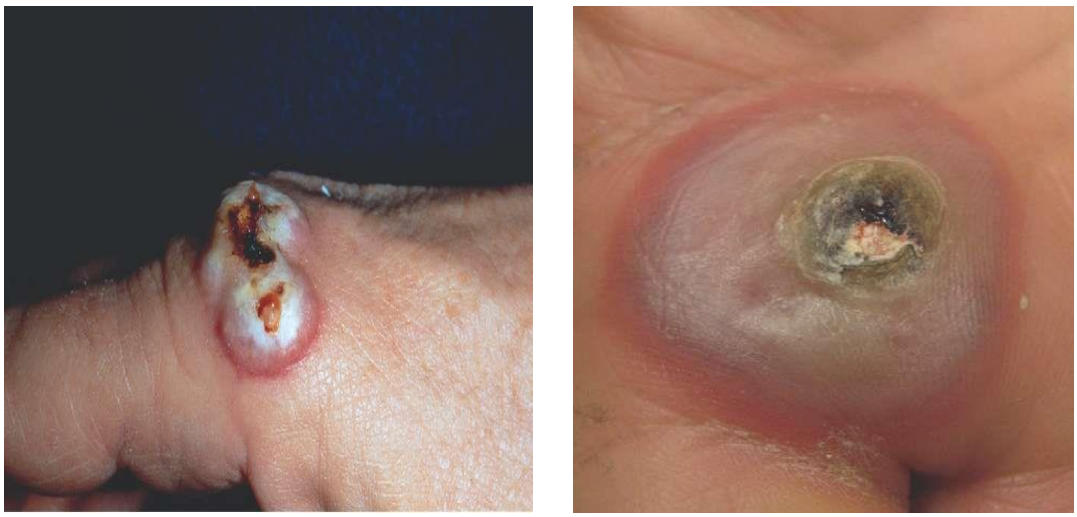


Fig. 39-40 Milker's nodule.

Direct transmission from active lesions on lambs is most common, but infection from fomites is also frequent, since the virus is resistant to heat and

dryness. Autoinoculation to the genital area can occur, but human-to- human transmission is rare.

Clinical features

The incubation period for farmyard pox is about 1 week. Lesions are usually solitary and occur on the hands, fingers, or face. Lesions evolve through six stages:

- A papule forms, which then becomes a target lesion with a red center surrounded successively with a white ring and then a red halo.
- In the acute stage, a red, weeping nodule not unlike pyogenic granuloma appears.
- In a hairy area, temporary alopecia ensues.
- In the regenerative stage, the lesion becomes dry with black dots on the surface.
- The nodule then becomes papillomatous.
- The nodule finally flattens to form a dry crust, eventually healing.

Lesions are usually about 1 cm in diameter, except in immuno- suppressed patients, in whom giant lesions may occur. Spontaneous resolution occurs in about 6 weeks, leaving minimal scarring. Mild swelling, fever, pain, and lymphadenitis may accompany the lesions, but these symptoms are milder than those seen in cowpox. Orf may be associated with an erythema multiforme-like eruption in about 5% of cases. Treatment is supportive, although shave excision may accelerate healing.

Histologic features

Histologic features correlate with the clinical stage. Nodules show a characteristic pseudoepitheliomatous hyperplasia covered by a parakeratotic crust. Keratinocytes always demonstrate viropathic changes of nuclear vacuolization and cyto - plasmic 3-5 im eosinophilic inclusions surrounded by a pale halo. The papillary dermis is markedly edematous. The dermal infiltrate, which is dense and extends from the interface to the deep dermis, consists of lymphocytes, histiocytes,

neutrophils, and eosinophils. Massive capillary proliferation and dilation are present in the upper dermis.

Sealpox

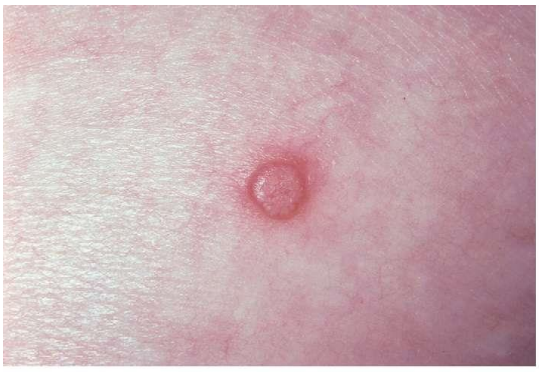
Sealpox, caused by a parapoxvirus, closely resembles orf and has been described in seal handlers who have been bitten by infected harbor or grey seals. Up to 40% of seals in Europe and North America are serologically positive for the virus, suggesting infection is common.

Human tanapox

Tanapox infection is a yatapoxvirus infection endemic to equatorial Africa. It is spread from its natural hosts, nonhuman primates, through minor trauma. Human-to-human transmission is rare. Tanapox infection is manifested by mild fever of abrupt onset lasting 3-4 days, followed by the appearance of one or two pock lesions. Lesions are firm and cheesy, resembling cysts. The disease is self-limited and smallpox vaccination would not be expected to be protective. Rare cases have been imported into Europe and the US.

Parapoxvirus infections from wildlife

Smith et al reported two patients with solitary lesions on the fingers, one following direct inoculation while cleaning a deer and another at the site of a cut sustained on a camping trip in an area with wild deer. Lesions were present for more than 2 months before biopsy. Histologically, there was marked hyperkeratosis, parakeratosis, and pseudoepitheliomatous hyperplasia. The midepidermal cells showed vacuolization with pyknotic nuclei. The dermis had prominent vascular proliferation. Viral particles were identified by electron microscopy in the keratinocytes. These may represent cases of red deer pox, caused by a distinct species of parapoxvirus. Reindeer poxvirus may cause similar disease.



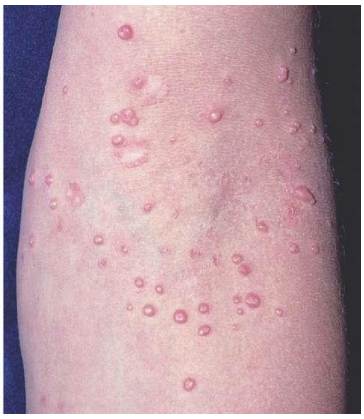


Fig. 41 Molluscum contagiosum

Fig. 42 Molluscum contagiosum, child with atopic dermatitis.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is caused by up to four closely related types of poxvirus, MCV-1 to 4 and their variants. Although the proportion of infection caused by the various types varies geographically, throughout the world MCV-1 infections are most common. In small children virtually all infections are caused by MCV-1. There is no difference in the anatomic region of isolation with regard to infecting type (as opposed to HSV, for example). In patients infected with HIV, however, MCV-2 causes the majority of infections (60%), suggesting that HIV infection-associated molluscum does not represent recrudescence of childhood molluscum.

Infection with MCV is worldwide. Three groups are primarily affected: young children, sexually active adults, and immunosuppressed persons, especially those with HIV infection. Molluscum is most easily transmitted by direct skin-to-skin contact, especially if the skin is wet. Swimming pools have been associated with infection.

In all forms of infection, the lesions are relatively similar. Individual lesions are smooth-surfaced, firm, dome-shaped, pearly papules, averaging 3-5 mm in diameter (Fig. 43). "Giant" lesions may be up to 1.5 cm in diameter. A central umbilication is characteristic. Irritated lesions may become crusted and even

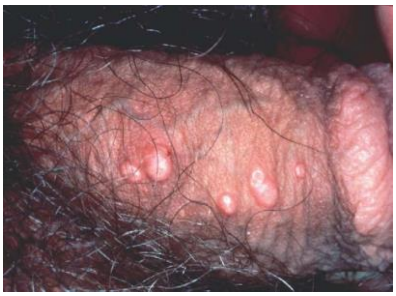


Fig. 43 Molluscum contagiosum of the penis.

pustular, simulating secondary bacterial infection. This may precede spontaneous resolution.

Lesions that rupture into the dermis may elicit a marked suppurative inflammatory reaction that resembles an abscess.

The clinical pattern depends on the risk group affected. In young children the lesions are usually generalized and number from a few to more than 100. Dermatitis surrounding a lesion usually heralds the resolution of that lesion. Lesions tend to be on the face, trunk, and extremities. Genital lesions occurring as part of a wider distribution occur in 10% of childhood cases. When molluscum is restricted to the genital area in a child, the possibility of sexual abuse must be considered.

In adults, molluscum is sexually transmitted and other STDs may coexist. There are usually fewer than 20 lesions; these favor the lower abdomen, upper thighs, and the penile shaft in men (Fig. 19-33). Mucosal involvement is very uncommon.

Immunosuppression, either systemic T-cell immunosup- pression (usually HIV, but also sarcoidosis and malignancies) or abnormal cutaneous immunity (as in atopic dermatitis or topical steroid use), predisposes the individual to infection. In atopic dermatitis, lesions tend to be confined to dermatitic skin (Fig. 19-34).

Secondary infection may occur. In addition, in about 10% of lesions, a surrounding eczematous reaction is present (mol- luscum dermatitis). Rarely, erythema annulare centrifugum may be associated. Lesions on the eyelid margin or conjunctiva may be associated with a conjunctivitis or keratitis. Rarely, the

molluscum lesions may present as a cutaneous horn (mollus- cum contagiosum cornuatum).

Between 10 and 30% of AIDS patients not receiving anti- retroviral therapy have molluscum contagiosum. Virtually all Fig. 19-34 Molluscum contagiosum, child with atopic dermatitis.

HIV-infected patients with molluscum contagiosum already have an AIDS diagnosis and a helper T-cell count of less than 100. In untreated HIV disease, lesions favor the face (especially the cheeks, neck, and eyelids) and genitalia. They may be few or numerous, forming confluent plaques. Giant lesions are not uncommon and may be confused with a basal cell carcinoma. Involvement of the oral and genital mucosa may occur, virtually always indicative of advanced AIDS (helper T-cell count less than 50). Facial disfigurement with numerous lesions can occur.

Molluscum contagiosum has a characteristic histopathology. Lesions primarily affect the follicular epithelium. The lesion is acanthotic and cup-shaped. In the cytoplasm of the prickle cells, numerous small eosinophilic and later basophilic inclusion bodies, called molluscum bodies or Henderson-Paterson bodies, are formed. Eventually, their bulk compresses the nucleus to the side of the cell. In the fully developed lesion each lobule empties into a central crater. Inflammatory changes are slight or absent. Characteristic brick-shaped poxvirus particles are seen on electron microscopy in the epidermis. Latent infection has not been found, except in untreated AIDS patients, in whom even normal-appearing skin may contain viral particles. Molluscum contagiosum virus contains an *IL-18* binding protein gene it apparently acquired from humans. This blocks the host's initial effective Th1 immune response against the virus by reducing local IFN-y production.

The diagnosis is easily established in most instances because of the distinctive central umbilication of the dome-shaped lesion. This may be enhanced by light cryotherapy that leaves the umbilication appearing clear against a white (frozen) background. For confirmation, express the pasty core of a lesion, squash it

between two microscope slides (or a slide and a cover glass) and stain it with Wright, Giemsa, or Gram stains. Firm compression between the slides is required.

Treatment is determined by the clinical setting. In young immunocompetent children, especially those with numerous lesions, the most practical course may be not to treat or to use only topical tretinoin. Aggressive treatment may be emotionally traumatic and can cause scarring. Spontaneous resolution is virtually a certainty in this setting, avoiding these sequelae. Individual lesions last 2-4 months each; the duration of infection is about 2 years. Continuous application of surgical tape to each lesion daily after bathing for 16 weeks led to cure in 90% of children so treated. Topical cantharidin, applied for 4-6 h to approximately 20 lesions per setting, led to resolution in 90% of patients and 8% of patients improved. This therapy is well tolerated, has a very high satisfaction rate for patients and their parents, and has rare complications. If lesions are limited and the child is cooperative, nicking the lesions with a blade to express the core (with or without the use of a comedo extractor), light cryotherapy, application of trichloroacetic acid (35-100%), or removal by curettage are all alternatives. The application of EMLA cream for 1 h before any painful treatments has made the management of molluscum in children much easier. Topical 5% sodium nitrite with 5% salicylic acid cures about 75% of patients. No controlled trials have confirmed the efficacy of imiquimod and it cannot be recommended for the treatment of molluscum.

In adults with genital molluscum, removal by cryotherapy or curettage is very effective. Neither imiquimod nor podo- phyllotoxin has been demonstrated to be effective. In fact, the failure of these agents to improve "genital warts" suggests the diagnosis of genital molluscum contagiosum. Sexual partners should be examined; screening for other coexistent STDs is mandatory.

In patients with atopic dermatitis, application of EMLA followed by curettage or cryotherapy is most practical. Caustic chemicals should not be used on atopic skin. Topical steroid application to the area should be reduced to the minimum strength possible. A brief course of antibiotic therapy should be

considered after initial treatment, since dermatitic skin is frequently colonized with *S. aureus.*

In immunosuppressed patients, especially those with AIDS, management of molluscum can be very difficult. Aggressive treatment of the HIV infection with HAART, if it leads to improvement of the helper T-cell count, is predictably associated with a dramatic resolution of the lesions. This response is delayed 6-8 months from the institution of the treatment. Molluscum occurs frequently in the beard area, so shaving with a blade razor should be discontinued to prevent its spread. If lesions are few, curettage or core removal with a blade and comedo extractor is most effective. EMLA application may permit treatment without local anesthesia. Cantharone or 100% trichloroacetic acid may be applied to individual lesions. Temporary dyspigmentation and slight surface irregularities may occur. Cryotherapy may be effective but must be used with caution in persons of pigment. When lesions are numerous or confluent, treatment of the whole affected area may be required because of the possibility of latent infection. Trichloroacetic acid peels above 35% concentration (medium depth) or daily applications of 5-fluorouracil (5-FU) to the point of skin erosion may eradicate lesions, at least temporarily. At times, removal by curette is required. In patients with HIV infection, continuous application of tretinoin cream once nightly at the highest concentration tolerated seems to reduce the rate of appearance of new lesions. Topical 1-3% cidofovir application and systemic infusion of this agent have been reported to lead to dramatic resolution of molluscum in patients with AIDS.

Picornavirus group

Picornavirus designates viruses that were originally called enteroviruses (polioviruses, coxsackieviruses, and echo- viruses), plus the rhinoviruses. The picornaviruses are small, single-stranded RNA, icosahedral viruses varying in size from 24 to 30 nm. Only the coxsackieviruses, echoviruses, and enterovirus types 70 and 71 are significant causes of skin disease.

Enterovirus infections

Person-to-person transmission occurs by the intestinal-oral route and, less commonly, the oral-oral or respiratory routes. Enteroviruses are identified by type-specific antigens. The type-specific antibodies appear in the blood about 1 week after infection has occurred and attain their maximum titer in 3 weeks. Viral cultures obtained from the rectum, pharynx, eye, and nose may isolate the infecting agent. Usually, the diagnosis is by clinical characteristics, and except in specific clinical settings, the causative virus is not identified. Enteroviral infections most frequently occur in children between the ages of 6 months and 6 years.

Many nonspecific exanthems and exanthems that occur during the summer and early fall are caused by coxsackievirus or echovirus. The exanthems are most typically diffuse macular or morbilliform erythemas, which sometimes also contain vesicular lesions, or petechial or purpuric areas. Echovirus 9 has caused an eruption resembling acute meningococcemia. Each type of exanthem has been associated with many subtypes of coxsackievirus or echovirus (one exanthem, many possible viral causes). Echovirus 9, the most prevalent entero- virus, causes a morbilliform exanthem, initially on the face and neck, then the trunk and extremities. Only occasionally is there an eruption on the palms and soles. Small red or white lesions on the soft palate may occur. The most common specific eruptions due to enteroviruses are hand-foot-and-mouth disease, herpangina, and roseola-like illnesses. Rare reported presentations of enterovirus infection include a unilateral vesicular eruption simulating herpes zoster, caused by echovirus 6; a fatal dermatomyositis-like illness in a patient with hypo- gammaglobulinemia, caused by echovirus 24; and a widespread vesicular eruption in atopic dermatitis that simulated Kaposi varicelliform eruption, caused by coxsackievirus A-16. Pleconaril and other new antienteroviral agents may be useful in severe enteroviral infections.

While the cutaneous eruptions due to these viruses are quite benign, infections with enterovirus 71 can be quite severe, with the development of

brainstem encephalitis and fatal neu- rogenic pulmonary edema, as well as ascending flaccid paralysis resembling poliomyelitis. Epidemics with severe disease have been reported in Bulgaria, Hungary, Hong Kong, Japan, Australia, Malaysia, Singapore, and Taiwan; the latter had the worst epidemic, affecting more than 1 million people with 78 deaths in 1998.

Herpangina

Herpangina, a disease of children worldwide, is caused by multiple types of coxsackievirus (most frequently A8, A10, and A16), echoviruses, and enterovirus 71. In the severe outbreaks in Taiwan, 10% of the fatal cases had herpangina. It begins with acute onset of fever, headache, sore throat, dys- phagia, anorexia, and sometimes, stiff neck. The most significant finding, which is present in all cases, is of one or more yellowish-white, slightly raised 2 mm vesicles in the throat, usually surrounded by an intense areola (Fig. 44). The lesions are found most frequently on the anterior faucial pillars, tonsils, uvula, or soft palate. Only one or two lesions might appear during the course of the illness or the entire visible pharynx may be studded with them.

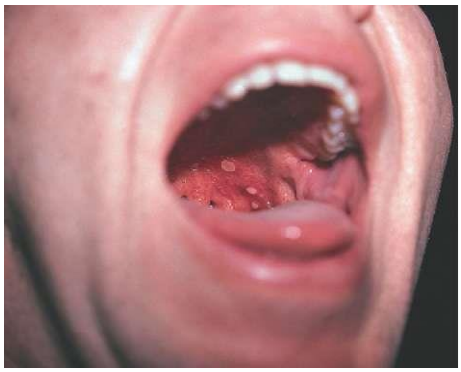


Fig. 44 Herpangina.

The lesions often occur in small clusters and later coalesce. Usually, the individual or coalescent vesicles ulcerate, leaving a shallow, punched-out, grayish-yellow crater 2-4 mm in diameter. The lesions disappear in 5-10 days. Treatment is supportive, consisting of topical anesthetics.

Herpangina is differentiated from aphthosis and primary herpetic gingivostomatitis by the location of the lesions in the posterior oropharynx and by isolation of an enterovirus. Coxsackievirus A10 causes acute lymphonodular pharyngitis, a variant of herpangina, characterized by discrete yellow- white papules in the same distribution as herpangina.

Hand-foot-and-mouth disease

Hand-foot-and-mouth disease (HFMD) is usually a mild illness. It primarily affects children from 2 to 10, but exposed adults may also develop disease. Infection begins with a fever and sore mouth. In 90% of cases oral lesions develop; these consist of small (4-8 mm), rapidly ulcerating vesicles surrounded by a red areola on the buccal mucosa, tongue, soft palate, and gingiva. Lesions on the hands and feet are asymptomatic red papules that quickly become small, gray, 3-7 mm vesicles surrounded by a red halo. They are often oval, linear, or crescentic, and run parallel to the skin lines on the fingers and toes (Fig. 45). They are distributed sparsely on the dorsa of the fingers and toes, and more frequently on the palms and soles. Especially in children who wear diapers, vesicles and erythematous, edematous papules may occur on the buttocks (Fig. 46). The infection is usually mild and seldom lasts more than a week. Treatment is supportive, with the use of oral topical anesthetics. Onychomadesis may follow enteroviral infection and HFMD, about 1 month after the acute viral syndrome.

HFMD is most frequently caused by coxsackievirus A16 and less commonly by other coxsackie viruses (A5, A7, A9, A10, B1, B3, and B5), as well as enterovirus 71. In the severe Taiwanese enterovirus 71 outbreak, 80% of cases with CNS disease had HFMD.

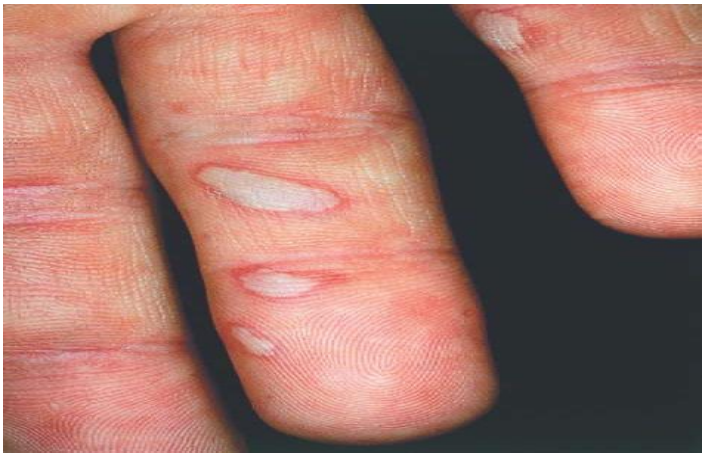


Fig. 45 Hand-foot-and-mouth disease.

No cases of HFMD associated with CNS disease were due to coxsackie A16, so the rapid discrimination of viral types may be vital in outbreaks of HFMD. The virus may be recovered from the skin vesicles. Histopathologic findings are those of an intraepidermal blister formed by vacuolar and reticular degeneration of keratinocytes similar to other viral blisters. Inclusion bodies and multinucleated giant cells are absent. HFMD is distinguished from herpangina by the distribution of the oral lesions and the presence of skin lesions. It is differentiated from erythema multiforme minor by the skin lesions, which are oval and gray, as opposed to targetoid, as in erythema multiforme. HFMD usually requires no treatment. Although the coxsackieviruses lack thymidine kinase, acyclovir has anecdotally been reported to hasten resolution of the eruption in two reports.

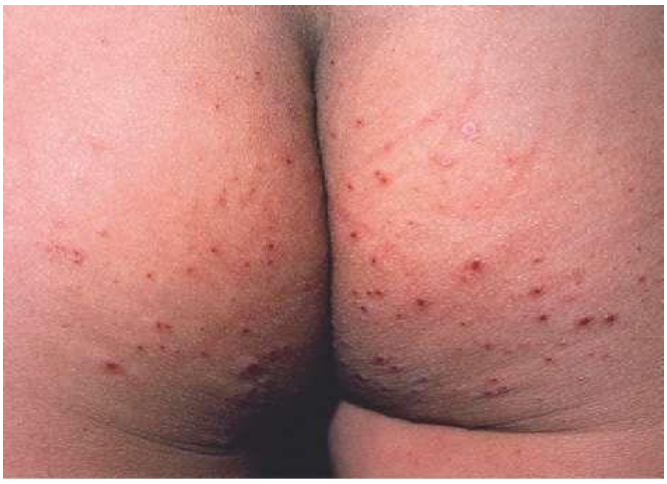


Fig. 46 Hand-foot-and-mouth disease.

Boston exanthem disease

The so-called Boston exanthem disease occurred as an epidemic in Boston and was caused by echovirus 16, a now uncommon cause of viral exanthems. The eruption consisted of sparsely scattered, pale red macules and papules. In severe cases, the lesions were morbilliform and even vesicular. The eruption was chiefly on the face, chest, and back, and in some cases on the extremities. On the soft palate and tonsils, small ulcerations like those of herpangina were noted. There was little or no adenopathy. The incubation period was 3-8 days.

Eruptive pseudoangiomatosis

Eruptive pseudoangiomatosis has been described in two clusters-in the Mediterranean region and in South Korea. It favors the summer months in both regions. The disorder is characterized by the sudden appearance of 2-4 mm blanchable red papules that resemble angiomas. In children, it is usually associated with a viral syndrome, but most affected adults have no viral symptoms. In adults, females outnumber males 2:1. The red papules blanch on pressure and are often surrounded by a 1-2 mm pale halo. Lesions often number about 10, but may be much more numerous. Most lesions appear on the exposed surfaces of the face and extremities, but the trunk may also be affected. In children, lesions are shortlived, virtually always resolving within 10 days. Lesions may last slightly longer in adults. Annual recrudescences may occur. Epidemics have been described in adults, and even healthcare workers caring for patients with eruptive pseudoangiomatosis have developed lesions. Histologically, dilated upper dermal vessels, but not increased numbers of blood vessels, with prominent endothelial cells are seen. Echoviruses 25 and 32 had been implicated in the initial reports. The occurrence in young children and the presence of miniepidemic outbreaks suggest an infectious trigger. This disorder closely resembles "erythema punctatum Higuchi," which is very common in Japan and known to be caused by *Culex pipiens pallens* bites. It appears that mosquito bites, viral infection, or enhanced insect bite reaction due to intercurrent viral infection are possible pathogenic causes of eruptive pseudoangiomatosis.

Paramyxovirus group

The paramyxoviruses are RNA viruses that range in size from 100 to 300 nm. In this group, the viral diseases of dermatologic interest are measles (rubeola) and German measles (rubella). Other viruses of this group are mumps virus, parainfluenza virus, Newcastle disease virus, and respiratory syncytial virus.

Measles

Measles is a highly infectious and potentially fatal viral infection. Highly effective two-dose vaccines are available, and when countries reach a rate of 95% vaccination, measles elimination has been achieved. However, measles remains a major health problem in many nations, including developed ones who provide immunizations to their populations. More than 12 000 cases of measles occurred in Europe in the 2-year period covering 2006-7. This epidemic is ongoing and has spurred an elimination program. Numerous hospitalizations and even deaths from measles are still occurring in these developed nations. The majority of cases are in unvaccinated persons, supporting the concept that vaccination (specifically two doses) is protective, and that these measles epidemics and deaths are preventable. Low vaccination levels exist in these countries for many reasons, some philosophical and some socioeconomic. Since the children in unvaccinated groups may share common schools, camps, and social networks, they provide a prime breeding ground for epidemics. Some developed European and Asian countries (notably Japan, with 200 000 cases annually) have not been able to achieve high immunization levels, meaning that their populations are still at risk. The lack of "herd" immunity in these nations leaves at particular risk those infants and susceptible children who cannot be immunized due to other medical conditions. In addition, the introduction of a case of measles can lead to an outbreak since many unprotected children can propagate the spread of the virus. Although cases of measles continue to be imported into the US, the high immunization rate has prevented such outbreaks. Countries with low immunization rates also serve as the source of nonendemic cases in countries with high immunization rates. In Africa

and Southeast Asia, multiple socioeconomic factors have resulted in lack of immunization. Dermatologists and pediatricians in the Americas need to be alert for cases of measles when seeing persons from these countries or unvaccinated persons from the Americas who have traveled to nations known to have ongoing measles outbreaks.

Also known as rubeola and morbilli, measles was a worldwide disease that most commonly affected children under 15 months of age. In the current epidemics, however, older children and frequently adolescents are the age group primarily affected. Measles is spread by respiratory droplets and has an incubation period of 9-12 days.

The prodrome consists of fever, malaise, conjunctivitis, and prominent upper respiratory symptoms (nasal congestion, sneezing, coryza, and cough). After 1-7 days, the exanthem appears, usually as macular or morbilliform lesions on the anterior scalp line and behind the ears. Lesions begin as discrete erythematous papules that gradually coalesce. The rash spreads quickly over the face (Fig. 47), then by the second or third day (unlike the more rapid spread of rubella) extends down the trunk to the extremities. By the third day, the whole body is involved. Lesions are most prominent and confluent in the initially involved areas and may be more discrete on the extremities. Purpura may be present, especially on the extremities, and should not be confused with "black measles," a rare, disseminated intravascular coagulation-like complication of measles. Koplik spots, which are pathognomonic, appear during the prodrome (Fig. 48). They appear first on the buccal mucosa nearest to the lower molars as 1 mm white papules on an erythematous base. They may spread to involve other areas of the buccal mucosa and pharynx. After 6-7 days the exanthem clears, with simultaneous subsidence of the fever.

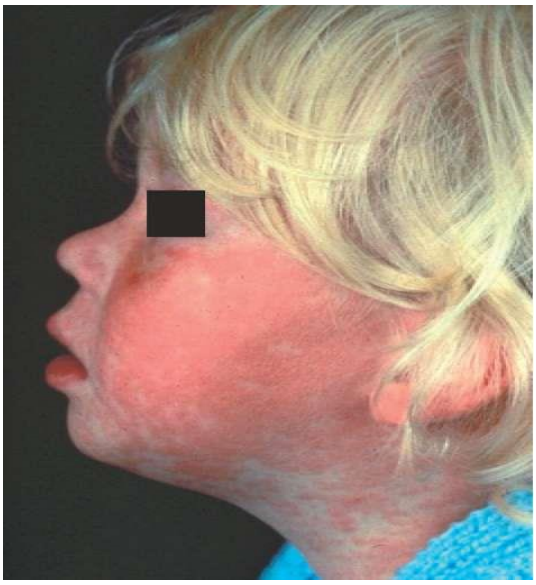


Fig. 47 Measles.

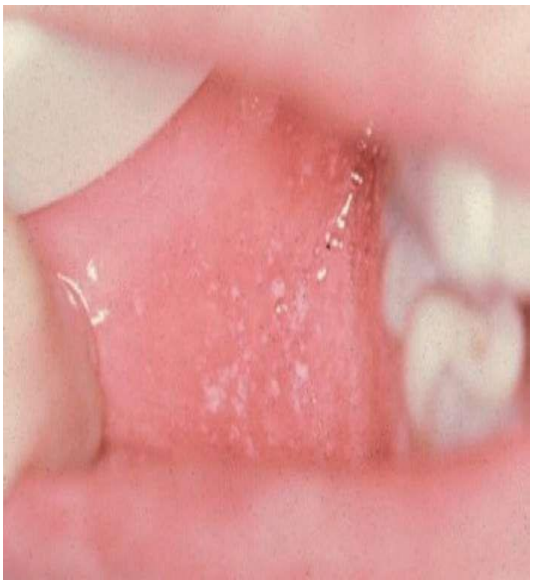


Fig. 48 Koplik spots.

Complications include otitis media, pneumonia, encephalitis, and thrombocytopenic purpura. Encephalitis, although rare (less than 1% of cases), can be fatal. Infection in pregnant patients is associated with fetal death. Complications and fatalities are more common in children who are undernourished or have T-cell deficiencies. In HIV-infected children, the exanthem may be less prominent.

Modified measles occurs in a partially immune host as a result of prior infection, persistent maternal antibodies, or immunization, and is a milder disease. Patients may have only fever, or fever and a rash. The course is shorter, the exanthem is less confluent, and Koplik spots may be absent. It is difficult to differentiate it from other viral exanthems.

A diagnosis of measles is established by the presence of a high fever, Koplik spots, the characteristic conjunctivitis, upper respiratory symptoms, and typical exanthem. Lymphopenia is common, with a decreased white blood cell count. Biopsies of skin lesions may show syncytial keratino- cytic giant cells, similar to those seen in respiratory secretions. Laboratory confirmation can be with acute and convalescent serologic tests. Identification of virus-specific IgM (5 days after the rash is present) is highly suggestive of infection in an unimmunized individual. Too early a serum IgM assay may lead to a false-negative result and the test should

be repeated. Virus isolation is also possible, but can be costly and technically challenging. The combination of IgM serological testing and virus isolation is the current gold standard. Immunofluorescence techniques can identify virus from clinical material. New PCR-based technologies can rapidly detect the measles virus genome in urine, oropharyngeal secretions, and blood, and are highly useful in modified and previously vaccinated patients. Rubella, scarlet fever, secondary syphilis, enterovirus infections, and drug eruptions are in the differential diagnosis. Administration of high doses of vitamin A will reduce the morbidity and mortality of hospitalized children with measles. Two doses of retinyl palmitate, 200 000 IU 24 h apart, are recommended for all children 6-24 months of age, immunodeficient children, children with malnutrition or evidence of vitamin A deficiency, and recent immigrants from areas of high measles mortality. Otherwise, treatment is symptomatic, with bed rest, analgesics, and antipyretics.

Live virus vaccination is recommended at 12 months, with a booster prior to entering school (4-5 years). A faint maculo- papular exanthem may occur 7-10 days after immunization. Prophylaxis should be offered to exposed susceptible persons. It must be provided within the first few days following exposure, so identification of susceptible persons is critical. Vaccination can be effective if given within 3 days of exposure and normal immune globulin at a dose of 0.25 mL/kg up to 6 days after contact. In an Australian outbreak, these strategies prevented 80% of possible secondary cases.

Rubella

Rubella, commonly known as German measles, is caused by a togavirus and probably spreads by respiratory secretions. The incubation period is 12-23 days (usually 15-21). Live virus vaccination is highly effective, providing lifelong immunity. There is a prodrome of 1-5 days consisting of fever, malaise, sore throat, eye pain, headache, red eyes, runny nose, and adenopathy. Pain on lateral and upward eye movement is characteristic. The exanthem begins on the face and progresses caudad, covering the entire body in 24 h and resolving by the third day.

The lesions are typically pale pink, morbilliform macules, smaller than those of rubeola. The eruption may resemble roseola or erythema infectiosum. An exanthem of pinhead-sized red macules or petechiae on the soft palate and uvula (Forchheimer's sign) may be seen. Posterior cervical, suboccipital, and postauricular lymphadenitis occurs in more than half of cases. Rubella is in general a much milder disease than rubeola. Arthritis and arthralgias are common complications, especially in adult women. These last a month or longer. The diagnosis is confirmed by finding rubella-specific IgM in oral fluids or the serum. This IgM develops rapidly, but 50% of sera drawn on the first day of the rash are negative. The virus is rapidly cleared from the blood, being absent by day 2 of the rash. However, the virus is found in oral secretions for 5-7 days after the rash has appeared. PCR-based techniques to identify virus in oral secretions may detect infection more effectively in earlier samples. The combination of PCR-based virus detection tests and identification of rubella virus-specific IgM will result in rapid confirmation of most cases of rubella within the first few days of appearance of disease symptoms.

Congenital rubella syndrome

Infants born to mothers who have had rubella during the first trimester of pregnancy may have congenital cataracts, cardiac defects, and deafness. Numerous other manifestations, such as glaucoma, microcephaly, and various visceral abnormalities, may emerge. Among the cutaneous expressions are thrombo-cytopenic purpura; hyperpigmentation of the navel, forehead, and cheeks; bluish-red, infiltrated, 2-8 mm lesions ("blueberry muffin" type), which represent dermal erythropoiesis; chronic urticaria; and reticulated erythema of the face and extremities.

Asymmetric periflexural exanthem of childhood (APEC)

This clinical syndrome, also known as unilateral laterothoracic exanthem, occurs primarily in the late winter and early spring, and appears to be most common in Europe. It affects girls more often than boys (1.2-2 : 1). It occurs in children 8 months to 10 years of age, but most cases are between 2 and 3 years of

age. Multiple cases have been reported in adults from Europe and China. Its cause is unknown, but a viral origin has been proposed, since it occurs in young children and is seasonal, and secondary cases in families have been reported. No reproducible viral etiology has been implicated; however, at least three cases attributed to parvovirus B19 have been reported. Clinically, two-thirds to three-quarters of affected children have symptoms of a mild upper respiratory or gastrointestinal infection, usually preceding the eruption. The lesions are usually discrete 1 mm erythematous papules that coalesce to poorly marginated morbilliform plaques. Pruritus is usually present, but mild. Lesions begin unilaterally close to a flexural area, usually the axilla (75% of cases). Spread is centrifugal, with new lesions appearing on the adjacent trunk and proximal extremity. Normal skin may intervene between lesions. The contralateral side is involved in 70% of cases after 5-15 days, but the asymmetrical nature is maintained throughout the illness. Lymphadenopathy of the nodes on the initially affected side occurs in about 70% of cases. The syndrome lasts 2-6 weeks on average, but may last more than 2 months, and resolves spontaneously. Topical steroids and oral antibiotics are of no benefit, but oral antihistamines may help associated pruritus. Histologically, a mild to moderate lymphocytic (CD8+ T-cell) infiltrate surrounds and involves the eccrine ducts but not the secretory coils. There may be an accompanying interface dermatitis of the upper eccrine duct and adjacent epidermis.

Parvovirus group

Parvovirus B19 is the most common agent in this erythrovirus genus to cause human disease. Infection is worldwide, occurring in 50% of persons by age 15. The vast majority of elderly adults are seropositive. Infections are more common in the spring in temperate climates. Epidemics in communities occur about every 6 years. The virus is spread via the respiratory route and infection rates are very high within households. Most infections are asymptomatic. The propensity for parvo- virus B19 to affect the bone marrow is reflected by the presence of thrombocytopenia or leukopenias during the acute infection.

Parvovirus B19 is the prototype for the concept, "One virus, many exanthems." Erythema infectiosum and papular purpuric gloves and socks syndrome are both strongly associated with parvovirus B19 infection. Parvovirus B19 may also play a role in some cases of Gianotti-Crosti syndrome and APEC. Other known complications of this viral infection include arthropathy (especially in middle-aged females), aplastic crisis in hereditary spherocytosis and sickle cell disease, and chronic anemia in immunosuppressed patients. Infection of a pregnant woman leads to transplacental infection in 30% of cases and a fetal loss rate of 5-9%. Acute viral myocarditis and pericarditis are frequently secondary to parvovirus B19 infection.

Erythema infectiosum (fifth disease)

Erythema infectiosum is a worldwide benign infectious exan- them that occurs in epidemics in the late winter and early spring. In normal hosts (but not immunosuppressed or sickle- cell patients in crisis), viral shedding has stopped by the time the exanthem appears, making isolation unnecessary. The incubation period is 4-14 days (average 7 days). Uncommonly, a mild prodrome of headache, runny nose, and low-grade fever may precede the rash by 1 or 2 days.

Erythema infectiosum has three phases. It begins abruptly with an asymptomatic erythema of the cheeks, referred to as slapped cheek. The erythema is typically diffuse and macular, but tiny translucent papules may be present. It is most intense beneath the eyes and may extend over the cheeks in a butterfly- wing pattern. The perioral area, lids, and chin are usually unaffected. After 1-4 days the second phase begins, consisting of discrete erythematous macules and papules on the proximal extremities and later the trunk. This evolves into a reticulate or lacy pattern (Fig. 49). These two phases typically last 5-9 days. A characteristic third phase is the recurring stage. The eruption is markedly reduced or invisible, only to recur after the patient is exposed to heat (especially when bathing) or sunlight, or in response to crying or exercise. About 7% of children with erythema infectiosum have arthralgias, whereas 80% of adults have joint involvement. Necrotizing

lymphadenitis may also occur in the cervical, epitrochlear, supracla- vicular, and intra-abdominal lymph nodes. Children with aplastic crisis due to parvovirus B19 usually do not have a rash. However, even healthy children can develop significant bone marrow complications, albeit transient and self-limited.

Papular purpuric gloves and socks syndrome

This syndrome, which is less common than erythema infectio- sum, occurs primarily in teenagers and young adults. Pruritus, edema, and erythema of the hands and feet appear, and a fever is present. The lesions are sharply cut off at the wrists and ankles (Fig. 50). Over a few days they become purpuric.

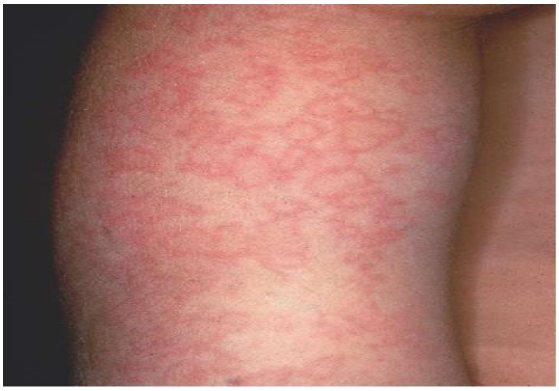


Fig. 49 Erythema infectiosum.

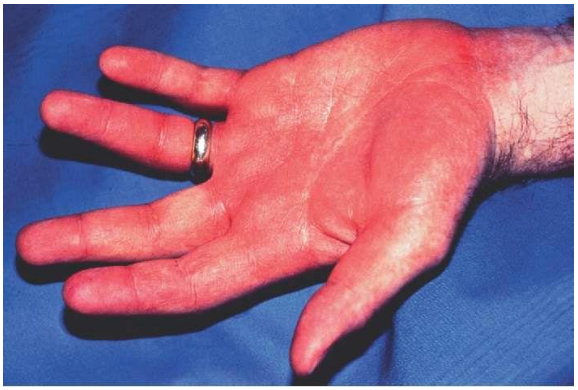


Fig. 50 Purpuric socks syndrome.

Here is a mild erythema of the cheeks, elbows, knees, and groin folds. Lesions in the groin may become purpuric. Oral erosions, shallow ulcerations, aphthous ulcers on the labial mucosa, erythema of the pharynx, Koplik spots, or petechial lesions may be seen on the buccal or labial mucosa. The lips may be red and swollen. Vulvar edema and erythema accompanied by dysuria may be seen. An unusual variant is a unilateral petechial and erythematous eruption of the axilla. The acral erythema may rarely move proximally along lymphatics, simulating a lymphangitis. Transient lymphocytopenia, a drop in platelet count, and elevation of liver function tests may be seen. The syndrome resolves within 2 weeks. Evidence of seroconversion for parvovirus B19 has been found in most reported patients. Histologically, there is a dermal infiltrate of CD30+ T lymphocytes surrounding the upper dermal vessels.

here is an interface component and prominent extravasation of red blood cells in petechial lesions. Parvovirus B19 antigen has been found in the endothelial cells, sweat glands and ducts, and epidermis in three patients. In HIV-infected patients who develop papular purpuric gloves and socks syndrome (PPGSS), the eruption is more persistent (lasting 3 weeks to 4 months) and is associated with anemia.

ot all cases of PPGSS are caused by parvovirus B19. In adults, it may be associated with HBV infection. In children the syndrome occurs at an average age of 23 months. The eruption lasts an average of 5 weeks. In children CMV and EBV are the most common documented causes in Taiwan, where this syndrome appears to be very common in the last quarter of the year.

Ther skin findings attributed to parvovirus B19

n some cases the exanthem of parvovirus B19 affects primarily the flexural areas, especially the groin. This may present as APEC (see above), petechiae in the groin, or an erythema studded with pustules in the groin and to a lesser degree in the axillae, resembling baboon syndrome. The petechial eruption of PPGSS may also involve the perioral area and has been termed the "acropetechial syndrome." An outbreak in Kerala, India, described 50 children mostly under the age of 2 years, who presented with high fever and a diffuse, intensely erythematous, tender skin eruption. The children were very irritable and cried when held. The skin was markedly swollen. Whole-body edema was present. The acute exanthem was followed by diffuse desquamation. There were no secondary cases. IgM for parvovirus B19 was detected in 15 of 24 cases tested. This was termed "red baby syndrome" by the authors. Infection with parvovirus B19 may trigger a hemophagocytic (or macrophage activation) syndrome. This presents with progressive cytopenias, liver dysfunction, coagulopathy, high fer- ritin, and hemophagocytosis. Numerous nonspecific eruptions have been described with hemophagocytic syndrome, including nodules, ulcers, purpura, and panniculitis. The diagnostic hemophagocytic cells may occasionally be identified in skin

biopsies. Infection with parvovirus B19 may lead to cutaneous necrosis in persons with a hypercoagulable state, such as paroxysmal nocturnal hemoglobinuria.

Rbovirus group (togaviridae)

The arboviruses comprise the numerous arthropod-borne RNA viruses. These viruses multiply in vertebrates, as well as in arthropods. The vertebrates usually act as reservoirs and the arthropods as vectors of the various diseases.

Est Nile fever

West Nile virus (WNV) is a flavivirus that is endemic in East Africa. It first appeared in eastern North America in 1999 and reached California by 2004. It is primarily an infection of the crow family (crows, ravens, magpies, and bluejays). It is spread by *Culex* mosquitoes. Approximately 80% of infected persons will have no symptoms. After an incubation period of 3-15 days, a febrile illness of sudden onset occurs. Headache, myalgia, arthralgia, conjunctivitis, pharyngitis, cough, aden- opathy, abdominal pain, hepatitis, pancreatitis, and myocarditis are recognized clinical manifestations. The primary complications, however, are neurologic disease, including seizures (10% of symptomatic adults), ascending flaccid paralysis (like poliomyelitis), ataxia, meningitis, encephalitis, myelitis, cranial neuropathies, optic neuritis, and reduced level of consciousness. A significant percentage of affected persons are left with permanent neurologic sequelae. About 20% of hospitalized patients will have an exanthem. It is nonpruritic and composed of 50-100 erythematous, ill-defined macules 0.51 cm in diameter, primarily on the trunk and proximal extremities. It lasts 5-7 days and resolves without scaling.

Andfly fever

Sandfly fever is also known as phlebotomus fever and pappataci fever. The vector, *Phlebotomus papatasii,* is found in the Mediterranean area (Sicilian, Naples, and Toscana virus), Russia, China, and India. While Sicilian and Naples sandfly fever viral infections disappeared or dramatically decreased with mosquito

eradication programs, Toscana virus infection is still common. While most infected persons are asymptomatic, 80% of aseptic meningitis cases in the summer in endemic areas are due to this agent. Small pruritic papules appear on the skin after the sandfly bite and persist for 5 days. After an incubation period of another 5 days, fever, headache, malaise, nausea, conjunctival injection, stiff neck, and abdominal pains suddenly develop. The skin manifestations consist of a scarlatiniform eruption on the face and neck. Recovery is slow, with recurring bouts of fever. No specific treatment is available.

Dengue

More than 100 million cases of dengue occur annually worldwide, and the global prevalence is growing. In European hospitals evaluating patients with fever following trips to the tropics, dengue is the most common febrile illness in travelers returning from Southeast Asia who develop a fever within 1 month of the trip. It is transmitted by *Aedes* mosquitoes, which have adapted well to living around humans in urban environments. It affects primarily tropical regions where temperatures rarely drop below 20°C, favoring the reproduction of the mosquito vector. While Southeast Asia and the Western Pacific are most severely affected, India, Cuba, and the tropical Americas also have numerous cases. Persons of African ancestry appear to be at much decreased risk of developing dengue.

Dengue fever begins 2-15 days after the infectious mosquito bite. The clinical features are characteristic and consist of the sudden onset of high fevers accompanied by myalgias, headache, retro-orbital pain, and severe backache (breakbone fever). Common associated laboratory findings include elevated liver function tests (to about 3 times normal, on average), thrombocytopenia (platelet count below 100 000 in 50% of cases), and a leukopenia. These are present during the acute illness and help to suggest dengue as the correct diagnosis. About 50% of patients will develop a characteristic skin eruption. In 90% of patients, the eruption begins between days 3 and 5 of the illness, often as the fever defervesces. The skin eruption occurs in less than 10% of patients prior to the onset of fever.

The eruption is most commonly generalized (50%), or involves only the extremities (30%) or the trunk (20%). Lesions are macular or morbilliform, and are usually confluent, characteristically sparing small islands of normal skin—"islands of white in a sea of red" (Fig. 51). Facial flushing may be prominent.

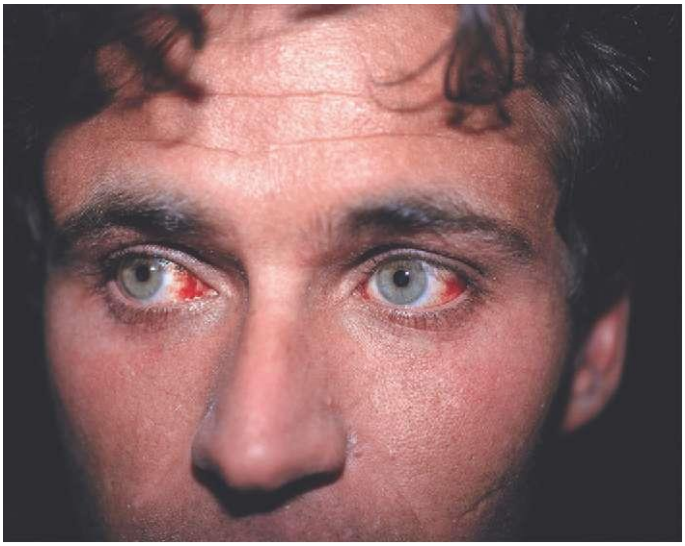


Fig. 51 Dengue.

The rash is either asymptomatic or mildly pruritic. Petechiae may be present, but the finding of cutaneous hemorrhage should raise the suspicion of dengue hemor- rhagic fever/dengue shock syndrome (DHF/DSS; see below). Complete recovery occurs in 7-10 days. Biopsy of the exan- them shows minimal findings and is of no value in predicting the severity of the patient's condition, or in identifying DHF/ DSS.

There are four serotypes of dengue. Following infection with one serotype, the individual is resistant to reinfection with that serotype. However, if that person becomes infected with another serotype, he/she is at risk of developing severe complications from the second episode of dengue. The patient's antidengue antibodies are incapable of preventing infection by or replication of the new dengue virus type. However, they do trigger increased viral phagocytosis by mononuclear cells and amplified cytokine production. The syndrome that results is characterized by hemorrhage (dengue hemorrhagic fever/ DHF), at times with extensive plasma leakage (dengue shock syndrome/DSS). The fatality rate for DSS may be as high as 40%. DHF/DSS have been clearly defined by the World Health

Organization (WHO). Persons with sickle-cell disease are at particular risk of developing DSS and death. DHF grade I presents with findings of dengue with thrombocytopenia, and a positive tourniquet test. Scrotal edema may be present. DHF grade II is DHF grade I plus spontaneous bleeding, most commonly into the skin, conjunctiva (20%), and oral cavity. DSS is grade II DHF plus circulatory failure (hypotension) and agitation. DSS may progress to grade IV, which is grade III plus profound shock (a blood pressure of 0). Only one-third of patients with DHF/DSS will have skin lesions, so their absence does not exclude the diagnosis.

The diagnosis of dengue is made by detection of dengue- specific IgM in the sera by ELISA, by acute and convalescent serologies demonstrating seroconversion. Some laboratories can detect viral RNA in acute serum samples. Given the theoretical risk of increasing DHF/DSS cases by immunizing persons against a single dengue virus type if they were to be exposed to another type, a quadrivalent vaccine would seem prudent. It has not been developed, so travelers' only preventive strategy is to avoid mosquito bites. In children, dengue fever and Kawasaki disease have occurred simultaneously. Since these two syndromes may be nearly identical in their presentation, this differential diagnosis can be extremely difficult. When both diagnoses have been made simultaneously, it was because there was persistent fever (beyond 1 week), a reactive thrombocytosis following the initial thrombocyto- penia, and in some cases the development of characteristic cardiac lesions.

Alphavirus

In Finland, Sindbis virus infection is transmitted by the *Culiseta* mosquito. An eruption of multiple, erythematous, 2-4 mm papules with a surrounding halo is associated with fever and prominent arthralgias. The eruption and symptoms resolve over a few weeks. Histologically, the skin lesions show a perivascular lymphocytic infiltrate with large atypical cells, simulating lymphomatoid papulosis. CD30 does not stain the large cells, however, allowing their distinction.

Chikungunya virus is transmitted by the *Aedes* mosquito. Chikungunya is from the Makonde language of sub-Saharan Africa and means "that which bends up," describing the characteristic stooped posture due to the joint symptoms of the disease. It is endemic in Africa, India, Sri Lanka, Southeast Asia, the Philippines, Hong Kong, and the islands of the Indian Ocean. The incubation period is 2-7 days. The patient presents with the abrupt onset of high fever. Significant joint symptoms are characteristic and occur in 40% of infections. Most typically, there is swelling and pain in the small joints of the hands and feet. The joint symptoms may persist for weeks to months, with about 50% still having some symptoms at 6 months. Patients may develop neuropathic acral findings, including Raynaud, erythromelalgia, or severe acral coldness, as late sequelae. Headache occurs in 70% of patients, and nausea and vomiting in 60%. Lymphopenia, thrombocytopenia, and elevated liver function tests can be observed in the first week of the illness. While generally a nonfatal and selflimited illness, severe complications can occur, resulting in death in about 1 in 1000 infected persons.

About one-half to threequarters or more of patients with Chikungunya virus infection develop a rash. It is pruritic in 20-50% of the patients. The most common and characteristic exanthem is described as morbilliform, and most frequently affects the arms, upper trunk, and face. It can be confluent and islands of sparing can be seen. It appears by the second day of the fever in more than half of patients, and in another 20% on the third or fourth day; only about one-fifth develop the eruption after the fifth day of the illness. Ecchymoses may appear during the acute illness. Aphthous-like ulcerations can occur in the oral, penoscrotal, and less commonly the axillary regions. These may be preceded by intense erythema and pain in the affected area. Following acute Chikungunya infection, hyperpigmentation of the skin may occur.

A bullous eruption may occur in acute Chikungunya virus infection. Ninety percent of those with a bullous eruption are under 1 year of age, and most of the severe bullous eruption cases occur in children under the age of 6 months. Seventeen percent of children develop a vesiculobullous component to their

eruption, compared to only 3% of adults. There is an initial exanthem, followed in hours or days by flaccid or tense nonhemorrhagic blisters that rupture easily. Nikolsky's sign is positive. The genitalia, palms, and soles are spared. There is a close resemblance to toxic epidermal necrolysis (TEN) and up to 80% of the total body surface area may become denuded. High titers of virus are recovered from blister fluid (in excess of what is present in blood). Biopsy demonstrates an intra-epidermal blister with acantholytic cells free-floating in the blister cavity. These patients are managed like burn patients and most recover. Skin grafting is usually not required.

The diagnosis of Chikungunya virus infection is made by detecting virus-specific IgM in the serum. Confirmation is with seroconversion over the next several months, with development of virus-specific IgG. PCR-based methods may detect viral genome in the blisters or serum during the acute illness.

It may be quite difficult to differentiate dengue fever from Chikungunya fever, since they are both endemic in the same geographic regions, and their clinical symptoms and laboratory findings are quite similar. Arthralgias occur in a significant percentage of patients with Chikungunya virus infection (approaching 100% of those with a rash), and are rare in patients with dengue. Neutropenia is seen in 80% of dengue patients and only 10% of Chikungunya patients. A positive tourniquet test does not distinguish these two infections, but thrombocytopenia is more common in dengue (85+%) as compared with Chikungunya (35%).

Papovavirus group

Papovaviruses are double-stranded, naked DNA viruses characterized as slow-growing. They replicate inside the nucleus. Because they contain no envelope, they are resistant to drying, freezing, and solvents. In addition to the human papillomaviruses (HPVs), which cause warts, papillomaviruses of rabbits and cattle, polyomaviruses of mice, and vacuolating viruses of monkeys are some of the other viruses in this group.

Warts (verruca)

There are more than 100 types of HPV. The genome of HPV consists of early genes *(E1, E2, E4, E5, E6,* and E7), two late genes *(L1* and L2), and in between an upstream regulatory region (URR). *L1* and *L2* code for the major and minor capsid proteins. A new HPV type is defined when there is less than 90% DNA homology with any other known type in the *L1* and *E6* genes. Viruses with 90-98% homologies are classified as subtypes. The gene sequences from HPVs throughout the world are similar. Most HPV types cause specific types of warts and favor certain anatomic locations, such as plantar warts, common warts, genital warts, and so on. Some wart types, e.g. HPV-27, may be found in several different locations. A large proportion of the HPV types rarely cause warts and appear to be pathogenic only in immunosuppressed patients or those with epidermodysplasia verruciformis. However, many persons may carry or be latently infected with these rare wart types, explaining the uniformity of gene sequence and clinical presentation all over the world. In the setting of immunosuppression, HPV types may cause warty lesions of a different clinical morphology than they would cause in an immunocompetent host. Infection with HPV may be clinical, subclinical, or latent. Clinical lesions are visible by gross inspection. Subclinical lesions may be seen only by aided examination (e.g. the use of acetic acid soaking). Latent infection describes the presence of HPV or viral genome in apparently normal skin. Latent infection is thought to be common, especially in genital warts, and explains in part the failure of destructive methods to eradicate warts. HPV infection is very common, as most people will experience infection during their lifetime. In schoolchildren in Australia, 22% were found to have nongenital cutaneous warts, with 16% having common warts, 6% having plantar warts, and 2% having flat (plane) warts. In the UK, the prevalence has been reported at between 4% and 5%. The peak age for cutaneous warts is in the teenage and early adult years, when infection rates reach 25% in some studies. White persons have visible cutaneous warts twice as frequently as other ethnicities. Genital warts begin to appear with sexual activity, and infection rates, including latent infection,

exceed 50% in sexually active populations in many parts of the world. HPVs have coexisted with humans for many millennia, and humans are their primary host and reservoir. HPVs have been successful pathogens of human because they evade the human immune response. This is primarily by avoiding expressing antigens on the surface of keratinocytes until the keratinocytes are above the level of the antigen-presenting cells in the epidermis. They also reduce Langerhans cells in the vicinity of infection. Through *E6* and *E7,* HPV reduces local production of key immune reactants such as TLR9 and IL-8, muting the local immune response. HPVs thus live in equilibrium with their human hosts through a combination of immune evasion and programmed immune suppression (tolerance). Management of warts is based on their clinical appearance, their location, and the immune status of the patient. In general, warts of all types are more common and more difficult to treat in persons with suppressed immune systems. Except in WHIM syndrome (warts, hypogammaglobulinemia, infection, and myelokathexis), syndromes of reduced immunoglobulin production or B-cell function are not associated with increased HPV infection. However, situations where cell-mediated immunity is suppressed are associated with high rates of clinical HPV infection and HPV-induced neoplasias. The common clinical scenarios are iatrogenic medications (as in organ transplant recipients), viral infections that damage T cells (such as HIV), and congenital syndromes of T-cell immunodeficiency. WILD syndrome is the association of primary lymphedema, disseminated warts and anogenital dysplasia with depressed cell-mediated immunity. HPV 57 is present in the skin warts and multiple warts types are found in the genital lesions (HPV types 6, 51, 52, 61, 84). Because warts in some settings are important cofactors in cancer, histologic evaluation of warty lesions in these situations may be important.

Verruca vulgaris

Common warts are a significant cause of concern and frustration on the part of the patient (Figs 52 and 53). Social activities can be affected, lesions can be uncomfortable or bleed, and treatment is often painful and frustratingly ineffective.

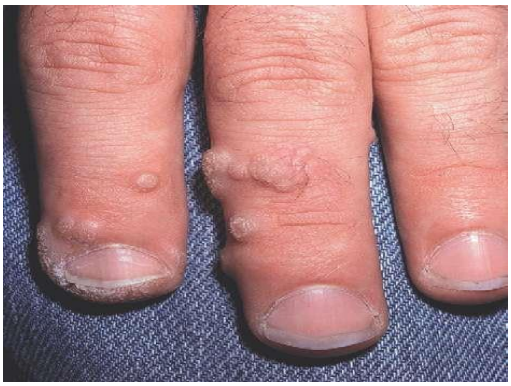


Fig. 52 Verruca vulgaris. **Fig. 53** Verruca, nail biter with periungual warts.

HPV-1, 2, 4, 27, 57, and 63 cause common warts. Common warts occur largely between the ages of 5 and 20, and only 15% occur after the age of 35. Frequent immersion of hands in water is a risk factor for common warts. Meat handlers (butchers), fish handlers, and other abattoir workers have a high incidence of common warts of the hands. The prevalence reaches 50% in those persons with direct contact with meat. Warts in butchers are caused by HPV-2 and 4, and up to 27% of hand warts from butchers are due to HPV-7. HPV-7 is very rarely found in warts in the general population (less than 0.3%), and in butchers it is found only on the hands where there is direct contact with meat. The source of HPV-7 is unknown, but HPV-7 is not bovine papillomavirus and does not come from the slaughtered animals. HPV-57 has been reported to cause dystrophy of all 10 fingernails, with marked subungual hyperkeratosis and destruction of the nail plate without periungual involvement.

The natural history of common warts is for them to resolve spontaneously. Reported clearance rates in children are 23% at 2 months, 30% at 3 months, 65-78% at 2 years, and 90% over 5 years. Common warts are usually located on the hands; they favor the fingers and palms. Periungual warts are more common in nail biters and may be confluent, involving the proximal and lateral nailfolds. Fissuring may lead to bleeding and tenderness. Lesions range in size from pinpoint to more than 1 cm, most averaging about 5 mm. They grow in size for weeks to months and usually present as elevated, rounded papules with a rough, grayish surface,

which is so characteristic that it has given us the word verrucous, used to describe lesions with similar surface character (e.g. seborrheic keratosis). In some instances, a single wart (mother wart) appears and grows slowly for a long time, and then suddenly many new warts erupt. On the surface of the wart, tiny black dots may be visible, representing thrombosed, dilated capillaries. Trimming the surface keratin makes the capillaries more prominent and may be used as an aid in diagnosis. Warts do not have dermatoglyphics (fingerprint folds), as opposed to calluses, in which these lines are accentuated.

Common warts may occur anywhere on the skin, apparently spreading from the hands by autoinoculation. In nail biters, warts may be seen on the lips and tongue, usually in the middle half, and uncommonly in the commissures. Digitate or filiform warts tend to occur on the face and scalp, and present as single or multiple spikes stuck on the surface of the skin.

Pigmented warts

Pigmented warts have commonly been reported in Japan. They appear on the hands or feet, and resemble common warts or plantar warts, except for their hyperpigmentation. They are caused by HPV-4, 65, and 60. The pigmentation is due to melanocytes in the basal cell layer of the HPV-infected tissue, which contain large amounts of melanin. This is proposed to be caused by "melanocyte blockade" or the inability of the melanocytes to transfer melanin to the HPV-infected cells.

Flat warts (verruca plana)

HPV-3, 10, 28, and 41 most often cause flat warts. Children and young adults are primarily affected. Sun exposure appears to be a risk factor for acquiring flat warts. They are common on swimmers and on the sun-exposed surfaces of the face and lower legs. Flat warts present most typically as 2-4 mm flat- topped papules that are slightly erythematous or brown on pale skin and hyperpigmented on darker skin. They are generally multiple and are grouped on the face, neck, dorsa of the hands, wrists, elbows, or knees (Fig. 19-45). The forehead, cheeks,

and nose, and particularly the area around the mouth and the backs of the hands are the favorite locations. In men who shave their beards and in women who shave their legs, numerous flat warts may develop as a result of autoinocula- tion. A useful finding is the tendency for the warts to Koebnerize, forming linear, slightly raised, papular lesions. Hyperpigmented lesions occur, and when scarcely elevated, may be confused with lentigines or ephelides. Plaque-like lesions may be confused with verrucous nevus, lichen planus, and molluscum contagiosum. When lesions occur only on the central face and are erythematous, they can be easily confused with papular acne vulgaris. Of all clinical HPV infections, flat warts have the highest rate of spontaneous remission.

Plantar warts (verruca plantaris)

HPV-1, 2, 4, 27, and 57 cause plantar warts. These warts generally appear at pressure points on the ball of the foot, especially over the mid-metatarsal area.

They may, however, be anywhere on the sole. Frequently, there are several lesions on one foot. Sometimes they are grouped or several contiguous warts fuse so that they appear as one. Such a plaque is known as a mosaic wart. The soft, pulpy cores are surrounded by a firm, horny ring. Over the surface of the plantar wart, most clearly if the top is shaved off, multiple small black points may be seen that represent dilated capillary loops within elongated dermal papillae. Plantar warts may be confused with corns or calluses, but have a soft central core and black or bleeding points when pared down, features that calluses do not have.

The myrmecia type of verruca occurs as smooth-surfaced, deep, often inflamed and tender papules or plaques, mostly on the palms or soles, but also beside or beneath the nails, or, less often, on the pulp of the digits (Fig. 54). They are distinctively dome-shaped and much bulkier beneath the surface than they appear. Myrmecia are caused by HPV-1. They can be mistaken for a paronychia or digital mucinous cyst.

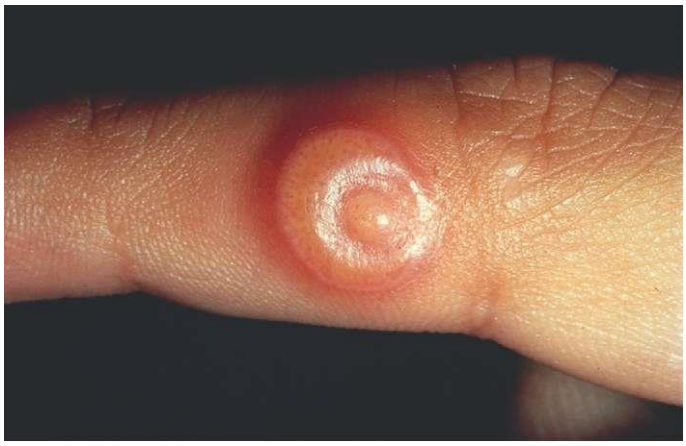


Fig. 54 Myrmecia.

HPV-60 causes a peculiar type of plantar wart called a ridged wart because of the persistence of the dermatoglyphics across the surface of the lesion. Typically, the warts are slightly elevated, skin-colored, 3-5 mm papules. They occur on non- weight-bearing areas and lack the typical features of plantar warts. HPV-60 also causes plantar verrucous cysts, 1.5-2 cm, epithelium-lined cysts on the plantar surface. These cysts tend to occur on weight-bearing areas, suggesting that HPV- infected epidermis is implanted into the dermis, forming the cyst. It is common to see ridged warts near plantar verrucous cysts.

Histologic features

Typical nongenital warts rarely require histologic confirmation. A biopsy may be useful in several settings, however. Histology can be used to distinguish warts from corns and other keratotic lesions that they resemble. This is enhanced by immunoperoxidase staining for HPV capsid antigen. Cytologic atypia and extension into the dermis suggest the diagnosis of an HPV-induced squamous cell carcinoma. There is a correlation between HPV type and the histologic features of the wart, allowing identification of the HPV types that cause specific lesions, a useful feature in the diagnosis of epidermodysplasia verruciformis, for example.

Treatment

The form of therapy used depends on the type of wart being treated, age of the patient, and previous therapies used and their success or failure. With any

treatment modality at least 2 or 3 months of sustained management by that method is considered a reasonable therapeutic trial. Do not abandon any treatment too quickly. Since many nongenital warts will spontaneously regress, the treatment algorithm should allow for nonaggressive options and the patient should be offered the option of no treatment. Indications for treatment are pain, interference with function, social embarrassment, and risk of malignancy. Aims of therapy are:

- to remove the wart
- not to produce scarring
- to induce lifelong immunity to prevent recurrence.

There are very few controlled studies on the treatment of cutaneous warts, so the evidence for all forms of treatment except cryotherapy is fair to poor.

Flat warts

Flat warts frequently undergo spontaneous remission, so therapy should be as mild as possible and potentially scarring therapies should be avoided. If lesions are few, light cryo- therapy is a reasonable consideration. Topical salicylic acid products can also be used. Treatment with topical tretinoin once or twice a day, in the highest concentration tolerated to produce mild erythema of the warts without frank dermatitis, can be effective over several months. Tazarotene cream or gel may also be effective. Imiquimod 5% cream used up to once a day can be effective. If the warts fail to react initially to the imiquimod, tretinoin may be used in conjunction. Should this fail, 5-FU cream 5%, applied twice a day, may be very effective. Anthralin, although staining, could be similarly used for its irritant effect. For refractory lesions, laser therapy in very low fluences or photodynamic therapy might be considered before electrodesiccation because of the reduced risk of scar- ring. Ranitidine, 300 mg twice a day, cleared 56% of refractory flat warts in one study. Cimetidine alone or with levamisole may be considered. Topical immunotherapy with dinitrochlo- robenzene (DNCB), squaric acid, or dyphencyprone, or intra- lesional *Candida* antigen injections, can be used on limited areas of flat warts. The induced dermatitis requires careful dose monitoring when treating facial lesions.

Common warts

Treatments for common warts involve two basic approaches: destruction of the wart and induction of local immune reactions (immunotherapy). Destructive methods are most commonly used as initial therapy by most practitioners. Cryotherapy is a reasonable first-line therapy for most common warts. The wart should be frozen adequately to produce a blister after 1 or 2 days. This correlates with a thaw time of 30-45 s for most common warts. A sustained 10 s freeze with a spray gun was found to be more effective than simply freezing to obtain a 2-3 mm halo around the wart. Aggressive cryotherapy can produce significant blistering and may be complicated by significant postprocedural pain for several days. Berth-Jones et al found that a single freeze-thaw cycle was as effective as two cycles. The ideal frequency of treatment is every 2 or 3 weeks, just as the old blister peels off. A spray device, while more costly, is quicker, and cannot spread infectious diseases (especially viral hepatitis) from one patient to the next. Children may be frightened by such a device, so a cotton-tipped swab is an option for them. Cryotherapy can be effective for periungual warts. Damage to the matrix is unusual or rare, since periungual warts usually affect the lateral nailfolds, not the proximal one. Complications of cryo- therapy include hypopigmentation, uncommonly scarring, and rarely, damage to the digital nerve from freezing too deeply on the side of the digit. Patients with Fanconi anemia, cryoglobulinemia, poor peripheral circulation, and Raynaud may develop severe blisters when cryotherapy is used to treat their warts. Doughnut warts, with central clearing and an annular recurrence, may complicate cryotherapy.

Products containing salicylic acid with or without lactic acid are effective patient-applied treatments; these have an efficacy comparable to that of cryotherapy. After the wart-affected area is soaked in water for 5-10 min, the topical medication is applied, allowed to dry, and covered with a strip bandage for 24 h. This is repeated daily. The superficial keratinous debris may be removed by scraping with a table knife, pumice stone, or emery board.

A small amount of cantharone (0.7% cantharidin) is applied to the wart, allowed to dry, and covered for 24 h. A blister, similar to that produced by cryotherapy, develops in 24-72 h. These blisters may be as painful as or more painful than those following cryotherapy. Treatment is repeated every 2-3 weeks. Perhaps more than any other method, there is a tendency for cantharidin to produce doughnut warts, a round wart with a central clear zone at the site of the original wart. None the less, this agent is a very useful adjunct in the management of difficult-to-treat verrucas.

Simple occlusion with a relatively impermeable tape can be effective in eradicating warts. The key appears to be to keep the wart occluded as much of the time as possible. Duct tape, moleskin, or transparent tape (Blenderm) is a practical option. Fenestrated and semipermeable dressings have not been studied and may not be effective. This is a good initial option for children and others unwilling to have other forms of treatment. Unfortunately, in adults, the efficacy of duct tape for common warts is very low. Two months of treatment resolved common warts in only 20% of patients, and 75% of "resolved" warts recurred.

Bleomycin has high efficacy and is an important treatment for recalcitrant common warts. It is used at a concentration of 1 U/mL, which is injected into and immediately beneath the wart until it blanches. The multiple puncture technique of Shelley-delivering the medication into the wart by multiple punctures of the wart with a needle through a drop of bleomycin-may also be used, as may an air jet injector. For small warts (less than 5 mm), 0.1 mL is used; 0.2 mL is used for larger warts. The injection is painful enough to require local anesthesia in some patients. Pain can occur for up to 1 week. The wart becomes black, and the black eschar separates in 2-4 weeks. Treatment may be repeated every 3 weeks, but it is unusual for common warts to require more than one or two treatments. Scarring is rare. Response rates vary by location, but average 90% with two treatments for most common, nonplantar warts, even periungual ones. Treatment of finger warts with bleomycin may uncommonly be complicated by localized Raynaud phenomenon of treated fingers. Bleomycin treatment of digital warts may rarely

result in digital necrosis and permanent nail dystrophy, so extreme caution should be used in treating warts around the nailfolds. Lymphangitis/cellulitis is a rare complication. In a patient receiving a total of 14 U for plantar warts, flagellate urticaria followed by characteristic bleomycin flagellate hyperpigmen- tation occurred.

Surgical ablation of warts can be effective treatment, but even complete destruction of a wart and the surrounding skin does not guarantee that the wart will not recur. Surgical methods should be reserved for warts that are refractory to more conservative approaches. Pulsed dye laser therapy appears to have similar efficacy to cryotherapy. With pulsed dye laser therapy less plume is produced than with CO_2 laser therapy. Depending on the fluences used, the treatment can be performed in two-thirds of patients without anesthesia, although some pain occurs. The energy setting is dependent on the particular device being used. The energy may be as low as 7 J/cm^2 for thinner lesions and up to 15 J/cm^2 for more hyperkeratotic ones. A short pulse duration (0.45 ms) is most effective. A 5 or 7 mm spot size is used and treatment is extended 2 mm beyond the visible wart. Immediately after treatment, the skin has a gray-black discoloration, which evolves to an eschar over 10-14 days. Treatment is repeated every 2-4 weeks and up to five treatments may be required. In immunocompetent patients, response rates for refractory warts range from 70% to 90%. CO_2 laser destruction requires local anesthesia, causes scarring, and may lead to nail dystrophy. Its efficacy is between 56% and 81% in refractory warts. A potentially infectious plume is produced. Frequency- doubled Nd:YAG and 532 nm KTP lasers are also reported to be effective, but there is less evidence for their use. Photodynamic therapy with aminolevulinic acid 20%, using broad-band sources with variable intensities, produces a clearance rate of 40-75% for recalcitrant warts. Several treatments at 3 weekly intervals may be required. Significant pain can occur during treatment and lasts for up to 24 h, which limits its use in children.

Oral cimetidine, 30-40 mg/kg/day, has been anecdotally reported to lead to resolution of common warts, perhaps because of its immunomodulatory effects.

When used as a single agent, however, in both children and adults, the efficacy is low (30%), comparable with a placebo. It may be beneficial as an adjunct to other methods, however, or for treatment of refractory warts. Oral zinc sulfate at a dose of 10 mg/kg, to a maximum of 600 mg per day, has been reported to clear 80% of warts in children and young adults in Iran. No recurrences were observed at 6 months. If other groups find this therapy efficacious, it might become a useful agent in wart therapy. There appear to be limited side effects. Heat treatment, either localized to the wart and delivered by radiofrequency or by application to the affected part by soaking it in a hot bath, has been reported to be effective. Treatment for 15 min at 43-50°C (107.6-122°F) to as short as 30 s at higher temperatures has been used. Extreme caution must be exercised to avoid scalding. Oral administration of acitretin or isotretinoin may also be used in refractory cases. Hypnotic suggestion and hypno- analysis for warts have been reviewed by Shenefelt.

Immunotherapy with topical and intralesional agents has become a mainstay of wart therapy. The hope is that not only will the wart be eradicated, but the immune reaction induced in the wart may also lead to widespread and permanent immunity against warts. The commonly used agents are topical DNCB, squaric acid dibutyl ester, and diphencyprone, as well as intralesional *Candida* or mumps antigen. Patients may be initially sensitized at a distant site (usually the inner upper arm) with the topical agents, or the agent may be applied initially to the warts directly. Two treatment approaches are used and their efficacies have not been compared. Some practitioners apply topical agents in the office in higher concentrations (2-5%), but only every 2 weeks or so. Others give their patients take-home prescriptions to use on a daily basis, albeit at lower concentrations to start with (0.20.5%). In most cases the agents are dissolved in acetone. The treated wart should be kept covered for 24 h after application. If the reaction is overly severe, the strength of the application may be reduced. Wart tenderness may indicate the need to reduce treatment concentration. Warts may begin to resolve within a week or two, but on average, 2-3 months of treatment or more are

required. For intralesional *Candida* antigen, treatments are repeated every 3-4 weeks. Overall cure rates for all three topical sensitizers and for intralesional antigen injection is 60-80%. Side effects of treatment include local pruritus, local pain, and a mild eczematous dermatitis. Intralesional *Candida* injections may be associated with IFN-mediated side effects such as swelling, fever, shaking chills, and a feeling of having "flu." This begins 6-8 hours after the treatment and resolves over 24-28 hours. Patients should be advised of these possible side effects. Most patients have no limitation of activities or function with topical immunotherapy. Scarring has not been reported.

The efficacy of imiquimod for common warts appears to be significantly less than cryotherapy or topical immunotherapy and it is considerably more expensive. The routine use of imi- quimod in the treatment of common or plantar warts cannot be recommended. Topical cidofovir has been used in desperate situations, compounded in a 1-5% concentration applied directly to the wart on a daily basis. Local irritation and erosion may occur.

Plantar warts

In general, plantar warts are more refractory to any form of treatment than are common warts. Initial treatment usually involves daily application of salicylic acid in liquid, film, or plaster form after soaking. In failures, cryotherapy or canthari- din application may be attempted, alone or in combination. A second freeze-thaw cycle is beneficial when treating plantar warts with cryotherapy. Bleomycin injections, laser therapy, or topical immunotherapy, as discussed above, may be used in refractory cases. Surgical destruction with cautery or blunt dissection should be reserved for failures with nonscarring techniques, since a plantar scar may be persistently painful. CO_2 laser may also result in plantar scars. Photodynamic therapy may be effective in some cases. The optimum photo-sensitizing agent and light source are unknown.

Genital warts (external genital warts, EGW)

Genital warts are the most common STD. Among sexually active young adults in the US and Europe, infection rates as high as 50% in some cohorts have been found using sensitive PCR techniques. It is estimated that the lifetime risk for infection in sexually active young adults may be as high as 80%. The number of new cases of genital wart infection diagnosed in the US yearly may approach 1 million. In the vast majority of couples in whom one has evidence of HPV infection, the partner will be found to be concordantly infected. The risk of transmission is not known, however. A large portion of genital HPV infection is either subclinical or latent. Unfortunately, the infectivity of subclinical and latent infection is unknown. Subclinical and latent infection is probably responsible for most "recurrences" following treatment of genital warts. Since the methodology for determining HPV infection in males is less accurate and since women suffer the major complication of HPV infection—cervical cancer, virtually all data on HPV infection rates and epidemiology are derived from studies of women.

Genital HPV infection is closely linked with cancer of the cervix, glans penis, anus, vulvovaginal area, and periungual skin. Cancer occurs when there is integration of the HPV genome into the host DNA. In high-risk genital HPV types, E6 and E7 gene products bind to and inactivate p53 and retinoblastoma protein (pRb), respectively. This is felt to be important in relation to their ability to cause cancer. In most persons, genital HPV infection appears to be transient, lasting about 1-2 years, and results in no sequelae. In a small proportion (about 2% of immunocompetent persons), infection persists and in a small proportion of persons with persistent HPV infection cancer may develop (Fig. 55). Certain cofactors, such as the HPV type causing the infection, location of infection, cigarette smoking, uncircumcised status, and immuno- suppressed status, are associated with progression to cancer. The transition zones of the cervix and anus are at highest risk for the development of cancer.

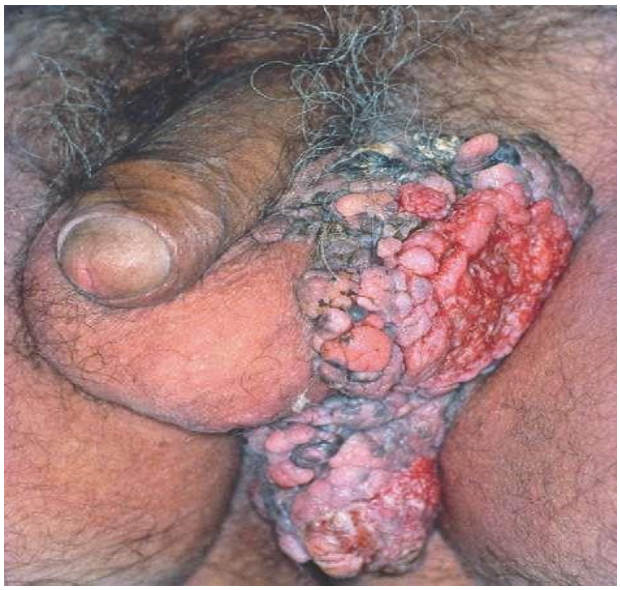


Fig. 55 Squamous cell carcinoma in persistent HPV infection.

More than 30 HPV types are associated with genital warts. Patients are commonly infected with multiple HPV types. The HPV types producing genital infection are divided into two broad categories—those that produce benign lesions, or low- risk types (at least 12 types); and those associated with cancer, the so-called high-risk or oncogenic types (at least 15 types).

The most common low-risk genital HPV types are HPV-6 and 11, and most HPV-induced genital dysplasias are caused by HPV-16 and 18. There is a strong correlation between the HPV type and the clinical appearance of HPV-induced genital lesions. Virtually all condylomata acuminata are caused by "benign" HPV-6 and 11. High-risk HPV-16 and 18 produce flat or sessile, often hyperpigmented lesions. For this reason, biopsy and HPV typing of EGW is rarely necessary.

Genital HPV infection is strongly associated with sexual intercourse. Female virgins rarely harbor HPV (about 1%). For women, insertive vaginal intercourse is strongly associated with acquiring genital HPV infection, with 50% of women testing positive for genital HPV within 5 years of the time of first sexual intercourse. However, sexual contact does not need to be penile-vaginal, as the risk of acquiring genital HPV infection was 10% in women who had nonpenetrative sexual exposure as compared to 1% of women who had no such exposure. Infection may occur at the introitus and then be spread to other sites by self-

inoculation. Women who have sex with women may have genital HPV infection and still require regular gynecologic evaluations. Condom use may be partly, but not completely, protective for acquisition of genital HPV infection. In men the risk of genital HPV infection is associated with being uncircumcised, having had sex before age 17, having had more than six lifetime sexual partners, and having had sex with professional sex workers.

Condylomata acuminata

Condylomata on the skin surface appear as lobulated papules that average 2-5 mm in size, but they may range from microscopic to several centimeters in diameter and height. Lesions are frequently multifocal. Numerous genital warts may appear during pregnancy. Condylomata acuminata occur in men anywhere on the penis (Fig. 56) or about the anus. Scrotal condylomata occur in only 1% of immunocompetent male patients with warts (Fig. 57). Intraurethral condylomata may present with terminal hematuria, altered urinary stream, or urethral bleeding.

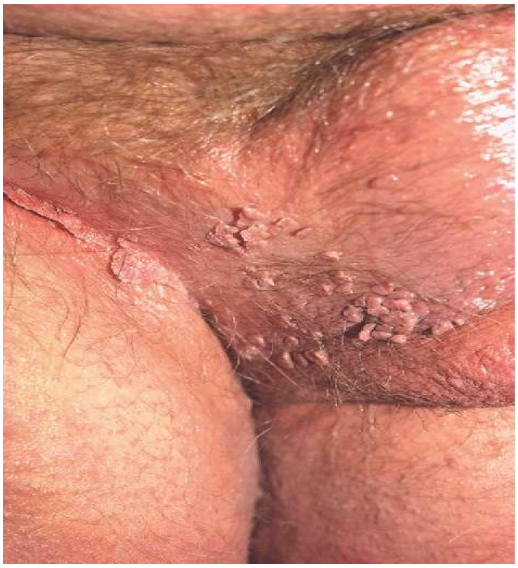


Fig. 56 Genital warts, keratotic type. **Fig. 57** Genital warts, condylomata acuminata.

In women, lesions appear on the mucosal surfaces of the vulva or cervix, on the perineum, or about the anus. Cauliflowerlike masses may develop in moist, occluded areas such as the perianal skin, vulva, and inguinal folds. As a result of

accumulation of purulent material in the clefts, these may be malodorous. Their color is generally gray, pale yellow, or pink. When perianal lesions occur, a prior history of receptive anal intercourse will usually predict whether intra-anal warts are present and will help to determine the need for anoscopy. Immunosuppressed individuals and those with known high-risk HPV types should have routine anal pap smears to detect malignant change.

Genital warts are sexually transmitted and other STDs may be found in patients with genital warts. A complete history should be taken and the patient screened for other STDs as appropriate. Women with EGW should have a routine cervical cytologic screening to detect cervical dysplasia.

Bowenoid papulosis and HPV-induced genital dysplasias

Bowenoid papulosis is characterized by flat, often hyperpigmented papules a few millimeters to several centimeters in diameter. These occur singly or, more often, may be found in multiples on the penis, near the vulva, or perianally (Fig. 58). At times, similar lesions are seen outside the genital area in the absence of genital bowenoid papulosis. They occur most commonly on the neck or face and are more common in men. They contain HPV-16, 18, or other high-risk HPV types. Histologically, bowenoid papulosis demonstrates abnormal epithelial maturation and cellular atypia closely resembling Bowen's disease. It is usually caused by HPV-16. On the glabrous external genitalia, bowenoid papulosis usually behaves similarly to other EGWs, but may progress to squamous cell carcinoma (SCC). On the glans penis of an uncircumcised male, and on the cervical, vaginal, or rectal mucosa, progression to invasive SCC is more likely (Fig. 59). Female partners of men with bowenoid papulosis and women with bowenoid papulosis have an increased risk of cervical dysplasia.

Fig. 58 Genital warts, bowenoid papulosis.

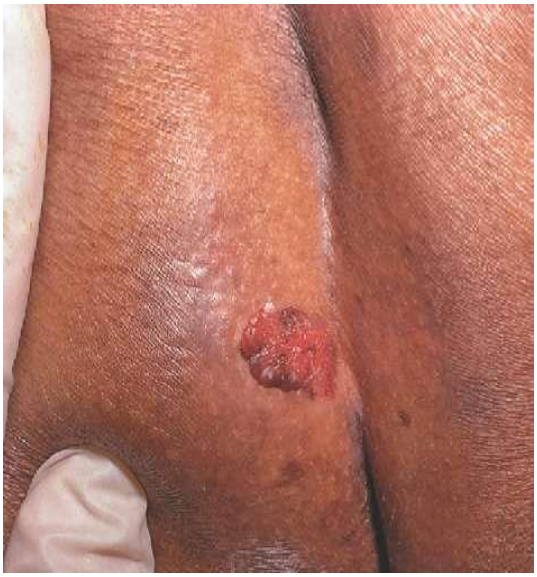


Fig. 59 Genital Bowen's disease.

Giant condyloma acuminatum (Buschke - Lowenstein tumor).

Giant condyloma acuminatum is a rare, aggressive, wart-like growth that is a verrucous carcinoma. Unlike other HPV- induced genital carcinomas, this tumor is usually caused by HPV-6. It occurs most often on the glans or prepuce of an uncircumcised male; less often, it may occur on perianal skin or the vulva. Despite its bland histologic picture, it may invade deeply, and uncommonly it may metastasize to regional lymph nodes. Treatment is by complete surgical excision. Recurrence after radiation therapy may be associated with a more aggressive course.

Diagnosis

Even in women with confirmed cervical HPV infection, sero- logic tests are positive in only 50%, making serologic diagnosis of HPV infection of no use to the practicing clinician. HPV cannot be cultured. HPV typing via in situ hybridization or PCR is useful in managing HPV infection of the cervix and in some cases of prepubertal HPV infection, but not in the management of EGW. Virtually all condylomata can be diagnosed by inspection. Bright lighting and magnification should be used when examining for genital HPV infection. Flat, sessile, and pigmented lesions are suggestive of bowenoid papulosis and may

require a biopsy. Subclinical and latent infections are no longer sought or investigated because they are very common and there is no management strategy known to eradicate these forms of HPV infection. Soaking with acetic acid is not generally necessary, but may be helpful to detect early lesions under the foreskin. In patients with multiple recurrences, acetic acid soaking may determine the extent of infection, helping to define the area for application of topical therapies. The procedure is performed by soaking the external genitalia in men and the vagina and cervix in women with 3-5% acetic acid for up to 10 min. Genital warts turn white (acetowhitening), making them easily identifiable. Any process that alters the epidermal barrier will be aceto- white, however (dermatitis, for example), so only typical acetowhite lesions should be treated as warts. In atypical cases, a 2-week trial is attempted with a 1% hydrocortisone preparation plus a topical anticandidal imidazole cream. If the acetowhitening persists, a biopsy is performed and histologic evidence of HPV infection sought. Immunoperoxidase or in situ hybridization methods may aid in evaluation. PCR should probably not be performed on such biopsied specimens, except possibly in childhood cases. The high background rate of latent infection (up to 50%) makes interpretation of a positive PCR impossible. In contrast, chromogenic in situ hybridization clearing demonstrates the localization of positive nuclei within the lesion.

Treatment

Because no effective virus-specific agent exists for the treatment of genital warts, their recurrence is frequent. Treatment is not proven to reduce transmission to sexual partners or to prevent progression to dysplasia or cancer. Specifically, the treatment of male sexual partners of women with genital warts does not reduce the recurrence rate of warts in these women. Therefore, the goals of treatment must first be discussed with the patient, and perhaps with his/her sexual partner. Observation represents an acceptable option for some patients with typical condylomata acuminata. In some patients, only wart-free periods are achieved. As genital warts may cause discomfort, genital pruritus, malodor, bleeding, and substantial emotional distress, treatment is indicated if the patient desires it.

Bleeding genital warts may increase the sexual transmission of HIV and hepatitis B and C. Bowenoid papu- losis may be treated as discussed below when it occurs on the external genitalia. Lesions with atypical histology (squamous intraepithelial lesion) on mucosal surfaces and periungually are special cases and treatment must be associated with histo- logic confirmation of eradication in cases where topical methods are used.

The treatment chosen is in part dictated by the size of the warts and their location. The number of EGWs at the time of initial evaluation is strongly predictive of wart clearance. Patients with four or fewer EGWs will be clear with three or fewer treatments, whereas only 50% of patients with ten or more EGWs will be clear after three treatments. Only 1% of patients with 1-4 EGWs will still have lesions after eight treatments, but 20% of patients with ten or more EGWs will still have lesions after eight treatments. A more effective or aggressive treatment approach might be considered in patients with high numbers of EGWs. Podophyllin is more effective in treating warts on occluded or moist surfaces, such as on the mucosa or under the prepuce.

It is available as a crude extract, usually in 25% concentration in tincture of benzoin. It is applied weekly by the physician and can be washed off 4-8 h later by the patient, depending on the severity of the reaction. After six consecutive weekly treatments, approximately 40% of patients are free of warts and 17% are free of warts at 3 months after treatment. Purified podophyllotoxin 0.5% solution or gel is applied by the patient twice a day for 3 consecutive days of each week in 4- to 6-week treatment cycles. Efficacy approaches 60% for typical condylomata and side effects are fewer than with standard, physician-applied podophyllin preparations. Therefore, ql whenever possible, podophyllotoxin should be used instead of classic podophyllin solutions.

Imiquimod, an immune response modifier that induces IFN locally at the site of application, has an efficacy similar to cryo- therapy (about 50%) and yields a low recurrence rate (22%). It is available in a 250 mg sachet containing a 5% cream formulation. One sachet can cover up to 350 cm^2 when applied appro-

priately, allowing for several treatments with a single sachet if the treatment area is limited. It is more effective than podophyllotoxin in treating women with EGW, but only equally or slightly less effective in men, especially for warts on the penile shaft. Imiquimod is less effective than cryotherapy in the treatment of EGW. Therapeutic response to imiquimod is slow, requiring 10 or more weeks in some patients to see any effect. It is patient-applied, once a day for 3 alternate days per week (usually Monday, Wednesday, and Friday). Treatment results in mild to moderate irritation (less than with podophyllin or cryotherapy in men, but with a similar side-effect profile in women). Rare complications include flaring of psoriasis and psoriatic arthritis, vitiligo-like hypopigmentation, and the production of a local neuropathy. Imiquimod should be used cautiously in persons with psoriasis. Neuropathy is associated with application of excessive amounts, occlusion of the medication, and application to an eroded mucosa.

Imiquimod may be used to treat penile condyloma in circumcised and uncircumcised men, anal and perianal condy- loma, and vulvar condyloma. It may be used as the initial treatment or in cases in which recurrence has been frequent after other forms of treatment were attempted. Several trials have demonstrated that the use of imiquimod following elec- trosurgical destruction of warts results in a significant reduction in recurrences (20% vs 65% in one study and 8% vs 25% in another). While the percentage of recurrences differed significantly in these studies, the imiquimod-treated patients in both studies had a 3-4-fold reduction in wart recurrence. The use of imiquimod following surgical destruction of condyloma should be considered in all immunocompetent patients, especially those who have had recurrence after a previous surgical procedure. It is unclear whether the imiquimod should be started before the surgical procedure or after healing of the surgical procedure. The duration of continued imiquimod therapy after ablation is also unknown, but since most recurrences occur during the first 3-6 months, 3 months of therapy would be reasonable. Application of imiquimod three times weekly following surgery may be more effective than use only twice weekly, although these two approaches have not been compared head to head.

Suppositories containing about 5 mg of imiquimod appear to reduce the risk of recurrence of anal condyloma in immunocompetent men after surgical ablation of extensive anal disease.

Imiquimod has been effective in the treatment of bowenoid papulosis in scattered case reports. The topical application of green tea extract containing sine-catechins (Polyphenon E or Veregen) can be effective in treating EGW. A 15% ointment applied three times daily leads to EGW clearance in 60% of women and 45% of men. The average time to complete clearance is 16 weeks. Erythema and erosions at the application site occur in 50% of patients.

Bichloroacetic or trichloroacetic acid (TCA) 35-85% can be applied to condylomata weekly or biweekly. TCA is safe for use in pregnant patients. When compared with cryotherapy, TCA has the same or lower efficacy and causes more ulcera- tions and pain. It is not generally recommended for EGW, as other available treatments are more effective and cause less morbidity.

Cryotherapy with liquid nitrogen is more effective than podophyllin and imiquimod, approaching 70-80% resolution during treatment and 55% 3 months after treatment. One or two freeze-thaw cycles are applied to each wart every 1-3 weeks. A zone of 2 mm beyond the lesion is frozen. Cryotherapy is effective in dry as well as moist areas. Perianal lesions are more difficult to eradicate than other genital sites and two freeze-thaw cycles are recommended in this location. Cryotherapy is safe to use in pregnant patients. EMLA cream with or without subsequent lidocaine infiltration may be beneficial in reducing the pain of cryotherapy. The addition of podophyllin to cryotherapy does not result in statistically better results after 2 months of therapy and cannot be recommended as standard treatment.

Electrofulguration or electrocauterization with or without snip removal of the condyloma is more effective than TCA, cryotherapy, imiquimod, or podophyllin. Wart clearance during therapy is nearly 95% and wart cure at 3 months exceeds 70%. Local anesthesia is required and scarring may occur. Surgical removal is ideal for large exophytic warts that might require multiple

treatments with other methods. It has high acceptance in patients who have had recurrences from other methods because results are immediate and cure rates higher.

The use of CO laser in the treatment of genital warts has not been demonstrated to be more effective than simpler surgical methods. Although visible warts are eradicated by the laser, HPV DNA can still be detected at the previous site of the wart. The CO laser has the advantage of being bloodless, but it is costlier and requires more technical skill on the part of the surgeon to avoid complications. It should be reserved for treatment of extensive lesions in which more cost-effective methods have been attempted and failed. Adjunctive photo-dynamic therapy does not prevent recurrence of EGW after CO laser ablation. When compared to CO laser ablation of EGWs, ALA-PDT demonstrated higher efficacy, fewer recurrences, and was less painful. ALA-PDT response rate is about 75%.

Any surgical method that generates a smoke plume is potentially infectious to the surgeon. HPV DNA is detected in the plumes generated during CO laser or electrocoagulation treatment of genital warts. The laser-generated plume results in longer-duration HPV aerosol contamination and wider spread of detectable HPV DNA. If these methods of wart treatment are used, an approved face mask should be worn, a smoke evacuator should be operated at the surgical site during the procedure to remove the plume, and decontamination of the equipment after the surgery should be carried out.

5-FU 5% cream applied twice a day may be effective, especially in the treatment of flat, hyperpigmented lesions, such as those in bowenoid papulosis. Care must be taken to avoid application to the scrotum, as scrotal skin is prone to painful erosions. Twice-a-day instillation of 5-FU into the urethra can be used to treat intraurethral condylomata. The cone from a tube of Xylocaine jelly will fit on to the thread of the 5-FU tube, or the cream may be instilled with a syringe. It is typically left in place for 1 h before the patient voids. Care should be taken that drips of urine containing the medication do not contact the scrotum. 5-FU may also

be used to treat intravaginal warts by instillation in the vagina, but is often associated with severe irritation. Intermittent therapy (twice a week for 10 weeks) is better tolerated than daily therapy. 5-FU is not commonly recommended for the treatment of typical EGWs because other methods of treatment are available.

The efficacy of systemic and intralesional IFN-a therapy has been found to be relatively low in eradicating genital warts. Intralesional therapy eradicates 40-60% of warts and systemic IFN treatment will eradicate warts in only about 20% of patients. IFN treatment of genital warts in patients with AIDS has even lower efficacy rates. Response rates to IFN have never reached the levels achieved with electrosurgical methods. Because of the high cost, frequent side effects, and low efficacy associated with IFN therapy, the CDC no longer recommends the use of IFN for the treatment of genital warts.

Human papillomavirus vaccination

HPV virus-like particles (VLPs) composed of spontaneous assembling L1 molecules have been used to develop a polyvalent vaccine against HPV 6, 11, 16, and 18. This vaccine is highly effective and is now approved in more than 100 countries for the immunization of prepubertal girls. In older women (age 24-45) the vaccine is also effective and may be given as a "catch-up" vaccine in women with no evidence of prior genital HPV infection with these HPV types. The protection was type- specific and did not prevent squamous intraepithelial lesions from other HPV types. Since HPV-16 and 18 are the primary HPV types associated with cervical cancer, it is hoped that the rate of cancers induced by these high-risk genital HPV types can be reduced by vaccination.

Genital warts in children

Children can acquire genital warts through vertical transmission perinatally, and through digital inoculation or autoinocu- lation, fomite or social nonsexual contact, and sexual abuse. HPV typing has demonstrated that most warts in the genital area of children are "genital" HPV types, and most children with genital warts have family members with a genital HPV infection.

HPV typing can be performed; however, the presence of genital types of HPV does not prove abuse and a finding of a nongenital HPV type does not exclude the possibility of sexual abuse. In children younger than 1 year of age, vertical transmission is possible and is probably the most common means of acquisition. The risk for sexual abuse is highest in children older than 3 years of age. When abuse is suspected, children should be referred to child protection services if the practitioner is not skilled in evaluating children for sexual abuse. Children between 1 and 3 years of age are primarily nonverbal and are difficult to evaluate. Management of such patients is on a case-by-case basis. Other STDs should be screened for in children who have a genital HPV infection. Usually, the management of children with anogenital warts (Fig. 60) requires a multidisciplinary team that should include a pediatrician. Genital warts in children often spontaneously resolve (75%), so nonintervention may be a reasonable consideration. Genital warts in children usually respond quickly to topical therapy, such as podophyllotoxin, imiquimod, or light cryotherapy. In refractory cases, surgical removal or electrocautery may be used. The use of a topical anesthetic is recommended before treatment.

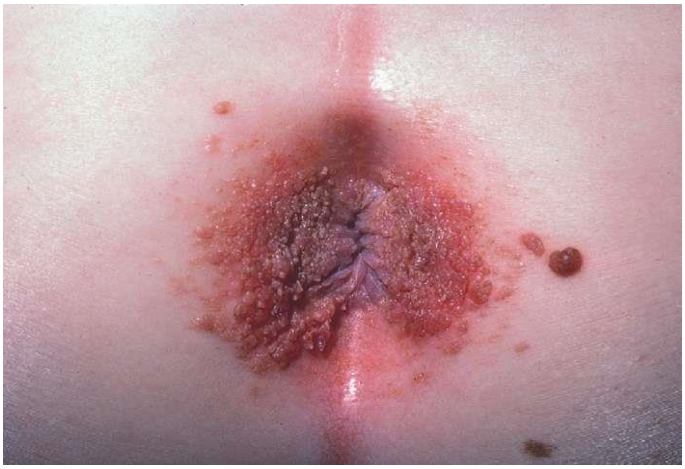


Fig. 60 Perianal warts in an 18-month-old child.

Recurrent respiratory (laryngeal) papillomatosis

HPV-associated papillomas may occur throughout the respiratory tract, from the nose to the lungs. Recurrent respiratory papillomatosis has a bimodal

distribution—in children under 5, and after the age of 15. Affected young children are born to mothers with genital condylomata and they present with hoarseness. The HPV types found in these lesions, HPV-6 and 11, are the types seen in genital condylomata. Treatment is with CO laser surgery and IFN. Carcinoma that is often fatal develops in 14% of patients, even in young children. The incidence of carcinoma is higher in those treated with radiation therapy.

Heck's disease

Small white to pinkish papules occur diffusely in the oral cavity in this disease, also known as focal epithelial hyperpla- sia. It occurs most commonly in Native Americans, in Greenland, and in Turkey. HPV-13, 24, and 32 have been associated. Lesions may spontaneously resolve. Treatment options include cryosurgery, CO_2 laser, electrosurgery, and topical (P), intralesional, and systemic IFN.

Epidermodysplasia verruciformis

Epidermodysplasia verruciformis (EV) is a rare, inherited disorder characterized by widespread HPV infection and cutaneous SCCs. Virtually always, it is inherited as an autosomal-recessive trait, although one well-documented kindred demonstrates an X-linked inheritance. About 10% of EV patients are products of consanguineous marriages. HPV types associated with this syndrome include those infecting normal hosts, such as HPV-3 and 10, as well as many "unique" HPV types. These HPV types, now numbering 19, are called EV HPVs and include HPV-5, 8, 9, 12, 14, 15, 17, 19 through 25, and 36 through 38. The genetic mutations causing EV are found in two closely linked genes, *EVER1* and *EVER2*. Seventy- five percent of all EV cases worldwide have homozygous invalidating mutations in one of these two genes. The *EVER* genes are transmembrane channel-like genes, so *EVER1* is also *TMC-6* and *EVER2* is also *TMC-8.* The functions of these genes and how they cause this syndrome are unknown.

The condition presents in childhood and continues throughout life. Skin lesions include flat wartlike lesions of the dorsal hands, extremities, face, and neck. They appear in childhood or young adulthood, apparently earlier in sunnier climates. The characteristic lesions are flatter than typical flat warts and may be quite abundant, growing to confluence (Fig. 61).

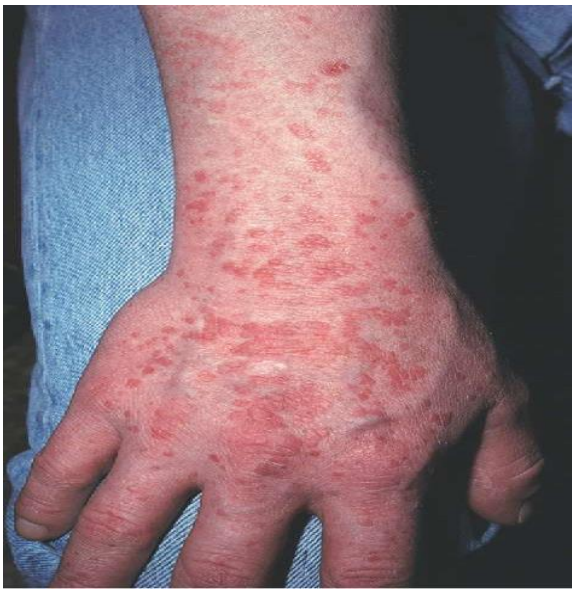


Fig. 61 Epidermodysplasia verruciformis.

Typical HPV 3-and 10-induced flat warts may be admixed. In addition, on the trunk are lesions that are red, tan, or brown patches/plaques or hypopigmented, very slightly scaly plaques resembling tinea versicolor. Plaques on the elbows may resemble psoriasis. Seborrheic keratosis-like lesions may also be seen on the forehead, neck, and trunk. Common warts are reported to be uncommon in some EV cohorts. In other EV patients, typical common warts of the hands and feet may be present also. Some patients with extensive (more than 100) common and plantar warts that never resolve and simply grow to confluence have been called "generalized verrucosis." These patients do not develop skin cancers and live into adulthood. There are reports of patients with generalized verrucosis who also are infected with EV HPV types, suggesting a common pathogenesis. The genetic basis of generalized verrucosis is unknown.

The histologic features of an EV-specific HPV infection are very characteristic. The cells of the upper epidermis have a clear, smoky, or light-blue pale cytoplasm and a central pyknotic nucleus.

SCCs develop in about one-third of EV patients, an average of 24 years after the appearance of the characteristic EV skin lesions. Most often, skin cancers appear on sun-exposed surfaces, but they can appear on any part of the body. They begin to appear at the age of 20-40, again earlier in patients living in regions with high sun exposure. Skin cancers are less common in African patients, suggesting a protective effect of skin pigmentation. HPV-5, 8, and 47 are found in more than 90% of EV skin cancers. The SCCs may appear de novo, but usually appear on the background of numerous actinic kera- toses and lesions of Bowen's disease (Fig. 62).

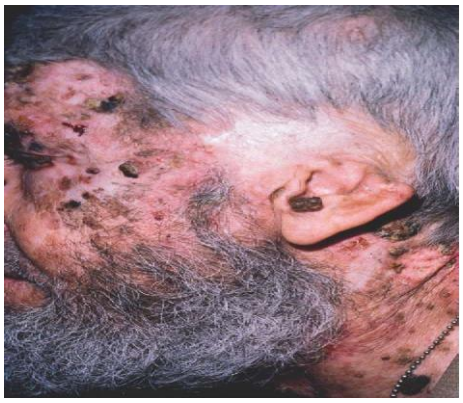


Fig. 62 Multiple SCCs in epidermodysplasia verruciformis.

Surgical treatment is recommended. Radiation therapy is contraindi- cated. If skin grafting is required, the grafts should be taken from sun-protected skin, such as the buttocks or inner upper arm.

Aside from surgical intervention for skin cancer, treatment for EV consists largely of preventive measures. Strict sun avoidance and protection should be started as soon as the syndrome is diagnosed. An approach similar to that for children with xeroderma pigmentosa could be instituted. ALA-PDT, topical 5-FU, imiquimod, cimetidine, systemic interferons, and oral retinoids may all have a place in managing patients with EV.

The mechanism by which cancer occurs in patients with EV is unclear. HPV-5 proteins do not bind to p53 or pRb. The p53 mutations present in the SCCs of patients with EV are characteristic of those induced by UVB, confirming the close association of UV exposure and the development of cancer in patients with EV. EV HPV DNA has been reported to be found in a large percentage (35%) of the general population in very low copy number. EV HPV DNA is reported to be present on the skin in up to 80% of patients with psoriasis. EV HPV is not universally present in the skin cancers of EV patients, but is usually present in the precancerous lesions (AKs and SCC in situ). This suggests that EV HPV may be required only in early phases of carcinogenesis and therefore may not be found in well-developed SCCs.

Infection with EV HPV types has been reported in the immunosuppressed, especially those with HIV. Typical flat scaly lesions resembling tinea versicolor are most common. SCC has not been reported in these patients.

Immunosuppressed patients

Patients with defects in their cell-mediated immunity may have an increased frequency of HPV infection. Predisposing conditions include organ transplantation, immunosuppressive medications, congenital immunodeficiency diseases, lym- phoma, and HIV infection.

Organ transplant recipients begin to develop warts soon after transplantation and by 5 years up to 90% of transplant patients have warts. Initially, these are common and plantar warts, but later numerous flat warts appear, particularly in sun-exposed areas. Depending on the background level of UV radiation, the lifetime risk for cutaneous carcinomas may exceed 40%. Skin cancers begin to appear 4 years or more after transplantation, occur in sun-exposed sites, and are more common in persons with skin types I and II. The duration and intensity of immunosuppression appear more important in causing the skin cancers than are the specific immunosuppres- sive agents used. The use of Voriconazole as prophylaxis or treatment for aspergillus infection may lead to accelerated

development of skin cancers, especially squamous cell carcinomas and melanoma. Malignant lesions may resemble Bowen's disease, keratoacanthomas, SCCs, or warts. Genital warts are also increased and, especially in women, genital dysplasias are more frequent. The presence of keratotic lesions of any type on the skin is a strong predictor for the development of nonmelanoma skin cancer (NMSC) in organ transplant patients. The skin of organ transplant patients should be examined closely, and once skin cancers begin to appear, regular dermatologic examinations should be performed. It is especially important in immunosuppressed patients to monitor the genital and anal areas regularly for changing lesions and to have a low threshold for performing a biopsy.

In HIV disease, common, plantar, flat, oral and genital warts are all very common. Warty keratoses at the angle of the mouth, often bilateral, are a characteristic, and perhaps unique, manifestation of HPV infection in patients with AIDS. The warts are caused predominantly by HPV-2, 27, and 57. HPV-7 can be found in cutaneous, oral, and perioral warts in non- butchers with HIV infection. HPV-6 may be found in common warts. Genital warts are increased 15-fold among HIV-infected women. Fifty percent or more of HIV-infected MSM have evidence of anal HPV infection. Genital neoplasia associated with HPV-16 and 18 occurs much more frequently in HIV-infected women and MSM. Uncommonly, HIV-infected patients develop HPV 5- and 8-induced EV-like lesions. Although nongenital skin cancers are also common in some fair-skinned HIV-infected patients, HPV has not been demonstrated in the nongenital SCCs of these patients. With HAART therapy, warts may disappear. Paradoxically, increased rates of genital and oral warts are seen in HIV-infected persons with adequate control of their HIV infection. The likelihood of clearance of common warts in persons with HIV is related to the nadir of their helper T-cell count. HIV-infected persons whose helper T-cell count never falls below 200 are more likely to have sustained remission of their warts.

The treatment of warts in immunosuppressed hosts is very difficult. Although standard methods are used, their efficacy may be reduced. Imiquimod

has low efficacy in this setting, but can be attempted. The addition of a second modality (podophyllin, 5% 5-FU, or surgery) to the imiquimod treatment may lead to improvement. Topical cidofovir (in concentrations from 1% to 5%) and intralesional cidofovir (7.5 mg/mL) have been effective in refractory anogenital and common warts in immunodeficient patients. Topical cidofovir is very expensive, is irritating, and can cause skin erosion and ulceration. Addition of sirolimus to the immunosuppressive regimen may be associated with decrease in the number of warts in organ transplant patients. Oral retinoids can be effective in reducing the rate of appearance of SCCs in organ transplant patients. In organ transplant patients with widespread actinic damage and many precancerous lesions, photodynamic therapy can be considered.

Viral-associated trichodysplasia (cyclosporine-induced olliculodystrophy)

Organ transplant recipients on immunosuppressive regimens rarely develop a characteristic eruption of erythematous 1-3 mm facial papules. The midface, glabella, and chin are primarily affected. Lesions are numerous, may reach confluence, and can cause nasal distortion similar to that seen in rosacea and sarcoidosis (Fig. 63).

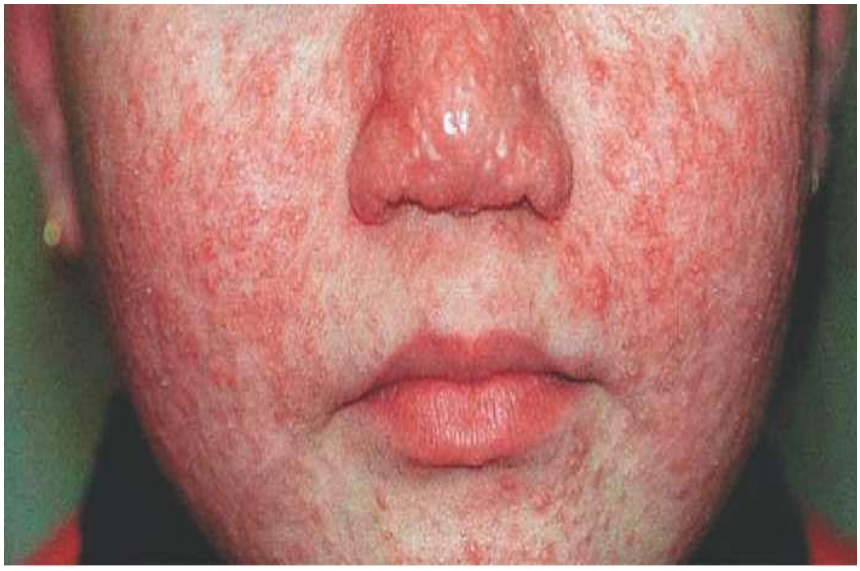


Fig. 63 Trichodysplasia.

Some papules have a central, keratotic white excrescence. Alopecia of the eyebrows and eyelashes may occur, but the scalp is spared. Histology is characteristic, showing massively distended, bulbous follicles with expansion of the inner root sheath cells containing numerous trichohyaline granules. Abrupt inner root sheath-type cornification is present. No hair shafts (or hair cortex) are present in the affected follicles. Electron microscopy demonstrates numerous viral particles about 40 nm in size with features suggestive of a papovavirus. Topical cidofovir 3% cream slowly improved one patient.

Retroviruses

These oncoviruses are unique in that they contain RNA, which is converted by a virally coded reverse transcriptase to DNA in the host cell. The target cell population is primarily CD4+ lymphocytes (primarily helper T cells), but also, in some cases, macrophages. For this reason they are called human T-lymphotropic viruses (HTLV). Transmission may be by sexual intercourse, blood products/intravenous drug use, and from mother to child during childbirth and breastfeeding. There is often a very long "latent" period from the time of infection until presentation with clinical disease.

Human T-lymphotropic virus-1

HTLV-1 is endemic in Japan, the Caribbean, South America (Brazil, Peru, Columbia), sub-Saharan Africa, Romania, among Australian Aborigines, and in the southeastern US. In endemic areas, infection rates may be quite high, with only a small percentage of infected patients ever developing clinical disease (estimated at about 3%). HTLV-1 is spread primarily by mother-to-infant transmission during breastfeeding, but also can be transmitted sexually (primarily male to female) or via blood transfusion or intravenous drug use. HTLV-1 uses the GLUT glucose transporter to enter cells. HTLV-1 is responsible for several clinical syndromes. About 1% of persons who are infected will develop adult T-cell leukemia-lymphoma (ATL), with more HTLV-1-infected persons in Japan developing ATL than in other populations. Infection in childhood through breastfeeding seems to

be a risk factor for developing ATL. HTLV-1-associated myelopathy or tropical spastic paraparesis (HAM/TSP) is a less common degenerative neurologic syndrome.

There are four forms of ATL: smoldering, chronic, acute, and lymphomatous, usually progressing in that order. A primary cutaneous tumoral variant of ATL has been proposed. ATL is characterized by lymphadenopathy, hepatosplenomegaly, hypercalcemia, and skin lesions. Skin lesions in ATL include erythematous papules or nodules (Fig. 64).

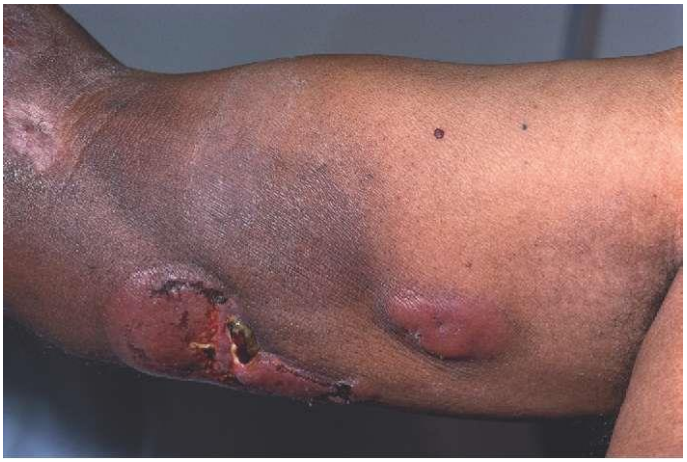


Fig. 64 HTLV-1-associated adult T-cell leukemia-lymphoma.

Prurigo may be a prodrome to the development of ATL. Histologically, the cutaneous infiltrates are pleomorphic, atypical lymphocytes with characteristic "flower cells" representing HTLV-1-infected lymphocytes. Epidermotropism may be present, mimicking mycosis fungoides.

HTLV-1-infected patients often have an abnormal skin examination. If they are seropositive but asymptomatic, der- matophytosis (34%), seborrheic dermatitis (6%), and xerosis/ acquired icthyosis (7%) are most commonly found. Vitiligo is also associated. Xerosis occurs in 82% of patients with HAM/ TSP, seborrheic dermatitis in 33%, candidiasis and palmar erythema in 15%, and chronic eczema/photosensitivity in up to 20 %. Biopsies from the areas of chronic eczema / photosensitivity may show features of ATL in up to 25% of these patients (smoldering ATL). Areas of positive biopsies are described as "atrophic." Scabies

is seen in 2% of asymptomatic HTLV-1- infected patients and in 5% of those with HAM/TSP. The scabies may be of the hyperkeratotic (crusted) type and the finding of this pattern of scabies in a person from an HTLV-1 endemic region should trigger serologic testing for HTLV-1. The spectrum of skin disease seen in symptomatic HTLV-1- infected patients is remarkably similar to that seen in HIV-infected patients with CNS disease (xerosis/eczema, seborrheic dermatitis, and scabies).

"Infective dermatitis" occurs in children and less commonly in adults infected with HTLV-1. It is much rarer in Japan than other HTLV-1 endemic countries. Infective dermatitis is diagnosed by major and minor criteria, as delineated by La Grenade et al. Clinically, the children present at an early age (on average, about 7 years) with a chronic eczema of the scalp, axilla, groin, external auditory canal, retroauricular area, eyelid margins, paranasal areas, and neck. Exudation and crusting are the hallmarks of the skin lesions. Pruritus is mild. Clinically, infective dermatitis resembles a cross between infected atopic dermatitis and infected seborrheic dermatitis. There is a chronic nasal discharge. Cultures from the skin and nares are positive for *S. aureus* or P-hemolytic streptococcus, and the condition responds rapidly to antibiotics and topical steroids. Infective dermatitis is relapsing and recurrent. Skin biopsies show a nonspecific dermatitis; however, close examination may show atypical CD4+ cells infiltrating the epidermis, at times simulating ATL or cutaneous T-cell lymphoma. Up to one-third of patients with infective dermatitis have comorbidities, including pneumonitis, corneal opacities, and lymphocytosis with atypical lymphocytes. Careful neurological examination of children with infective dermatitis will often reveal abnormal neurological findings (weakness, lumbar pain, dysesthesias, and urinary disturbances).

Human immunodeficiency virus

Human immunodeficiency virus (HIV) infects human helper T cells, leading to a progressive immunodeficiency disease. In its end stages it is called acquired immunodeficiency syndrome (AIDS). Cutaneous manifestations are prominent,

affecting up to 90% of HIV-infected persons. Many patients have multiple skin lesions of different kinds. The skin lesions or combinations of skin conditions are so unique that the diagnosis of HIV infection or AIDS can often be suspected from the skin examination alone. The skin findings can be classified into three broad categories: infections, inflammatory derma- toses, and neoplasms. The skin conditions also tend to appear at a specific stage in the progression of HIV disease, making them useful markers of the stage of HIV disease.

The natural history of HIV infection in the vast majority of patients is a gradual loss of helper T cells. The rate of this decline is variable, with some patients progressing rapidly and others very slowly or not at all (long-term nonprogressors). Soon after infection there is a seroconversion syndrome called primary HIV infection, or acute infection (group I). Patients recover from this syndrome and enter a relatively long latent period (asymptomatic infection or group II), which averages about 10 years. During this period patients may have persistent generalized lymphadenopathy (group III). When symptoms begin to appear they are often nonspecific and include fever, weight loss, chronic diarrhea, and mucocutaneous disease (group IV A). Helper T-cell counts in group II, III, and IV A patients usually range from 200 to 500. The skin findings at this stage (originally called AIDS-related complex [ARC]) include seborrheic dermatitis, psoriasis, Reiter syndrome, atopic dermatitis, herpes zoster, acne rosacea, oral hairy leuko- plakia, onychomycosis, warts, recurrent *S. aureus* folliculitis, and mucocutaneous candidiasis.

Once the helper T-cell count is 200 or less, the patient is defined as having AIDS. In this stage of HIV disease, the skin lesions are more characteristic of immunodeficiency and include characteristic opportunistic infections: chronic herpes simplex, molluscum contagiosum, bartonellosis (bacillary angiomatosis), systemic fungal infections (cryptococcosis, histoplasmosis, coccidioidomycosis, and penicilliosis), and mycobacterial infection. Paradoxically, patients at this stage also have hyper-reactive skin and, frequently, inflammatory, often pruritic skin

diseases. These skin conditions include eosinophilic folliculitis, granuloma annulare, drug reactions, enhanced reactions to insect bites, and photodermatitis.

When the T-cell count falls below 50, the patient is often said to have "advanced AIDS." These patients may have very unusual presentations of their opportunistic infections, including multicentric, refractory molluscum contagiosum; chronic herpes simplex; chronic cutaneous varicella zoster infection; cutaneous acanthamebiasis, cutaneous atypical mycobacterial infections (including *Mycobacterium avium* complex and *Mycobacterium haemophilum),* and crusted scabies. Treatment of their infections is often very difficult because of the significant chronic immunosuppression.

It is now clear that HIV itself is the cause of the loss of helper T cells and that effective treatment of HIV infection may halt or reverse the natural history of HIV disease. There are numerous antiretroviral agents and they are usually used in combinations called "cocktails." This combination treatment is called highly active antiretroviral therapy (HAART). A significant percentage of HIV-infected patients respond to HAART and may show dramatic improvement of their HIV disease. HIV disappears from the blood and helper T-cell counts rise. As expected, in patients who respond to HAART, opportunistic infections no longer occur, and subsequently mortality decreases. This is also true of cutaneous infectious conditions.

HIV-associated psoriasis usually improves substantially, especially if the patient did not have psoriasis prior to HIV infection.

HAART is typically associated with resolution of all forms of HIV-related cutaneous complications. However, some conditions may initially appear or be exacerbated by the sudden improvement of the immune status that occurs with eradication of HIV viremia and with increase in helper T-cell counts. This complex of manifestations has been termed the "immune reconstitution" or "immune restoration" syndrome (IRIS). IRIS occurs in between 15% and 25% of HIV-infected persons started on HAART. Persons with an opportunistic infection (OI), specifically cryptococcosis, tuberculosis, or *Pneumocystis* pneumonia, may

be at higher risk if HAART is started as the OI is being treated. This marked inflammatory syndrome can be severe, and in resource-poor countries 5% of AIDS- related deaths in treated patients can be attributed to IRIS during the first year of HAART therapy. Half of IRIS- related conditions are dermatological. Three forms of IRIS occur:

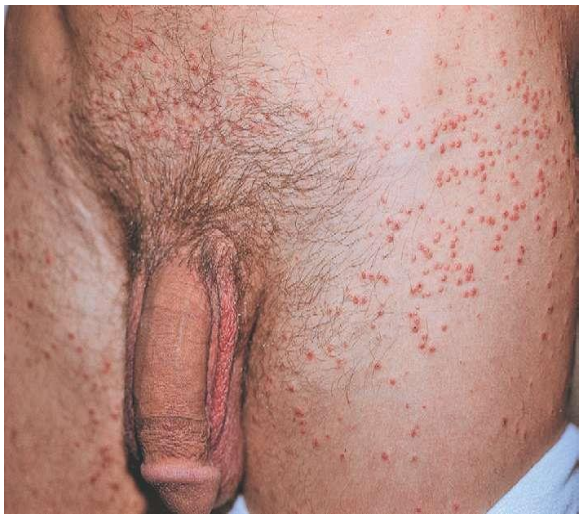
2007 hidden OI is unmasked as the reconstituted immune system attacks the hidden pathogen. The presentation may be atypical. The appearance of cutaneous mycobacterial infections with HAART is an example.

2008 In the setting of a documented OI, when HAART is started, the patient has worsening of the infection with new findings. This is not treatment failure, but enhanced immune response to the pathogen. This typically occurs with tuberculosis or cryptococcosis.

2009 The development of new disorders is seen, infectious or inflammatory, or enhanced inflammatory responses around malignancies, especially Kaposi sarcoma. Eosinophilic folliculitis, acne flares, drug eruptions, Reiter's syndrome, lupus erythematosus, alopecia universalis, at times HPV infections (especially oral and genital), increased outbreaks of genital and orolabial herpes simplex, or molluscum contagiosum, herpes zoster, cytomegalovirus ulcerations, type I reactions in Hansen's disease, cutaneous mycobacterial and fungal infections, leishmaniasis, tattoo and foreign body granulomas, and sarcoidosis can be part of IRIS in the skin.

Primary HIV infection (acute seroconversion syndrome)

Several weeks after infection with HIV, an acute illness develops in a large proportion of individuals. The clinical syndrome is much like EBV infection, with fever, sore throat, cervical adenopathy, a rash, and oral, genital, and rectal ulceration. The skin eruption can be polymorphous (Figs 65 and 66). Most characteristic is a papular eruption of discrete, slightly scaly, oval lesions of the upper trunk. The lesions have a superficial resemblance to pityriasis rosea, but the peripheral scale is not prominent, and there is focal hemorrhage in the lesions.



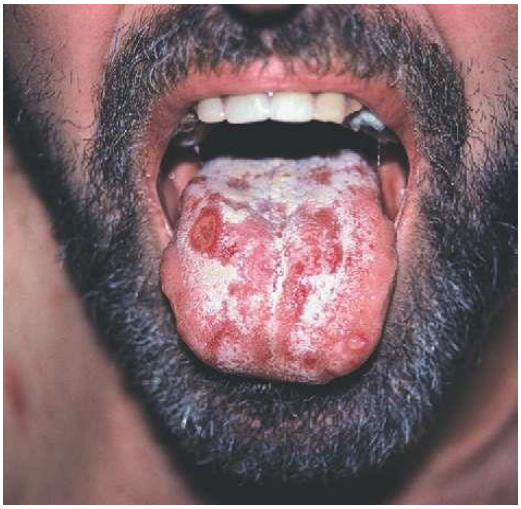


Fig. 65 Primary HIV infection. **Fig. 66** Primary HIV infe

A Gianotti-Crostilike papular eruption may also occur. Purpuric lesions along the margins of the palms and soles, as seen in immune complex disease, have been reported. The mucosal erosions resemble aphthae but are larger and can affect all parts of the mouth, pharynx, esophagus, and anal mucosa. Dysphagia may be prominent. The helper T-cell count falls abruptly during seroconversion. The level of immune impairment may be adequate to allow oral candidiasis or even *Pneumocystis jirovecii* (formerly *carinii)* pneumonia to develop. The diagnosis should be suspected in any at-risk individual with the correct constellation of symptoms. A direct measurement of HIV viral load will confirm the diagnosis. Combination antiviral therapy is instituted immediately.

HIV-associated pruritus

From early in the HIV epidemic, it was clear that pruritus was a marker of HIV infection throughout the world, occurring in up to 30% of patients. Pruritus is usually not caused by HIV disease itself but is related to inflammatory dermatoses associated with the disease. "Papular pruritic eruption" is not a specific disease, but a wastebasket diagnosis used to encompass patients with many forms of HIV-associated pruritus. Worldwide, it most commonly represents enhanced insect bite reactions. These pruritic eruptions are best subdivided into fol- licular and nonfollicular eruptions. The relative prevalence of these two patterns of pruritic eruptions is geographically distinct. In tropical and semitropical regions where

biting insects are prominent, nonfollicular eruptions are most common, and probably represent insect bite hypersensitivity. In temperate regions, follicular pruritic eruptions are more common.

Eosinophilic folliculitis (EF) is the most common pruritic follicular eruption. It is seen in patients with a helper T-cell count of about 200. Clinically, it presents with urticarial fol- licular papules on the upper trunk, face, scalp, and neck (Fig. 67).

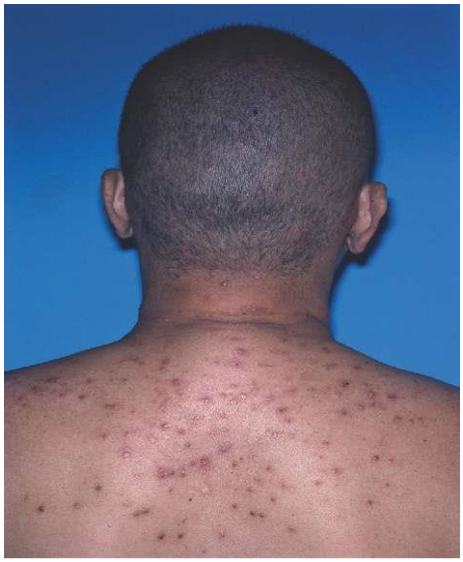


Fig. 67 Eosinophilic folliculitis.

Pustular lesions are uncommon; pustules are usually smaller than in bacterial folliculitis and represent end-stage lesions. They are uncommonly seen, since the pruritus is so severe that they are excoriated before the lesion evolves to this degree. Ninety percent of lesions occur above the nipple line on the anterior trunk, and lesions typically extend down the midline of the back to the lumbar spine. The disease waxes and wanes in severity and may spontaneously clear, only to flare unpredictably.

A peripheral eosinophilia may be present and the serum IgE level may be elevated, suggesting this is a disorder mediated by T-helper 2 cells. Histologically, an infiltrate of mononuclear cells and eosinophils is seen around the upper portion of the hair follicle at the level of the sebaceous gland. As lesions evolve, eosinophils and lymphocytes enter the follicular structure and the sebaceous

glands. Pustules are formed late and represent aggregates of eosinophils in the uppermost part of the follicle.

Initial treatment of eosinophilic folliculitis is topical steroids and antihistamines. If the patient fails to respond, phototherapy (UVB or PUVA) or itraconazole, 200 mg twice a day, may be effective. In some patients repeated applications of per- methrin (every other night for up to 6 weeks) may be of benefit. This latter therapy is directed at *Demodex* mites, which may be the antigenic trigger of this condition. Isotretinoin is also effective, often after a few months, in a dose of about 0.5-1 mg/ kg/day. HAART may lead to a flare of EF, but usually leads eventually to its resolution. Staphylococcal folliculitis, which may be severely pruritic in patients with HIV disease, and *Pityrosporum* folliculitis should be included in the differential diagnosis. These are excluded by bacterial culture and skin biopsy, respectively.

The other pruritic dermatoses that are not follicular can be divided into the primarily papular eruptions and the eczema- tous ones. The papular eruptions include scabies, insect bites, transient acantholytic dermatosis, granuloma annulare, and prurigo nodularis. The eczematous dermatoses include atopic- like dermatitis, seborrheic dermatitis, nummular eczema, xerotic eczema, photodermatitis, and drug eruptions. Patients may have multiple eruptions simultaneously, making differential diagnosis difficult. A skin biopsy from a representative lesion of every morphologic type on the patient may elucidate the true diagnosis. Treatment is determined by the diagnosis and is similar to treatment in persons without HIV infection with these same dermatoses. Special considerations in AIDS patients include the use of topical therapy plus ivermectin for crusted scabies and thalidomide for prurigo nodularis and photodermatitis. Both of these systemic agents are very effective if used appropriately.

HIV-associated neoplasia

Neoplasia is prominent in HIV infection and in some cases is highly suggestive of HIV infection. Kaposi sarcoma is an example. Other common neoplasms seen in patients with HIV infection include superficial basal cell

carcinomas (BCCs) of the trunk, SCCs in sun-exposed areas, genital HPV-induced SCC, and extranodal B- and T-cell lymphomas. Lipomas, angiolipomas, and dermatofibromas may occur in association with HAART therapy. In the case of lipomas, their appearance is usually related to the peripheral fat loss that occurs with some HIV treatment regimens and with HIV disease itself.

Nonmelanoma skin cancers (NMSC) are very common in HIV-infected persons. HAART does not protect against the development of NMSC in HIV. The rate of development of BCC and SCC is not increased in persons with HIV infection. BCCs usually occur as superficial multicentric lesions on the trunk in fair-skinned males in their twenties to fifties. The ratio of BCC to SCC is not reversed in HIV disease, as it is in organ transplant recipients. BCCs behave in the same manner as they do in the immunocompetent host and standard management is usually adequate.

Actinically induced SCCs are also quite common and present in the standard manner as nodules, keratotic papules, or ulcerations. In most cases, their behavior is relatively benign and standard management is adequate. Removal of SCCs in sun- exposed areas by curettage and desiccation in patients with HIV infection is associated with an unacceptably high recurrence rate of about 15%. Complete excision is therefore recommended. The use of imiquimod to treat SCC in situ in the setting of HIV infection should be considered experimental, and if it is undertaken, very close followup is recommended. In a small subset of patients with AIDS, actinic SCCs can be very aggressive-they may double in size over weeks and may metastasize to regional lymph nodes or viscerally, leading to the death of the patient.

Genital SCCs, including cervical, vaginal, anal, penile, and nailbed SCC, all occur in patients with HIV infection. These neoplasms are increased in frequency, and the progression from HPV infection to neoplasia appears to be accelerated. This is analogous to the situation in organ transplant and other immunosuppressed patients. It appears that these cancers are associated with primarily "high-risk" HPV types.

For the dermatologist, there are three important manifestations of high-risk genital HPV infection in patients with HIV. Most common is perianal dysplasia, seen most frequently in MSM with a history of receptive anal intercourse. Dysplasia in this area may present as velvety white or hyperpigmented plaques involving the whole anal area and extending into the anal canal. These lesions may erode or ulcerate. Histology will demonstrate SCC in situ. The risk of progression of the lesions to anal SCC is unknown but is estimated to be at least 10 times higher than the rate of cervical cancer in women in the general population. The management of such lesions is unclear, but regular follow-up is clearly indicated and any masses in the anal canal should be immediately referred for biopsy. At some centers pap smear equivalents are performed. Imiquimod has been used as an adjunct in the management of genital warts and HPV-associated genital in situ dysplasias (not genital SCC). While it may be of benefit in patients with reconstituted immune systems on HAART, especially in combination with surgical ablation, the response rate is much lower than in immunocompetent patients. In the only placebo-controlled trial, done before standard HAART was available, imiquimod was no more effective than placebo in clearing genital warts in HIV infection (11% of genital warts cleared). Small case series of patients on HAART suggest clearance rates of about 30-50%.

The vulvar and penile skin may develop flat white or hyperpigmented macules from a few millimeters to several centimeters in diameter. These show SCC in situ and are analogous to bowenoid papulosis in the immunocompetent host. Rare cases of progression to SCC have occurred. Such lesions are best managed conservatively as warts and watched closely. Lesions of the penis and vulva, not at a transition zone or on mucosal surfaces, have a low risk of progressing to invasive SCC. Lesions of the glans penis that are red and fixed should be biopsied. If the changes of SCC in situ are found, these should be managed aggressively as SCC in situ. Topical 5-FU and superficial radiation therapy are effective. Close clinical follow-up is indicated. Periungual SCC has also been seen in patients with HIV infection. Any persistent keratotic or hyper-

pigmented lesion in the periungual area must be carefully evaluated. Management is surgical excision.

Extranodal B-cell and, less commonly, T-cell lymphomas are associated with the advanced immunosuppression of AIDS. The B-cell lymphomas and some of the T-cell lymphomas present as violaceous or plum-colored papules, nodules, or tumors.

Once the diagnosis is established by biopsy, systemic chemotherapy is required. EBV is found in some cases. HAART is both protective against the development of non-Hodgkin lymphoma (NHL) and Hodgkin disease in HIV and substantially improves prognosis of HIV-infected patients with NHL. Mycosis fungoides can also be seen in patients with HIV infection, often in patients who have not yet developed AIDS. It presents with pruritic patches or plaques and may progress to tumor stage. EBV is not found in these cases. CD8+ pseudolymphoma is also seen in patients with untreated HIV infection, and may resolve with HAART.

Malignant melanoma (MM) is occasionally seen in persons with HIV infection. The rate of MM is up to four times higher in HIV-infected persons. These patients demonstrate the same risk factors as do other melanoma patients-multiple nevi, fair skin type, and prior intermittent intense sun exposure. HIV- infected patients with melanoma in the era prior to HAART had a significantly shorter disease-free survival and a reduced overall survival. Many fair-skinned patients infected with HIV complain of the new onset of atypical moles (analogous to organ transplant patients). Whether these confer an increased risk of melanoma is unknown.

AIDS and Kaposi sarcoma

Kaposi sarcoma (KS) was, along with *Pneumocystis* pneumonia, the harbinger of the AIDS epidemic. Many MSM and bisexual men presented with this tumor in the early 1980s, with a prevalence of up to 25% in some cohorts. HHV-8, a y-herpesvirus, has been identified in these lesions. The clinical features of KS in patients with AIDS are different than those seen in elderly men who do not have AIDS. Patients with AIDS present with symmetrical widespread lesions,

often numerous. Lesions begin as macules that may progress to tumors or nodules (Fig. 68). Any mucocutaneous surface may be involved, but areas of predilection include the hard palate, face, trunk, penis, and lower legs and soles. Visceral disease may be present and progressive. Edema may accompany lower leg lesions, and if it is significant, it is often associated with lymph node involvement in the inguinal area.

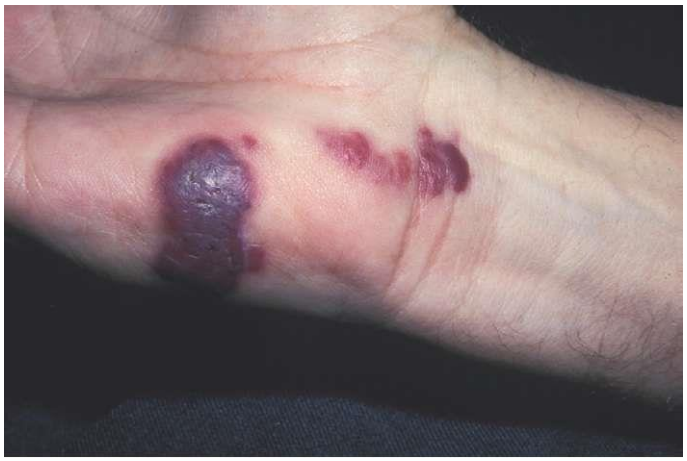


Fig. 68 Kaposi sarcoma in AIDS.

A diagnosis of KS is established by skin biopsy, which should be taken from the center of the most infiltrated plaque. Excessive bleeding is not usually a problem. Early macular lesions show atypical, angulated, ectatic vessels in the upper dermis associated with an inflammatory infiltrate containing plasma cells. Plaque lesions show aggregates of small vessels and endothelial cells in the upper dermis and surrounding adnexal structures. Nodules and tumors show the classic pattern of a spindle cell neoplasm with prominent extravasation of red blood cells.

2008 HAART has reduced the incidence of KS in HIV-infected patients by 10-fold. However, KS remains an important complication of HIV infection for two reasons: HIV-associated KS is still common in sub-Saharan Africa. With HAART therapy, survival in Africa for HIV-infected persons over 1 year is nearly 100%, if they do not have KS. In patients with HIV disease and KS, however, survival is only 77%. This is due to the lack of effective cytotoxic therapy for KS in Africa. HIV-KS is more common in women than men in some clinics in Africa.

While HAART has substantially reduced the prevalence of KS in HIV disease in the developed world, HAART has not eliminated the disease. In fact, there remains a fairly substantial proportion of primarily gay men with HIV disease who also have KS (up to 13% of some cohorts). Twenty percent or more of these AIDS-KS patients have well-controlled HIV disease with long-term undetectable viral load and CD4 counts above 300. These patients have an overall good prognosis, but still may require cytotoxic or radiation therapy to control their KS. Patients with AIDS-KS and lower CD4 counts and detectable viral loads are more likely to have visceral disease. Up to one-third of these AIDS-KS patients died despite HAART and chemotherapy, suggesting that AIDS-KS in the setting of poor HIV control is a bad prognostic finding.

The treatment of AIDS-associated KS depends on the extent and aggressiveness of the disease. Effective HAART after about 6 months is associated with involution of KS lesions in 50% of patients. This should be the initial management in most patients with mild to moderate disease (fewer than 50 lesions, and fewer than 10 new lesions/month) who are not receiving anti-HIV treatment. Intralesional vinblastine, 0.2-0.4 mg/mL, can be infiltrated into lesions (as for a hypertrophic scar) and they will involute over several weeks. Hyperpigmentation usually remains. Cryotherapy is also effective but will leave postinflammatory hypopigmentation in pigmented persons. Persistent individual lesions and lesions of the soles and penis respond well to local irradiation therapy (one single treatment of 80 Gy or fractionated treatments to 150 Gy). For patients with moderate disease (more than 10 lesions, or mucosal or visceral involvement), HAART alone may not be adequate in controlling KS, and liposomal doxorubicin may need to be added to their treatment. For patients with symptomatic visceral disease, aggressive skin disease, marked edema, and pulmonary disease, systemic chemotherapy is indicated. Options include IFN-a, vinca alkaloids, bleomycin, and lipo- somal doxorubicin as first-line therapies, and taxol for treatment failures.

TEST

1. The skin is develops from these following germ layers:

* ecto- and mesodermal

mesoderm

enteroderm

ectoderm

2. The weight of the skin without hypodermis is include:

15% of body weight

* 5% of body weight

20% of body weight

There is not correct answer

3. The area of the skin is cover:

* 1.5 - 2 sq. m

3.5 - 4 m

4.5 - 5 m

4. During the day, with the surface of the skin evaporates:

* 600 - 800 ml of water vapor

50 - 100 ml of water vapor

200 - 300 ml of water vapor

1000 - 1500 ml water vapor

5. The sebaceous glands secretes in a week:

* 100 - 200 gr. sebum

10 - 50 gr. sebum

300 - 400 gr. sebum

500 - 600 gr. sebum

6. In the epidermis approximately separates:

* 3 layers

4 layers

5 layers

6 layers

7. In the epidermis layers are distinguished, except:

Basal layer

Suprabasal layer

granular layer

* reticulat layer

8. Proliferative cells of the epidermis are include:

* basal cells

lymphocytes

Macrophages

mastocytes

9.Normal dermographism is:

white

*red

mixed

absent

10. what feels Vater – Paciniand Golgi – Mazzoni bodies:

* feeling of a deep pressure

feeling the heat

feeling cold

pain

11. What feels tactile corpuscle of the Meysner:

* tactile sensitivity

feeling cold

pain

not involved in the perception

12. What feels Ruffini corpuscles:

*heat

pain

sense of balance

feeling cold

13. What feels glomeruli Krause:

* feeling cold

pain

a deep sense of pressure

feeling the heat

14. bristling hair localized everywhere except:

* beard and mustache

field brow

edges of the eyelids

nasal vestibule

15. The outcome of a blister:

erosion

ulcer

spot

* disappears without a trace

16. An ulcer is:

skin defect within the epidermis

* deep skin defect

Changing of the color of the skin

slight thickening of the skin

17. What are the primary morphological elements came from the papillary layer of the dermis:

*blister

epidermal papule

bullas

surface pustule

18. Polymorphic lesions occur in diseases like, except:

* Psoriasis

Lichen planus rubra

molluscum contagiosum

secondary syphilis

19. follicular pustules are listed below, except:

osteofolliculitis

folliculitis

furuncle

*impetigo

20. After opening the vesicules is formed:

vegetation

ulcer

squama

*erosion

21. parakeratosis is typical for:

* Psoriasis

Lichen planus rubra

simple bullas stripping

secondary syphilis

22. acantholysis is typical for:

shingles

scarring pemphigoid

dermatitis Duhring

* acantholytic pemphigus

23. Spongiosis typical for:

* Eczema

pemphigus

simple bullas stripping

skin tuberculosis

24. granulosis typical for:

psoriasis

* lichen planus rubra

true eczema

furuncle

25. papillomatosis is typical for:

molluscum contagiosum

* vulgar warts

Lupus eritramatosis

zoonotic form microsporia

26. Lotions are prescribed for:

Hyperkeratosis

* acute inflammation to get wet

Squamation

itching

27. Disinfectants are:

corticosteroids

*boric acid

zinc oxide

menthol

28. Subcutaneous adiponecrosis is develops from:

* 1-2 weeks of life

1-2 months of life

in the second year of life

after puberty

29. streptoderma affected:

*smooth skin

hair follicles

sebaceous glands

sweat glands

30. hydradenitis cause:

* staphylococci

streptococci

Pseudomonas aeruginosa

mixed infection

31. Vulgar Sycosis differentiate with:

lupus erythematosus

psoriasis

* parasitic sycosis

eczema

32. Gidrodenit - an inflammation:

* apocrine glands

sebaceous follicles volosiny

eccrine glands

Breast

33. Superficial staphilodermatitis is:

* ostiofollikulit

folliculitis

furuncle

hydradenitis

34. The primary lesions of the streptococcal impetigo is:

pustule

* flictenas (flaccid bladder)

blister

nodule

35. vulgar impetigo cause:

streptococci

staphylococci

* mixed infection

viruses

36. What are the morphological lesion is typical for the herpes simplex virus:

* blisters, erosion, crust

nodules, scales

nodules, blisters

abscesses, ulcers

37. primary lesion of the contagious mollusk:

*papule

tubercle

vesicle

blister

38. Ways of infection genital warts:

*sexual

transfusing

close household contact

airborne

39. The infection in a child should take the following actions:

* Isolation of healthy children

Hormone Therapy

Ultrasound of internal organs

Antibiotic treatment

40. Cause of the scabies:

virus

protozoa

* Parasites

bacteria

41. In what layer of the skin the female mite lays itch move:

in shiny

in granular

* in the stratum corneum

in the suprabasal

42. The most frequent length of the incubation period for scabies:

* 5-12 days

21 day

6 weeks

4 months

43. Clinic of the Scabies characterized by the following morphological lesions:

lenticular papules

tubercles

* paired pruritic nodules and blisters

nodule

44. Symptoms Gorchakov-Hardy, Michaelis, Sezary detected in:

Scabies

lice

leishmaniasis

acne vulgaris

45. Symptom Gorchakov-Hardy - is:

* purulent and bloody crusts in the elbow

bloody crusts in the gluteal folds

itchy, worse in the evening

excoriations due to scratching

46. Specify the most frequent complications of scabies:

sepsis

* secondary pyoderma

eczema

dermatitis

47. On the basis of the method of laboratory diagnosis is established the final diagnosis "scabies":

sowing on fertile ground

REEF

PCR

*microscopy

48. Definitive diagnosis of scabies is the main criterion is :

itch

availability scratching

* detect scabies mite

blistering

49. What are the medicines used to treat head lice:

flutsinar

Neo-Penotran

* nittifor

Augmentin

50. Complications of head lice:

* pyoderma

alopecia

allergic reactions

temperature increase

51. Pubic lice can be transmitted in:

in the bath

* during sexual intercourse

when visiting the pool

on the beach

52. The source of infection zoonotic microsporia:

Rodents

* cats, dogs

cows, horses

birds

53. The source of chronic infection trichophytosis:

cats

*people

birds

calves

54. Superfecial trichophytosis common in:

milkmaid

*children

adult men

farm workers

55. rubromikoza causative agent is:

* Trichophyton rubrum

Epidermophyton floccosum

Corynebacteria minutissima

Pityrosporum orbiculare

56. anthroponotic microsporia causative agent is:

* Microsporum ferrugineum

Microsporum lanosum

Trichophyton schonleinii

Trichophyton violaceum

57. The causative agent is Trichophyton antropofilnymi:

* Trichophyton violaceum

Trichophyton rubrum

Trichophyton verrucosum

Microsporum ferrugenii

58 agents of parasitic sycosis is:

Trichophyton rubrum

Trichophyton Schoenleini

* Trichophyton gypseum

Trichophyton violaceum

59. The luminescence in the survey using a Wood's lamp is detected in patients with:

* zoonotic microsporia

surface trichophytosis

crusted ringworm

infiltrative-suppurative trichophytosis

60. At a height of 5 to 8 mm above the hairs break off at the skin:

trihofitii

* microsporia

crusted ringworm

alopecia areata

61. Smooth skin microsporia is not typicalfor:

Presence of the erythematiuos-squamous area

* fuzzy boundaries and fast healing

Squamation

vesicules around the edge of the focus

62. For favus is typical:

the presence of crusts

* brittle hair and papuleformation

scarring

atrophy of the hair

63. For Trichophyton of the Fold are not typical:

infiltration

brick-reddish color

corral-red glow when Luminescence

* papular lesions

64. For Trichophyton Rubra are typical:

acanthosis

* hyperkeratosis

spongiosis

parakeratosis

65. For the topical treatment of fungal infections do not apply:

mikoseptin

Lamisil

clotrimazole

* prednisolone

66. Treatment of the Erythrasma are carry out by:

* erythromycin ointment

oxolinic ointment

toxoids

Oksikort

67. Balzer test is positive for:

candidiasis

athlete's foot

* Tinea versicolor

Trychophyton Rubra

68. Candidiasis of the skin and mucous are causes by:

Trichophyton rubrum

* Candida albicans

Corynebacteria minutissima

Pityrosporum orbiculare

69. The causative agent of tinea versicolor are:

* Pityrosporum orbiculare

Corynebacterium minutissimum

Epidermophyton floccosum

Trichophyton mentagraphytes var interdigitale

70. The main type of allergic response in the skin vasculitis are:

anaphylactoid

cytotoxic

* immunocomplex

and cytotoxic anaphylactoid

71. Vasculitis are divided into:

* to the superfecial and deep

infectious and noninfectious

infectious and medicinal

inherited and acquired

72. In the hemorrhagic vasculitis of the skin, are affected:

nervous system

* vessels of internal organs

articular cartilage

endocrine system

73. itching dermatosis does not include:

hives

neurodermatitis

pruritus of the Gebre

* pink zoster Gibert

74. The morphological lesion that typical for the child pruritus:

blister

nodule

microvesicles

* seropapula

75. What lesions appears in the urticarial:

papules

* blisters

Vesicles

Bulla

76. Location of the primary lesionin the urticaria:

* in the papillary layer of the dermis

in the stratum corneum of the epidermis

in the granular layer of epidermis

in hypodermis

77. What dermographism are investigates urticaria in the patients:

*red

white

mixed

dermogrfizm are not appear

78. Bullous dermatoses does not apply:

pemphigus vulgaris

bullous pemphigoid

herpetiformis dermatosis

* pemphigus of the newborns

79. Bullous dermatosis, in which bulles usually start in the oral mucosa:

* pemphigus vulgaris

familial pemphigus

syphilitic pemphigus

Duhring-Brock disease

80. acantholytic pemphigus group does not include:

vulgar

seborrheic

vegetating

* Familiar

81. Levels of lying of the bulla with respect to the epidermis in the pemphigus are:

* intraepidermal

subepidermal

intradermal

intraepidermal

82. vulgar pemphigus are investigate in the:

* IgG deposition in the intercellular substance and thorny layer cells

IgG deposits in the basal membrane

immune complex deposition beneath the basement membrane

green light (Wood's lamp)

83. The skin around the bullas in the pemphigus:

hyperemic

* is not changed

infiltrated

purplish tone

84. To get the symptoms of asbestos-Hansen should:

* press the bullas

open top of the bullas

Pull top of the bullas

rub between bullas

85. For the treatment of pemphigus apply:

antibiotics

* glucocorticoid hormones

iron supplements

antihistamines

86. Seborrheic pemphigus includes the following symptoms:

* lupus, seborrheic dermatitis and pemphigus

Lichen planus rubra, vasculitis and pemphigus

lupus erythematosus, dermatomyositis, and pemphigus

scleroderma, psoriasis and pemphigus

87. Pemphigus is differentiate from dermatitis Dühring with:

severe itching

tense of the bulla

grouping bullas

* positive sign of Nikolsky

88. Polymorphism of the lesion are typical for:

pemphigus vulgaris

bullous pemphigoid

* Duhring disease

Leaf like-pemphigus

89. dermatosis, which a diagnostic significance with a positive test of iodine:

pemphigus vulgaris

* dermatitis Duhring

bullous pemphigoid

familial pemphigus

90. Laboratory tests for the diagnosis of disease Dühring are:

* eosinophilia in the blood and bullous fluid

Ttsanka cells in smears prints from the bottom of erosions

Sezary cells

a symptom of a ladies' heel

91. Except the skin at the scarring pemphigoid are affected:

skin folds

scalp

* conjunctival mucosa

nail plate

92. What primary lesions observed in psoriasis:

* papule

blister

bullas

tubercle

93. Symptom Pilnova in psoriasis are:

* bright red color of the papules

atrophic ring around papules

isomorphic skin reaction

desquamation in the center of papules

94. When heelpiece (heeling) of the papules in psoriasis are observed:

a symptom of a hidden desquamation

* psoriatic triad phenomena

a symptom of a ladies' heel

symptom "cobblestones"

95. What is the morphological basis of the phenomenon of "terminal membrane":

acantholysis

spongiosis

* acanthosis

ballooned degeneration

96. Positive isomorphic Koebner reaction is:

* the appearance of fresh papules at the site of injury in 7-14 days

the phenomenon of "stearin spot"

the phenomenon of "hidden desquamation"

Voronov rings

97. In the treatment of psoriasis do not apply:

hyposensitizing drugs

sedatives

vitamins

* antivirals

98. Polygon shiny papules with Umbriacal like impression observed at:

*Lichen Planus Rubra

psoriasis

secondary recurrent syphilis

secondary fresh syphilis

99. Pathological changes in lichen planus rubra:

* hypergranulesis

Akantolisis

swelling of the papillary layer of the dermis

endo-, meso-, periarteritis

100. Grid Wickham observed at:

* Lichen planus rubra

discoid lupus erythematosus

psoriasis

centrifugal erythema of Biett

102. lichen rosacea is localized mainly on:

scalp

shins

* the body, along the lines of skin tension

feet

103. For the treatment of lichen rosacea it is advisable to appoint:

* allergen therapy

hormones

antifungal antibiotics

lidase

104. Specify obligate precancerous disease:

Bowen's disease

* xeroderma pigmentosum

leukoplakia

Keira erythroplasia

105. The basal cell carcinoma is more often localized on:

palms

* Facial

trunk

hips

106. In chronic lupus eritematosis affected:

kidneys

liver

C.N.S

*skin

107. centrifugal erythema characterized by:

*erythema

follicular hyperkeratosis

atrophy

108. Currently lupus eritematosis relate to the:

infectious diseases

* autoimmune diseases

viral diseases

sexually transmitted diseases

109. For the topical treatment of lupus eritematosis apply

antibiotic ointments

* steroid ointment

salicylic ointment

antifungal ointment

110. discoid lupus erythematosus ends with:

* scarring

pigmentation spots

pass completely

transformed into lymphoma

111. For dermatomyositis is characterized by:

muscle hypertrophy

hemosiderosis

* kreatinuriya

anemia

112. For the treatment of localized scleroderma are used:

Lotion

UFO

*paraffin

PUVA - therapy

113. plaque of the scleroderma ends with:

* scar atrophy

pigmentation spots

pass completely

joining a secondary infection

114. Primary lesion of the tuberculosous lupus are:

* tuberculums

ulcers

nodules

papules

115. For the treatment of dermatomyositis is used:

* Corticosteroids

calcium supplements

tranquilizers

antistaphylococcal immunoglobulin

116. papule - necrotizing tuberculosis differentiate from:

exudative erythema multiforme

* pruritus

psoriasis

skrofulodermy

117. Skrofuloderma often localized:

* neck area

groin

hips

trunk

118. Verrucose tuberculosis are often localized at:

trunk

* back of the hand

scalp

palms

119. The diagnosis of tuberculosis of the skin is put on the basis of:

tuberculin tests

skin biopsies

fluorography of lungs

* All the above methods are correct

120. Tuberculosis of the skin are treated with:

penicillin

tetracycline

* rifampicin

gerpevir

121. Erythema nodosum of Bazin is localized on:

the face

trunk

* legs

scalp

122. The source of infection of old world type of leishmaniasis are:

sick cats

* Rodents

cattle

sick people

123. The sources of contamination new world leishmaniasis type are:

Rodents

cattle

*sick people

cats, dogs

124. Carriers Leishmania are:

* Mosquitoes

sick animals

sick people

Rodents

125. Leishmaniasis clinic is typical for:

tubercle

ulcer

scar

* All the above mentioned are correct

126. Treatment of leishmaniasis are used:

hormones

* Antibiotics

sulfa drugs

antifungals agents

127. The causative agent of leprosy:

protozoa

* mycobacteria

Spirochetes

Viruses

128. The incubation period for leprosy include:

a few days

a few months

*some years

few hours

129. Mycobacterium leprae looking for:

in sputum

in fecal masses

* in scrapings from the nasal mucosa

urine

130. lepromatous type of leprosy differentiates from:

psoriasis

lichen planus rubra

* gummy syphilides

Lichen rosacea

131. In the base of eczema are highlights histopathological changes:

parakeratosis

* spongiosa

Akantolizis

Vegetation

132. For Vitiligo is typical primary lesions:

papule

blister

* depigmentation spot

Nodule

133. The causative agent of syphilis:

* Treponema pallidum

Treponema balanitidis

Treponema pertenue

Treponema caratea

134. Treponema pallidum has been discovered:

in 1901year

1889 year

* in 1905 year

1926 year

135. The duration of the division of pathogenic Treponema pallidum is including:

6-8 hours

10-12 hours

15-20 hours

* 30-33 hours

136. The length of Treponema pallidum approximately include:

* 6-20 microns

50-60 microns

30-40 microns

40-50 microns

137. The incubation period for syphilis is shortened in:

In drug users (narcomoniac)

* in young, physically healthy people

in individuals with immunodeficiency

after taking antibiotics

138. Headless syphilis is possible in:

* in blood transfusion patient

Late congenital syphilis

indefective preventive treatment

the presence of extragenital chancre

139. After contact with patience syphilis, hard chancre appears within:

1 week

2 weeks

*4 weeks

6-7 weeks

140. What period begins "transfusion" Syphilis:

primary

* with secondary

Tertiary

with congenital

141. The scar after healing of the chancre is called:

Cain printing

* seal the devil

chancre-print

stellate

142. What is the re-infection of syphilis:

* reinfection

superinfection

Jarisch-Herxheimer-Lukashevich response

immunoblotting

143. Wasserman reaction after infection with syphilis will be positive within:

3-4 weeks

* 6-8 weeks

9-12 weeks

24 years

144. The most specific serologic test for syphilis is:

immunofluorescence

* immobilization reaction treponem

Wasserman reaction

microreaction

145. The reaction of immobilization treponema palidium is made purpose of:

confirm the diagnosis of primary syphilis

* confirm the diagnosis of latent syphilis

confirm the diagnosis of secondary syphilis fresh

to monitor of treatment

146. The increase in regional lymph nodes after the appearance of the chancre is usually observed within:

1^{st} -2^{nd} days

* 5^{th}-8^{th} days

9^{th}-12^{th} days

13^{th}-16^{th} days

147. The main drugs for the treatment of patients with syphilis are include:

* penicillin drugs

Tetracycline drugs

drugs erythromycin

macrolides

148. To the side effects in the treatment of syphilis with penicillin are all listed, except:

anaphylactic shock

toksidermia

candidiasis

* alopecia

149. The secondary period of syphilis begins from the moment of infection within:

2 weeks

2 months

*3 months

6 months

150. Secondary syphilides of the mucous membranes:

Occurs rare

* Observed in the form of a papules andspotty rash

Have a fuzzy boundaries

Not very contagious

151. After the appearance of hard chancre of syphilis in a second period occurs, approximately within:

5-6 weeks

6-7 weeks

* 6-8 weeks

8-9 weeks

152. The differential diagnosis of papular syphilides should be carried out with all the listed diseases, except:

Lichen planus rubra

guttate parapsoriases

* leaf form pemphigus

follicular hyperkeratosis

153. Wide warts appear:

* During the secondary recurrent syphilis

Two weeks after infection

1 month after infection

the primary seropositive period

154. Wide condylomas must be differentiated from:

* genital warts

Tinea versicolor

Lichen rosacea

Urticarial

155. "Crown of Venus" - is:

syphilitic alopecia

syphilitic leukoderma

* papules on the edge of the growth of hair on the head

papules on the genitals

156. Syphilitic leukoderma occurs:

* 6 months. after infection

in the incubation period

2 weeks after infection

in primary seronegative period

157. "necklace of Venus" - is:

syphilitic alopecia

* syphilitic leukoderma

papules on the edge of the growth of hair on the head

paraphimosis

158. Syphilitic alopecia occurs:

* in the secondary period

in the incubation period

After 2 weeks after infection

in primary seronegative period

159. Symptom Pincus observed in syphilitic involvement of the:

mucous

skin

*hair

Nails

160. Omnibus syphiloderm - is:

step-like eyelashes

* loss of the lateral ends of the eyebrows and eyelashes

papules on the edge of the growth of hair on the head

variety ofpustular syphilides

161. Most of secondary syphilides heels without treatment within:

* 1-2 months

2-3 months

3-4 months

4-5 months

162. visceral syphilis most often affects:

kidneys

mesostenium

*aorta

lungs

163. The Jarisch-Herxheimer-Lukashevich response in syphilis - is:

* acute reaction after the start of antibiotic therapy

regional lymphadenitis

polyadenylation

RIBT

164. Forms of latent syphilis are include all listed, except:

Late

unknown

unspecified

* seronegative

165. contribute to the development of tertiary syphilis:

alcoholism

immunodeficiency states

severe comorbidities

* all answers are correct

166. Scars at tuberculum syphilides could be:

atrophic

* Mosaic

Bridge-like

Stamped

167. Roseola Fournier as a manifestation of syphilis is found in:

primary seronegative period

secondary recurrent period

primary seropositive period

* Tertiary period of syphilis

168. The basis tuberculus and gummy syphilides are include:

dyskeratosis

gipergranulez

Epidermolysis

* infectious granuloma

169. Tuberculum of syphiloderm should be differentiated with all listed diseases, except for:

Skin tuberculosis

leishmaniasis

Leprosy

* Eczema

170. gummy damage on the skin should be differentiated with all listed diseases, except for:

skrofulodermy

trophic ulcers

Chronic ulcers of pyoderma

* parapsoriasis

171. There are all of these outcomes gummy syphilides except:

scar atrophy

* resorption without a trace

Necrosis

ulceration

172. Tertiary syphilis is characterized by all the above except:

limitations of the involvement

focus like location of the lesions

tendency to necrosis

* bright coloring of the lesions

173. reliable signs of late congenital syphilis:

syphilitic rhinitis

high "Gothic" palate

* Hutchinson's teeth

syphilitic pemphigus

174. The clinical signs of congenital syphilis in infants are not include:

saddle nose

scars Robinson-Fournier

fruit like skull

diffuse alopecia

* All of the above are correct

175. Late congenital syphilis develops within:

in late pregnancy

under the age of 1 year

under the age of 2 years

* after 2 years of life

176. Late congenital syphilis is characterized by:

Gunma palate

* parenchymal keratitis

Skin tubercules of the body

skin roseola of the body

177. Manifestations of late congenital syphilis occur in the age:

* after 2 years

from 4 to 17 years

from 17 to 20 years

from 20 to 23 years old

178. Early congenital syphilis appears between:

* from birth to 2 years

2 to 3 years

3 to 4 years

from 4 to 5 years

179. Syphilis of the infants is manifested in aged:

1 to 4 months

* from birth to one year

from birth to 2 years

28 days

180. The causative agent of chancroid:

Treponema pallidum

* Streptobacilus Ducrei

Chamidia trachomatis

Gardnerella vaginalis

181. 4th venereal disease is caused by:

virus

streptococcus

* Chlamydia

spirochete

182. The incubation period of the venereal lymphogranulema is:

1 day

1-2 weeks

* 3-4 weeks

5-6 weeks

183. The most accessible to involvement of gonococci are mucous membranes, listed above:

Multilayer flattened unkeratinized epithelium

transitional epithelium

* columnar epithelium

Multilayer flattened keratinized epithelium

184. There are the following clinical forms of gonorrhea, except:

fresh acute

fresh subacute

fresh torpid

* latent

185. The duration of the incubation period for acute gonorrhea is often equal:

1-2 days

* 3-4 days

5-7 days

8-10 days

186. The most frequent cause of recurrence gonorrhea an association withgonococci is include:

Chlamydia

Mycoses

* Trichomonas

Ureaplazm

187. What are the medium are used to culture research for gonorrhea:

Saburo

agar-agar

* ascites-agar

meat-peptone

188. Fresh acute anterior gonorrheal urethritis is characterized by all of the above features, except:

Plentiful purulent discharge

pain when urination

hyperemia of sponges meatus

* the presence of purulent filaments in the 1st and 2nd urine portions

189. Chronic total gonorrheal urethritis is characterized by the following features, except:

Stasis hyperemic mucosa color sponges meatus

drops "good morning"

presence of a minor amount of purulent filaments in the 1st and 2nd urine samples

* the presence of purulent threads in 1 st portion of urine

190. The treatment of chronic gonorrhea include:

immunotherapy

etiological treatment

local treatment

* All of the above are correct

191. Methods for local treatment of urethritis include all of the above except:

instillations

* mikroklizm

bougienage

tamponade

192. STI not include:

Chlamydia

*trichinosis

trichomoniasis

genital herpes

193. What are the causative agent of trichomoniasis:

Treponema pallidum

* Trichomonas vaginalis

Haemophillus Ducrei

Chlamidia trachomatis

194. Specify the current form of urogenital trichomoniasis:

acute

chronic

torpid

* all answers are correct

195. What are the drug of choice for treatment of urogenital trichomoniasis:

doxycycline

azithromycin

* Metronidazole

ketoconazole

196. Specify the pathogen of the Mycoplasma infection:

* Mycoplasma hominis

Trichomonas vaginalis

Trichophyton rubrum

Microsporum canis

197. The causative agent of urogenital chlamydia is:

Treponema pallidum

Chlamydia trachomatis *

Trichomonas vaginalis

Streptobacilus Haemophillus Ducrei

198. The cycle of development of chlamydia is include:

8-12 hours

2-3 days

*21 day

4-6 months

199. What forms of chlamydia infections are:

reticular cells

* elementary bodies

intermediate (transitional) calf

chlamydial inclusions

200. What material is taken for investigation by PCR on chlamydia:

discharge from the urethra, cervix

* scrape from the urethra, cervix

blood

vaginal discharge

201. Set your:

A) Stafilodermiya

B) strepto-stafilodermiya

a) folliculitis

b) gangrenous pyoderma

c) hydradenitis

g) Chronic deep ulcer-vegetating pyoderma

* A-a, a; B-b, d

A, b; B-c, d

Oh, g; B-b,

A, b, c; B-a, d

A-c, d; B-a, b

202. Set your:

A) hydradenitis

B) Vezikulopustulez

B) Furuncle

a) purulent inflammation of the apocrine sweat glands

b) necrotic lesion of the follicle and surrounding tissue

c) purulent inflammation of the sweat gland ekkrinnoy

* Ah; B-B; B-B

A B; B-A; The in-

Ah; B-B; The in-

A-b; B-B; At-a

A-B; B-A; B-B

203. Set your:

A) Sycosis

B) Periporit

B) Furuncle

a) Chronic inflammation follicles in growth zone short thick hair

b) necrotic lesion of the follicle and surrounding tissue

c) purulent inflammation of the sweat gland ekkrinnoy

*Ah; B-B; B-B

A B; B-A; The in-

Ah; B-B; The in-

A-b; B-B; At-a

A-B; B-A; B-B

204. Set your:

A) Zayed

B) Paronychia surface

B) Psevdofurunkulez

a) strep impetigo in the corners of the mouth

b) milliarnye multiple abscesses in children

c) defeated roller nail

*Ah; B-B; B-B

A B; B-A; The in-

Ah; B-B; The in-

A-b; B-B; At-a

A-B; B-A; B-B

205. Set your:

A) Zayed

B) Paronychia surface

B) Psevdofurunkulez

a) strep impetigo in the corners of the mouth

b) milliarnye multiple abscesses in children

c) defeated roller nail

*Ah; B-B; B-B

A B; B-A; The in-

Ah; B-B; The in-

A-b; B-B; At-a

A-B; B-A; B-B

206. Set your:

A) Surface streptoderma

B) Deep streptoderma

a) impetigo

b) Zayed

c) ecthyma

d) lichen simplex

*A, b, g; Bv

A, b; B-c, d

Oh, g; B-b,

A, b, c; B-a, d

A-c, d; B-a, b

207. Set your:

A) Surface streptostafilodermii

B) Deep streptostafilodermii

a) impetigo vulgar

b) chronic ulcerative pyoderma

c) ulcer-vegetating pyoderma

d) shankriformnaya pyoderma

*Ah; B-b, c, d

A, b; B-c, d

Oh, g; B-b,

A, b, c; B-a, d

A-c, d; B-a, b

208. Set your:

A) The defeat of the hair follicles

B) The defeat of the sweat glands

a) ostiofollikuit

b) vezikulopustulez

c) hydradenitis

g) boil

* Ah, g; B-b,

A, b; B-c, d

A-a, a; B-b, d

A, b, c; B-a, d

A-c, d; B-a, b

209. Set your:

A) Impetigo

B) hydradenitis

a) conflict

b) assembly

c) honey cake

d) a symptom "of bitch udder"

*A-a, a; B-b, d

A, b; B-c, d

Oh, g; B-b,

A, b, c; B-a, d

A-c, d; B-a, b

210. Set your:

A) Vezikulopustulez

B) hydradenitis

a) inflammation of the sweat glands mouths merokrinnyh

b) the disease of newborn

c) inflammation apocrine sweat glands

g) Adult disease

* Ah, b; B-c, d

A-a, a; B-b, d

Oh, g; B-b,

A, b, c; B-a, d

A-c, d; B-a, b

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CONTENT

ANDIJON DAVLAT TIBBIYOT INSTITUTI

GUVOHNOMA

ANDIJON – 2023

O‘QUV ADABIYOTINING NASHR RUXSATNOMASI

O‘zbekiston Respublikasi Oliy ta’lim, fan va innovatsiyalar vazirligi, Andijon davlat tibbiyot instituti rektorining 2023 yil “1” iyundagi “357-Sh”–sonli buyrug‘iga asosan

A.B.Pakirdinov, B.R.Abdullajanov
(muallifning familiyasi, ismi-sharifi)

Medical treatment - 5510100
(ta’lim yo‘nalishi (mutaxassisligi)

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_____ ning
talabalari (o‘quvchilari) uchun tavsiya etilgan.

Syphilis. Viral dermatosis. Pinta.
nomli o‘quv qo‘llanmasi
(o‘quv adabiyotining nomi va turi: darslik, o‘quv qo‘llanma)

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O‘zbekiston Respublikasi Vazirlar Mahkamasi tomonidan litsenziya berilgan nashriyotlarda nashr etishga ruxsat berildi.

Rektor _____ M.M. Madazimov
(imzo)

Ro‘yxatga olish raqami:
100155-357

NOTE

O‘QUV QO‘LLANMA

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BAXROMJON ABDULLAJANOV

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