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Chancroid, lymphogranuloma venereum, granuloma inguinale, genital herpes simplex infection, and molluscum contagiosum

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Abstract Chancroid, lymphogranuloma venereum, and granuloma inguinale may be considered as tropical venereal diseases. These diseases were a major diagnostic and therapeutic challenge in past centuries. Currently, patients with these bacterial infections that are endemic to the tropics occasionally consult with dermatologists in temperate climates. Due to the increasing frequency of travel to the tropics for tourism and work, as well as the increasing number of immigrants from these areas, it is important for dermatologists practicing in temperate climates to be familiar with the dermatologic manifestations of such infections, to be prepared to diagnose these diseases, and to treat these patients. All three "tropical" infections respond well to prompt and appropriate antimicrobial treatment, although herpes progenitalis still cannot be cured, and the number of people infected keeps growing; moreover, genital herpes can be transmitted by viral shedding before and after the visual signs or symptoms. Acyclovir, valacyclovir, and famciclovir can shorten outbreaks and make them less severe or even stop them from happening. There is currently no etiologic treatment for molluscum contagiosum, and the majority of treatment options are mechanical, causing a certain degree of discomfort. The molluscum contagiosum virus, unlike the other infectious agents mentioned, does not invade the skin.

Historical perspective

Chancroid, lymphogranuloma venereum (LGV), and granuloma inguinale are known as tropical venereal diseases. They were a major diagnostic and therapeutic problem in past centuries, even in industrialized countries.[1] Since the end of World War II, the number of patients has diminished, apparently due to successful antimicrobial intervention. Today, tropical venereal diseases are most common in the developing countries of Africa and Asia.

Viral diseases, namely, genital herpes simplex and molluscum contagiosum (MC), are also increasing worldwide.[2] Herpes simplex virus (HSV) infection and syphilis are currently the most common causes of genital ulcers in the United States.[3]

Chancroid

In our dermatologic department, between the years 1928 and 1937, 367 patients with chancroid were registered.[1] After World War II, no case was recorded until 1978, when seven sailors, having been infected in South America and Asia, were registered. Since then, we have had only a few such patients and then irregularly.[4] We had also two patients with mixed ulcer infection (Figure 1), being the combined infection of chancroid and syphilis simultaneously. Whereas California recorded 5035 patients in 1987, only 78 patients were registered in 2000.[5] In the UK, the Health Protection Agency has reported a

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total of 450 cases diagnosed in genitourinary medicine clinics for the years 1995 to 2000.[6] Chancroid accounted for eight cases (3%) of genital ulcers in the sexually transmitted disease clinic in Paris during the years 1995 through 2005.[7] Recent epidemics in western countries have usually been associated with commercial sex workers, the use of drugs, travel to tropical countries, and syphilis and HIV infections.[8]

Chancroid is a sexually transmitted, acute, ulcerative disease, caused by *Haemophilus ducreyi*, a Gram-negative, facultative anaerobic coccobacillus that requires hemin (X factor) for growth. *H ducreyi* is an extracellular pathogen found on the human epithelioid surfaces that resists human antimicrobial peptides. This antimicrobial peptide resistance mechanism contributes to bacterial virulence in humans.[9]

The incubation period is between 3 and 7 days, rarely up to 10 days. The soft chancre begins as a soft papule, surrounded by erythema, which becomes a painful soft ulcer with ragged undermined margins (Figure 2). Within a few days to 2 weeks, painful, in most cases, unilateral, inguinal adenitis occurs in up to 50% of the patients. There are also many clinical variants of chancroid: giant, large serpiginous, phagedenic, transient, follicular, and papular.[8]

Two unusual cases of nonsexually transmitted *H ducreyi* infection have resulted in chronic leg ulcers, which were reported from Australia. Both patients had visited Australia from the Pacific Islands, one from Papua New Guinea and the other from Vanuatu.[10]

For many years, bacterial culture of *H ducreyi* was the primary tool for the diagnosis of chancroid. Direct examination of material from the margins of ulcer, stained with Gram or Giemsa, may be helpful, but sensitivity and specificity are low.

The infection may be easily misidentified because of its rare occurrence in western countries. Previously, there were often difficulties in detecting the causative pathogen; however, with the advent of the polymerase chain reactions (PCRs), the bacterium can be readily identified.[11]

Recommended treatment regimens for chancroid are ceftriaxone 250 mg intramuscularly in a single dose, azithromycin 1 g orally in a single dose, ciprofloxacin 500 mg orally bid for 3 days, or erythromycin base 500 mg orally qds for 7 days.[11,12]

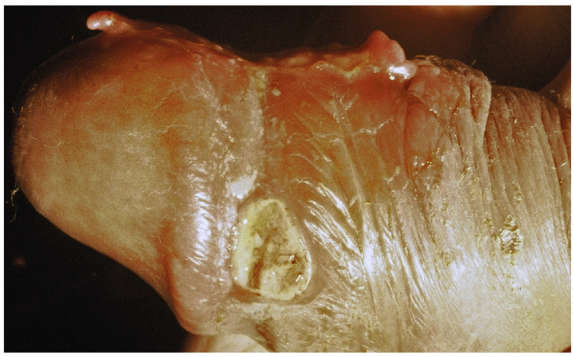

Fig. 1 Mixed ulcer infection.

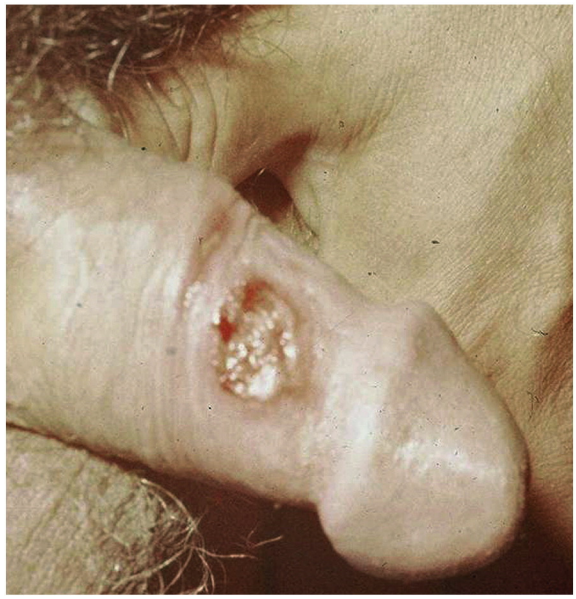

Fig. 2 Ulcus molle-chancroid.

Some other antibiotics are also efficient in the treatment of chancroid; that is, a single 2 g dose of spectinomycin results in a 98% cure rate 14 days after treatment.[13] A 2009 study compared a single-dose treatment of chancroid using thiamphenicol versus azithromycin. Cure rates were 73% with azithromycin and 89% with thiamphenicol; however, HIV seropositivity was found to be associated with treatment failure, so this drug should not be used in coinfected patients.[14]

The latest data suggest that the humoral immune response to the HgbA vaccine is protective against an *H ducreyi* infection, possibly by preventing acquisition of the essential nutrient heme. Active immunization with a native preparation of HgbA confers complete protection in the experimental swine model of chancroid.[15] Successful treatment has the potential to control chancroid infection in any given community.[16]

Lymphogranuloma venereum

LGV appeared also more often in our dermatologic department between the two World Wars. From 1928 until 1937, we had 300 patients with LGV.[17] After that, we did not register any patient until 1981. In the next three years, nine patients were registered, and after that only a few patients.

LGV is still endemic in Africa, Asia, South America, and Central America. The incidence of LGV was low in the developed world until 2003. Cases were usually limited to travelers returning from endemic areas. Since 2003, outbreaks of LGV have appeared in Europe and North America, particularly in the form of proctitis, among HIV-positive men who have sex with men.[18-21]

LGV is caused by *Chlamydia trachomatis* serovars L1, L2, and L3. It appears that the proctitis type of LGV is caused by a new genovariant of L2 serotype (L2b); however,

the analysis of L2b genome does not differ significantly from the L2 genome (L2/434 UB), for which L2b is considered as a classic L2 strain.[22]

Classically, the disease course consists of three separate stages. After an incubation period of 3 to 30 days at the site of inoculation, a small, painless papule or pustule appears that may erode into a small ulcer (Figure 3). This lesion usually heals within 1 week and often remains unnoticed. The second stage begins within 2 to 6 weeks after the onset of the primary lesion, accompanied by painful inflammation and infection of the inguinal lymph nodes, which may become fluctuant and rupture in one third of patients. In other cases, the nodes may develop into hard, nonsuppurative masses. Inguinal lymphadenopathy occurs in only 20% of women with LGV, where the infection more often involves the rectum, vagina, cervix, or posterior urethra, which then drains into the deep iliac or perirectal nodes. Constitutional symptoms, such as low-grade fever, chills, malaise, myalgias, and arthralgias are often present during the second stage of the disease. The third stage of disease is more often present in women. Patients experience development of proctocolitis, followed by perirectal abscess formation, fistulas, strictures, stenosis, and scarring, which can lead to elephantiasis.[23]

The new clinical picture is mostly seen among men who have sex with men (MSM). LGV proctitis mimics chronic inflammatory bowel disease, both clinically and in the pathologic substrate.[24] These cases may present with an incomplete or undisclosed history and proctosigmoiditis without characteristic adenopathy syndrome. During the initial evaluation and colonoscopy, there is a strong clinical and endoscopic suspicion of inflammatory bowel disease by virtue of presentation, endoscopic examination, and histologic findings. The diagnosis of inflammatory bowel disease is subsequently modified to LGV proctosigmoiditis, when one or more of the following transpire: (1) there is a failure of response to inflammatory bowel disease therapy, (2) additional components of history (MSM/travel) may be identified, (3) return of initially performed chlamydia antibody test is positive, and (4) response to antibiotics is effective against chlamydia.[25]

There are many reports of ongoing outbreak of LGV. From 2007 until the end of 2011, 146 cases of LGV were identified in Barcelona, Spain.[26] There are new cases in Finland,[27] the Czech Republic,[28] and France, where the first case of *C trachomatis* L2b proctitis was described in a woman.[29] Clinicians from the Netherlands reported a woman with bubonic LGV, caused by serovariant L2b, which was probably transmitted by her bisexual male partner.[30] There are also complicated cases, such as LGV infection mimicking deep vein thrombosis[31] and reactive arthritis associated with LGV.[32]

The diagnosis of LGV can be made by isolating the organism from culture and cell typing of the isolate. Serologic testing is also possible. With appropriate clinical presentation, a complement fixation antibody titer of higher than 1:64 is considered diagnostic. Titers greater than 1:256 are highly suggestive. In addition, a 4-fold increase in the complement fixation titer of blood samples taken 2 weeks apart is indicative.[23,33] Further diagnostic methods were immunofluorescent testing with monoclonal antibodies and PCR-based techniques.[34-37]

Fig. 3 Lymphogranuloma venereum. (Photo courtesy of the late Bernard Appel, MD, Lynn, MA).

The management of the ongoing LGV epidemic in industrialized Western countries, caused by *C trachomatis* variant L2b, still needs improvements in diagnosis, therapy, and prevention. The rapid *C trachomatis* variant L2b-specific PCR has been developed to circumvent laborious ompA gene sequencing.[38]

C trachomatis should be treated with antibacterial drugs reaching high intracellular concentrations. In general, intracellular acting agents, such as doxycycline, macrolides like azithromycin and erythromycin, and certain quinolones (ie, levofloxacin and ofloxacin) are suggested.[39]

Recommended treatment regimens for LGV are oral doxycycline 100 mg bid for 3 weeks, as the first choice, erythromycin base 500 mg four times a day for 3 weeks, or azithromycin (1 g orally once weekly for 3 weeks or in a single dose). Therapy may be prolonged in HIV-positive patients and, in general, should not be stopped until the complete resolution of all signs and symptoms.[33,40]

Granuloma inguinale

Granuloma inguinale or donovanosis is a rare tropical genitoulcerative disease. In our dermatolovenerologic department, we had only one case in 1982; the patient had

been infected in India (Figure 4). Granuloma inguinale is endemic in Papua New Guinea, South Africa, India, Brazil, and Australia.

The mode of transmission of granuloma inguinale is controversial. It is generally considered sexually transmitted, but fecal contamination and autoinoculation remain a possibility. The transmission rate between sexual partners is low. Transvaginal transmission during delivery has been reported, with an apparent predilection to ear structures of the newborn.[41]

The causative organism is *Klebsiella granulomatis comb.nov.* (formerly *Calymmatobacterium granulomatis*), which is a Gram-negative, nonmotile, pleomorphic bacterium that stains well with Giemsa, Wright, and silver stains. The mature form is encapsulated, whereas the immature form is not and may assume a closed-safety-pin appearance.[42] By sequencing a total of 2089 bp of the 16S rRNA and phoE genes, it was demonstrated that *C granulomatis* shows a high level of identity with klebsiella species, pathogenetic to humans. It has been proposed that *C granulomatis* should be reclassified as *Klebsiella granulomatis comb.nov*.[43]

The incubation period may be from a few days to several weeks, that is, approximately 50 days. Single or multiple papules or nodules later develop and grow into a painless ulcer that may extend to the adjacent tissues. Four types of lesions are described: ulcerogranulomatous, hypertrophic, necrotic, and sclerotic.[44] Lymph nodes are rarely involved.

Extragenital localization of granuloma inguinale are rare, but they are reported as oral ulcers[45] and foot changes without genital lesions.[46] Also, it can be disseminated with cervical ulceration, massive pelvic lymphadenopathy, osteomyelitis, and septic arthritis.[47] Granuloma inguinale can mimic cervical[48] and ovarian[49] carcinoma.

HIV coinfection may alter the clinical presentation of granuloma inguinale. The natural history is usually more rapid, and ulcers may persist for longer periods, leading to more tissue destruction, and need more prolonged antibiotic treatment.[42,50,51] In patients with HIV, granuloma inguinale can lead to such complications as amputation of penis[52] and malignant transformation.[53]

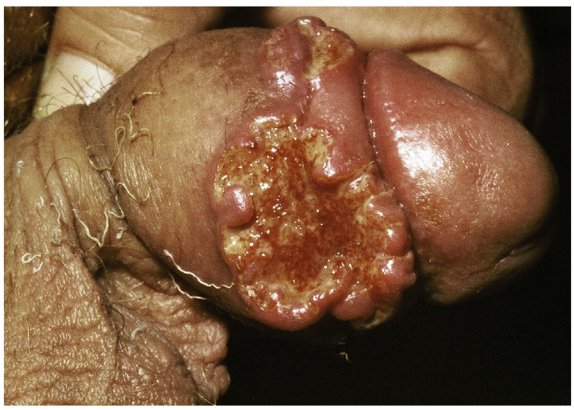

Fig. 4 Granuloma inguinale.

The diagnosis is usually confirmed by microscopic identification of the characteristic bipolar-staining intracytoplasmic inclusion bodies (Donovan bodies) on stained tissue smears or biopsies from the affected site. A rapid Giemsa method can be used to stain tissue smears that should be prepared by rolling a swab firmly across the lesions and then evenly across a glass slide to deposit the ulcer material.[54] Culture isolation of *K granulomatis* is difficult and impractical. Lately, a PCR method using a colorimetric detection system has been developed.[55]

The recommended treatment is azithromycin 1 g weekly, until complete healing is achieved.[44] Treatment in patients with significant HIV-induced immune deficiency may need to be prolonged. Azithromycin could be administrated also as 500 mg once daily for 7 days. A single dose of 1 g azithromycin should lead to a complete cure.[56]

Other treatment regimens for granuloma inguinale are doxycycline 100 mg bid for 3 weeks, ciprofloxacin 750 mg bid for 3 weeks, erythromycin base 500 mg four times a day for 3 weeks, trimethoprim/sulfamethoxazole 800 mg/160 mg bid for 3 weeks, or gentamycin 1 mg/kg every 8 hours IM or IV.[22,41,43] Some authors treated granuloma inguinale successfully with thiamphenicol.[57] In long-standing and complicated disease, surgical intervention may be needed.

The granuloma inguinale elimination program among Aborigines in Australia appears to be successful and is a model that could be adopted in other endemic areas.[58]

Genital herpes simplex infection

Genital herpes (herpes progenitalis) is defined as a sexually transmitted infection caused by HSV, commonly by HSV type 2 and now increasingly by type 1.[59,60]

In the United States, an estimated 40 to 60 million people are infected with HSV-2, with an incidence of 1 to 2 million infections a year.[61] The prevalence rate of genital herpes in developing countries varies from 2% to 74% according to the country. In some African countries that are experiencing HIV epidemics, HSV-2 is highly prevalent ($\geq$ 70%), and there is evidence that genital HSV increases the risk for HIV infection, with patients having both being more likely to transmit HIV infection.[62]

Most people with HSV infection have mild unrecognized or subclinical disease and are unaware of their infection. When symptomatic, the typical manifestations of a primary HSV-1 or HSV-2 genital infection are clusters of genital sores, consisting of inflamed papules and vesicles on the outer surface of the genitals, resembling cold sores (Figures 5 and 6). These usually appear 4 to 7 days after sexual exposure to HSV for the first time.[63] Other manifestations that may accompany the first (and less often future) outbreak of genital herpes are fever, headache, muscle aches, painful or difficult urination, vaginal discharge, and lymphadenopathy.[63] Recurrences are generally much milder than with the first outbreak of genital herpes and

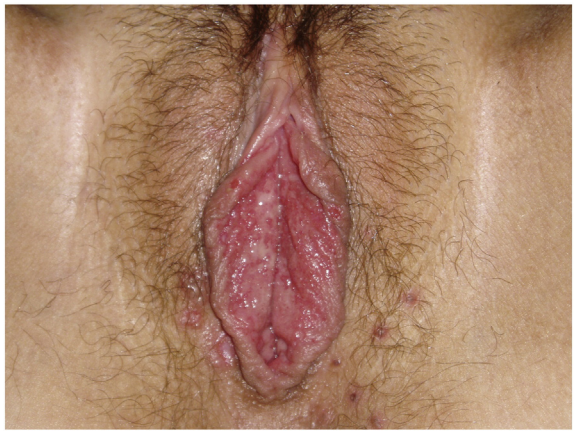

Fig. 5 Herpes genitalis.

are usually caused by genital HSV-2 infection. Genital HSV-1 infection recurs at a rate of about one sixth of that of genital HSV-2.[61] Risk of transmission appears to be greatest during lesional recurrences or the prodrome, and patients should be advised to abstain from sexual contact during this time.

The clinical diagnosis of genital herpes is both non-sensitive and nonspecific. Laboratory confirmation is recommended in all patients with suspected genital herpes, using methods that directly demonstrate the virus in genital specimens, typically swabs taken from the base of the lesion and placed in viral transport media.[64]

Virus isolation in cell culture has long been regarded as the diagnostic gold standard, but delayed sample processing and lack of refrigeration after collection significantly reduce the diagnostic yield.[64,65] HSV DNA detection by real-time PCR increases HSV detection rates in mucocutaneous swabs by 11% to 71% compared with viral culture and is recommended as the preferred diagnostic method.[63,66-68] The viral antigen can be detected by direct immunofluorescence assay, using fluorescein-labeled monoclonal antibodies on smears or by enzyme immunoassay on swabs. These assays are 10- to 100-fold less sensitive than virus culture and are not generally recommended. Because enzyme immunoassay performs satisfactorily in symptomatic patients, it may offer a rapid diagnostic alternative in settings with limited laboratory facilities. Enzyme immunoassay may not differentiate between HSV types.[69,70] Cytologic examination (Tzanck) has modest specificity and sensitivity, and is not recommended for diagnosis.[64,70] Serologic testing is not routinely recommended in asymptomatic patients.[64]

Genital herpes is a lifelong condition, and though outbreaks can be partially controlled, the virus cannot be eradicated from the body. Treatments fall into two main categories: antiviral medications and symptomatic care.[71]

Initial episodes of genital herpes are certain indications for therapy, because they are frequently associated with a prolonged disease course. Patients presenting within 5 days of the start of the episode, or while new lesions are still forming, should be given oral antiviral drugs. Acyclovir, valacyclovir, and famciclovir are all effective in reducing the severity and duration of episode.[64,70] No therapy alters the natural course of genital herpes infection.

The recommended regimens, all for 5 days, are acyclovir 200 mg five times a day, acyclovir 400 mg tid, famciclovir 250 mg tid, or valacyclovir 500 mg bid.[64]

The choice should be made by individual clinicians, considering the cost of therapy and likely compliance, as well as the insurance company formulary. Patients with sustained systemic symptoms, new lesion development, and complicated disease should continue therapy beyond 5 days. The only indication for the use of intravenous therapy is in the patient unable to swallow or tolerate oral medication because of vomiting of medication phobia. Topical agents are ineffective and cannot be recommended.[64,70]

Genital herpes recurrences are self-limiting and generally cause minor signs and symptoms. Decisions about how best to manage clinical recurrences should be made in partnership with the patient. The recommended regimens, all for 5 days, are acyclovir 200 mg five times daily, acyclovir 400 mg tid for 3 to 5 days, valacyclovir 500 mg bid, or famciclovir 125 mg bid. Short-course therapies are acyclovir 800 mg tid for 2 days, famciclovir 1 g bid for 1 day, or valacyclovir 500 mg bid for 3 days.[72,73]

The majority of trials of suppressive therapy have been done in patients with a recurrence rate equivalent to six or more recurrences per annum. Experience with suppressive antiviral therapy is most extensive with acyclovir.[64] The

Fig. 6 Herpes genitalis.

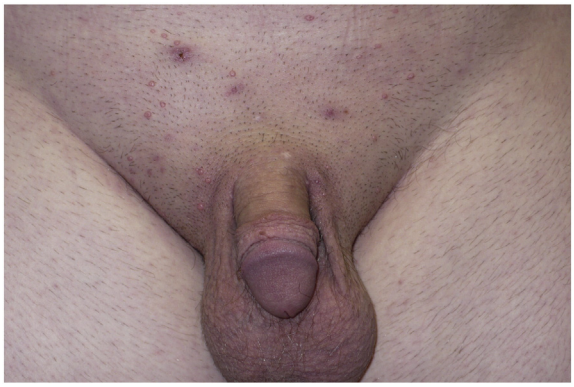

Fig. 7 Molluscum contagiosum.

optimal total daily dosage of suppressive acyclovir therapy is 800 mg. The only published clinical dose-ranging study concluded that 200 mg four times a day was marginally superior to 400 mg bid ($p < 0.02$).[70]

For those patients experiencing less than 10 recurrences per annum, a dosage of 500 mg daily valacyclovir will be adequate; for those patients experiencing 10 or more recurrences per annum, 250 mg bid is recommended.[74]

Counseling of infected persons and their sex partners is critical to the management of genital herpes. The goals of counseling include: (1) helping patients cope with the infection, and (2) preventing sexual and perinatal transmission.[75,76]

Any child with genital herpes needs to be evaluated by a physician to determine the cause and to assess for possible sexual abuse.[77] If a genital herpes blister or sore is present at the time of labor and delivery, a cesarean section is usually done. A cesarean section may also be recommended if a woman has tingling or pain (prodromal symptoms), suggesting an impending outbreak.[78]

There are no trial data for any antiviral in the initial episode of genital HSV in patients with HIV infection. Suppressive antiviral therapy has been shown to decrease the levels of HIV viremia in those patients with detectable HIV viral loads.[79]

Molluscum contagiosum

MC is a common cutaneous viral infection caused by the *Molluscipox* virus that affects both children and adults. Clinically, MC is characterized by small, waxy, dome-shaped umbilicated papules[80] (Figures 7 and 8). Secondary bacterial infection can occur, particularly if patients are scratching their lesions. Inflammatory reaction to MC, molluscum dermatitis, inflamed MC lesions, and Gianotti-Crosti syndrome–like reactions are common.[81] Plantar localization of MC is uncommon and can cause pain on walking.[82] MC involving the intraoral mucosa has been documented but is rare.[83]

Whereas mollusca contagiosa are rather frequent in 1- to 5-year-old children and can be localized almost anywhere on the body, their appearance in adults characteristically involves the genital area and is mostly regarded as a sexually transmitted infection case.[84] In these cases, the pubic area is typically involved. Shaving represents a risk factor for a high lesion number but not the extension beyond the pubis.[85] Sexually acquired molluscum is rare in younger children but becomes quite common during adolescence and young adulthood.[86]

The entity of congenital molluscum has been debated in the literature, but it is accepted that molluscum infections in neonates are likely vertically transmitted.[86-88]

The extragenital appearance of mollusca contagiosa in adults is more typically seen in patients with immunosuppressive conditions, especially in patients with HIV/AIDS. Patients with AIDS may experience development of large and extensive lesions, involving both genital and extragenital sites. The onset of mollusca contagiosa in HIV-positive individuals can be regarded as a part of the immune reconstitution inflammatory syndrome.[89]

Although easily diagnosed, MC may present as a single lesion or as several small, inflamed lesions of difficult diagnosis. If so, dermatoscopy performed on MC may be superior to dermatologic examination. The presence of orifices, vessels, and specific vascular patterns aids in the diagnosis.[90] Recently, a fluorescence resonance energy transfer–based real-time PCR has been developed that provides a very sensitive and specific detection of the MC virus.[91]

Spontaneous clearance occurs in immunocompetent individuals but often over a prolonged period of months to a few years. Most patients prefer treatment, if lesions persist more than a month or two.

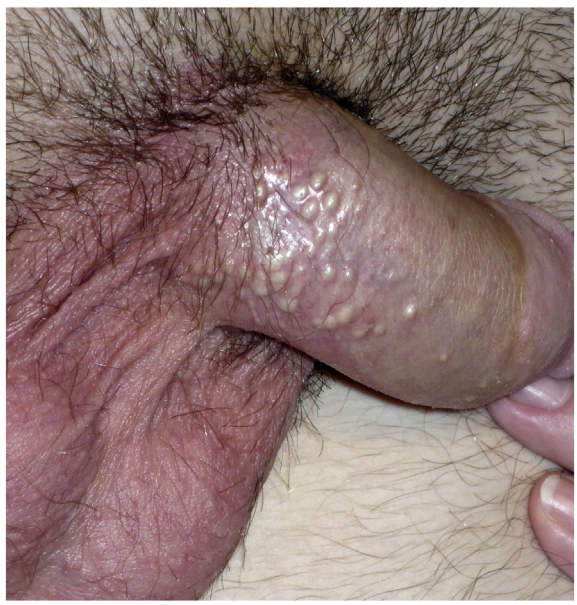

Fig. 8 Molluscum contagiosum.

There is no etiologically directed treatment of mollusca contagiosa, and the majority of treatment options are mechanical, causing a certain degree of discomfort.

Traditional treatment includes curettage as the most efficient[92] and cryotherapy. Both methods are painful but can be ameliorated with use of topical anesthetics. Some physicians use cantharidin 0.7% or 0.9% liquid for treatment of mollusca contagiosa. It must be applied with care and washed off 2 to 6 hours later. Use on the face or genital areas is not recommended.[93] Other topical therapeutic modalities include retinoid cream,[94] imiquimod cream,[95,96] salicylic acid, cidofovir,[97,98] silver nitrate paste and tape stripping,[99] 10% potassium hydroxide solution,[100] and topical application of essential oil of *Melaleuca alternifolia* and organically bound iodine.[101] Ultrapulsed dye laser is also a treatment.[102] Oral cimetidine is questionably helpful.[103]

Conclusions

Sexually transmitted diseases are some of the most common causes of illness worldwide, with approximately 300 million new cases annually. Prevention and education programs have helped to curb the rise of chancroid and granuloma inguinale, but the number of patients with LGV proctitis is increasing, especially among MSM. Genital herpes simplex and MC cases are also increasing throughout the world.

Historically, the diagnosis of sexually transmitted diseases has been difficult. The introduction of molecular biology techniques in microbiologic diagnosis and their application to noninvasive samples has produced significant advances in the diagnosis of these diseases. For *C trachomatis* infections, these techniques are considered to be the most sensitive and specific procedures for mass screening studies, as well as for the diagnosis of symptomatic patients. Molecular methods are advisable in *H ducreyi*, because of the difficulties of culture and its low sensitivity. Molecular techniques can be recommended in the diagnosis of granuloma inguinale, when performed by experts. In genital herpes simplex infection, molecular techniques have begun to be recommended for routine diagnosis and could soon become the technique of choice. PCR is also available in the diagnosis of MC.

In western countries, laboratory facilities are available for screening and establishing the microbiologic causes of earlier-mentioned diseases; however, such facilities may be unavailable especially in undeveloped parts of the world. In such cases, for genitoulcerative diseases, guidelines for syndromic management are available. Chancroid can be treated with single dose of azithromycin and ceftriaxone, LGV with prolonged course of tetracyclines (doxycycline), and granuloma inguinale with a single dose of azithromycin. Treatment of genital herpes does not cure the disease. The virus usually continues to live (in an inactive form) in an infected person. Most people (85%) with genital herpes will have recurring outbreaks, sometimes 6 to 10 a year. Recurrences are likely to have less severe symptoms, and lesions usually last a shorter period.

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