

GENITAL ULCERS

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It is difficult to give an accurate clinically based diagnosis in cases of genital ulcers disease, due mainly to abnormal appearance of the ulcerations, and the frequent occurrence of mixed infections. Etiology diagnosis required the availability of laboratory facilities, which are absolutely inexistent in most health care centers and hospitals in developing countries. This syndrome thus theaters to be one of the most complex clinical problems for those who deal with Sexually Transmitted Diseases (STD).

Genital Ulcer (GU) is best defined as a lesion characterized by the loss of tissue - epidermis and dermis or genital mucous membrane. A lymphadenopathy around the genital area generally accompanies the ulceration, but may occur in its absence, as in the case of Veneral Lymphangranulom (VLG).

The importance of this syndrome has increased extraordinarily since it became evident that are also indicated higher risks for the transmission of the human immunodeficiency virus (HIV).

Epidemiology

In general GU's often go unregistered and unreported, which limits the exact domains of its incidence and prevalence in the world, particularly in developing countries. With the exception of syphilis, the communication of the various causes of GU is all but incomplete, because etiologic diagnostic tests of the genital ulcer syndrome and adenopathy are not largely available, or are of difficult execution. Even when available, the specific microbiological agent remains unidentified in 15-50% of cases.

GU's are relatively more frequent in developing countries than in the industrialized world. Whereas in Europe and North America 1-5% of the patients observed in STD clinics show GU, in Africa and Asia these figures range from 20 to 70% of patients with STD. Some studies have shown geographical variations in GU etiology. Syphilis, chancroid and herpes seem to have ubiquitous geographical distribution, but Veneral Lymphangranuloma (VLG) and donovanosis apparently occur predominantly in the tropics. VLG and donovanosis are rarely found in big industrial areas. High prevalences of syphilis among pregnant women in countries of Southern Africa such as Mozambique with 15% in a rural area, Swaziland with 13% in 1988 and 12% in South Africa in 1989. These high rates are contrasted with the low prevalences found in countries in West and Central Africa such as the Ivory Coast and the Republic of Congo with 1% in 1992 and 1990 respectively.

The high prevalence of antibodies anti *H. ducreyi* observed in a rural population in Mozambique, suggests that chancroid was responsible for a large proportion of observed GU's. In this very same region of Southern Africa, the diagnosis of chancroid was obtained in 42% of GU examined in Swaziland, and in 22% and 14% respectively in men and women, in South Africa. The rate of STD patients who suffer from a GU, may be determined by multiple factors, such as the prevalence of other STD's, the preferences and sexual habits including intercourse with prostitutes, who are an usual source of infections, as well as the cultural tradition of circumcision. The organization of programs against STD's completely integrated with the struggle against AIDS has been recommended, consequently, a better knowledge of this syndrome is expected in the near future.

The risks factors vary equally according to population and etiology. Chancroid is more frequently observed in non-circumcised men, who belonging to the lower classes and whose infectious source was a prostitute. In several countries syphilis affects a large proportion of homosexual men. The use of condoms as a means of prevention is still very low, particularly in rural areas where the STD rates are high; generally, women are less familiar with condoms than men rates of womens who have never seen one in their lives reaching 43%.

As well as condom acceptability there is also the question of availability and accessibility in rural areas.

Clinical manifestations of GU's

Although the classical description of GU's in textbooks is not always found in clinical practice, there are, however, certain guidelines that can help in the clinical diagnosis of these infections.

Syphilis

Agent: A spirochete, *Treponema pallidum*.

Incubation period: Usually between 2 and 6 weeks, but could be relatively long - up to 90 days.

Signs and Symptoms: The first manifestation of Syphilis, a small papule which soon develops into an ulcer, the primary chancre, is classically a single lesion, round or oval, with very regular contours, and diameters varying from 0,5 to 2 cm, presenting a relatively clean surface, clear serous



3 - Primary syphilis.

liquid, or little purulent exudation; its base which is typically hardened, can be appreciated by tactile examination and it is this characteristic that gives it its name, indurated chancre (fig. 3, left). They are usually painless or slightly so without an inflammatory reaction. Nevertheless, a large variability in the clinical manifestation and evolution can be observed, and atypical cases are common.

As for location, the gland-preputial groove in man, and the labia majora and labia minora in woman are the most frequent; when located in the uterine neck, the papulous erosive aspect may be mistaken for exo or endocervicitis. Given the fact that it is often painless, in woman, the ulceration goes frequently unnoticed. Depending on type of sexual intercourse practiced, oral-pharyngeal, anal-rectal lesions and other (fingers, nipples, pubic region, etc.) may also exist.

This primary chancre is usually associated with a moderate increase in the inguinal lymphatic ganglia, hard, without periadenitis and little or not painful at all, however, the classical description of the lymphatic nodes in syphilis is a relatively constant feature in these patients, which lessens its value clinical diagnostic. No general symptom accompanies primary chancre.

If untreated, the chancre scars in between 1 and 8 weeks, leaving in most cases no trace, or a subtle variation in the pigmentation. Under these circumstances, after a few weeks or months the secondary manifestation of syphilis may arise.

Chancroid (Soft sore, Ulcus molle, Soft chancre)

Agent: A negative Gram bacillus - *Haemophilus ducreyi*.

Incubation period: It is usually shorter than a week, but 1 or 2 day-incubation periods are not rare. This aspect may clinically help to distinguish chancroid from syphilis and other ulcers. However, it can also occur with a prolonged incubation period of several weeks.

Signs and symptoms: The primary lesion is an erythematous papula or a painful pustule in the inoculation area (fig. 4, below). A patient in this phase of the evolution is hardly ever observed, and most victims describe the exordium as a "painful sore". In a large number of cases multiple ulcerous lesions are already shown, which are painful with non-hardened bases, some may be superficial, but in most cases are deep and purulent with furrowed edges. Atypical shapes are frequent: single lesions may be mistaken for syphilis chancre, painless herpes-like chancres, giant chancres similar to thrush and soft chancres of spontaneous healing; despite less frequency, phagedenic forms with vast tissue destruction can also be observed. Not rarely does mixed chancroid occur, which is substantially a simultaneous infection by *Treponema pallidum* and *Haemophilus ducreyi*. Concomitant infection by HIV can produce changes in the usual clinical picture, making it more atypical.

Associated lymphatic adenopathy could be a lead to diagnosis, since it is present in more than 50% of confirmed cases, usually unilateral, painful, voluminous and with inflammatory evidence, which can evolve into fistulization or even ulceration.

Bacilli have a particular tropism for the skin, so cutaneous lesions are more frequent than lesions on mucous membranes. In men, particularly uncircumcised, the lesion is frequently located in the prepuce, which can lead to its destruction, in the foreskin, where at times kissing ulcers are noticed, and in the anuses of the homosexuals. In women it is located in the labia majora and in the pubic region, and, in this case, may be accompanied by anal lesions due to self-inoculation of neighboring areas.



Figure 4: Chancroid

Veneral lymphogranuloma

Agent: A minute bacterium adapted to compulsory intracellular parasitism: *Chlamydia trachomatis* corresponding to the serotypes L1, L2, L3.

Incubation period: on average from 2 to 3 weeks, but may have a longer incubation period.

Signs and symptoms: The primary lesion is a micro chancre (fig. 5, next page). Located in any part of the external genitals, in the gland, or foreskin, rarely recognized in women. They are painless, of rapid manifestation and in most cases go unnoticed. However, this lesion may present with a purulent base, making it result in a hard very slightly painless lesion with no periadenitis indistinguishable from a chancroid minor lesion; in these cases, the relatively longer incubation period of LGV, can help establish a clinical diagnosis.

The classical clinical appearance consists in adenopathy (climatic bubo) which is characteristic (fig. 6, below). It usually occurs after the healing of the primary lesion and is unilateral or bilateral. There are several inflammatory ganglia, matted together, with periadenitis, affecting both the superficial and deep surfaces of the inguine-crural which gives it a characteristic appearance known as the groove sign considered to be pathognomonic of LGV, but occurring in only 10 to 15% of cases. They are painful, evolve with central softening, with fluctuation, giving place to the formation of multiple fistulae.



Fig. 5 - Venereal Lymphogranuloma.

Fig. 5



Fig. 6 - Adenopathy in venereal Lymphogranuloma.

Fig. 6

Posterior complications can appear as a result of lymphatic venous blockage caused by the infection, distal edema develops in the genital organs in the first two years after an acute infection, and results in genital elephantiasis, which, in women, is known as esthiomène, and in men as saxophone penis. Later on it may lead to a complication, the annu-rectal syndrome, characterized by hemorrhages, multiple abscesses and vegetant, lesions, evolving into rectal stenosis, the Jersild syndrome.

Genital herpes

Agent: A DNA virus belonging to the Herpesviridae family. Classically the Herpes simplex virus type 2 is observed in genital lesions, but an increasing contamination by the Herpes simplex virus type 1 in genital herpes has also been observed. Increased frequency of oral-genital relations may explain this phenomenon.

Three types of clinical manifestations caused by the HSV exist herpetic primary infection, the first episode post primary herpes and recurrent infection.

Incubation period: primary herpes (or herpetic prime-infection) appears early, 3 to 7 days after infection but can go up to 3 weeks.

Signs and symptoms: In primary herpes, the clinical status shows general and genital symptoms.

General signs: fever, headache, general indisposition, myalgia may appear and are more frequent in women than in men. Its appearance may precede local symptoms and persist for 8 to 10 days.

Genital signs, begin mostly with paresthesia, pruritus and a burning feeling of the genital area affected. In women the lesions are located in the vulval and perineal regions, whereas in men they are more frequent in the foreskin and in the glands. The initial lesions are the classical grouped small blisters over an erythematous surface. The extension to the neighboring regions is quick. The blisters burst more rapidly in the damp zones of the genitals, leaving confluent superficial furrows or ulcerations; the evolution into scarring occurs in 1, 2 or even 3 weeks, is the absence of secondary-infection; this case, resembling recent chancroid lesions which hinders the healing process. Pain accompanies the infectious process, particularly of the beginning, and is more intense in the damper areas than in the dry zones of the genitals; dysuria and vaginal or urethral discharge

flow may occur if lesions of the mucous membrane are present (cervical or urethral). Painful inguinal adenopathy accompanies the process. Neuropathic symptoms due to sacral nerves root involvement are common (lower urinary obstruction, obstipation, paresthesia, for instance).

First episode of post primary-infection: fewer lesions than in the primary-infection; they may be located laterally, bilaterally or medially the painful adenopathy is variable; usually there are no symptoms or general or neuropathic sign; if untreated, it evolves into scarring in 1 to 2 weeks.

Recurrent herpes: Approximately 2/3 of those who have a primary infection develop recurrence later on. There are a large number of factors which cause recurrence: stress, fatigue, intercurrent infection, fever, menstruation a local cutaneous trauma (frequent intercourse), prolonged exposition to sun and heat.

It appears with few blister lesions, usually in clusters, with a diameter of 2 to 5 mm over a small erythematous surface, located in a lateral zone to the median line; repeated outbreaks appear usually in the same area of the penis, vulva or buttocks, some patients (ca. 50%) refer to prodromic symptoms (parasthesias, cutaneous hyperesthesia, pruritus, burning generally located over or close to the lesion area) 1 to 2 days before the appearance of the lesions; lymphadenopathy general neuropathic signs are rare; if untreated, it lasts for 5 to 7 days.

Certain patients who suffer from HSV have episodes in which they eliminate the virus from genital areas in the absence of symptoms. Some of these individuals do not realize that they have genital herpes. It is a non-symptomatic form of genital herpes.

Genital herpes and HIV: in the course of an HIV infection, severe forms are observed, where the classic clinical presentations alters greatly, with confluent lesions, expanded, deep and without the usual tendency for spontaneous cure; pain may be present on touch or manipulation during the evolution. May be easily mistaken for chancroid: only a history of previous recurrences can be with a clinical diagnosis.

Donovanosis or inguinal granuloma

Agent: A negative Gram bacillus coccus, presently classified in a temporary genus associated to the Enterobacteriaceae family, named *Calymatobacterium granulomatis* found on the core of the cytoplasm of big mononuclear, and known, as Donovan corpuscles.

Incubation period: Usually from 2 to 3 months.

Signs and symptoms: it starts with a nodule which softens and then ulcerates. It is a genital ulcer that has a lengthy development, and does not have a tendency to spontaneous healing; it is normally with little or no pain at all.



ig. 7 - Multiple lesions of Donovanosis.

There may be multiple lesions (fig. 7, left); chronic cases can be very extensive with considerable tissue destruction up to the genitals or pubic region; the lesion progresses by extending itself over the neighboring skin and frequently spreads through self-inoculation or lymphatic systemic dissemination; the lesions are similar in men and women, but massive oedema in the labia majora is common in women. Although usually there are no systemic symptoms, generalized extra genital forms with bone, joints and even lung affection have been reported.

The lesion or lesions have a beefy-red base, hypertrophic at times, normally without purulent exudate; it is believed that the subcutaneous extension to the inguinal region can result in a mass similar to a lymphatic adenopathy - a pseudobubo - but there is no involvement of lymphatic ganglia. The vegetant forms, in oval protruberant or salient plaques, may simulate a carcinoma. There are also chancreform ulcerations, which simulate chancroid. The diagnosis is based on clinical data and on demonstration of intracellular Donovan bodies in the histocytes, and on exams carried out by biopsy or cytology rubbing.

The lesions regress and disappear with adequate treatment, but in cases of long lasting lesions there may be genital deformities, such as cutaneous hypo-pigmentation, and urethral, vaginal and anal stenosis.

Diagnosis of GU's

As it was stated above, the clinical diagnosis of the genital ulcer syndrome and associated lymphatic adenopathy is often inaccurate; however, a good clinical history and careful observation provides useful indications as to the etiology of the lesions, and can lead to a presumptive diagnosis. In order to reach an accurate etiologic diagnosis of GU's it is necessary to make use of laboratory tests currently available (Table 1).

There are new tests today for the diagnosis of GU's. They are tests for the amplification of the DNA, which have high sensitivity and specificity and have the advantage of not being invasive. There are three tests on the market: PCR multiplex - polymerase chain reaction assay (M-PCR), LCX - ligase chain reaction assay, and AMP CT - transcription mediated amplification assay. With these tests the presence of *T. pallidum*, *H. ducreyi*, HSV and *C. trachomatis* can be detected. These tests are not yet available in developing countries. The M-PCR can simultaneously detect the presence of *T. pallidum*, *H. ducreyi* and HSV from a single sample of UG secretion.

In developing countries, where genital ulcers and lymphatic associated adenopathy are more frequent and their etiology more complex, the availability of laboratory means is very limited or absolutely inexistent. An effort should be made in these countries to introduce syphilis serologic test (RPR or VDRL), at least for tracking the syphilitic infection in pregnant women. In the face of the limited availability or the inexistence of laboratory means, other solutions may be applied, namely the Syndromic management, with the use of algorithms adapted to each country or region.

Differential diagnosis

We previously stated that the clinical ulcers are atypical and any microorganism can produce a so-called typical status of another microbial agent. Thus, each genital ulcer produced by an agent usually transmitted via sex, is included in the differential diagnosis of other ulcers. Other agents may produce genital ulcers, some of which are occasionally transmitted also through sexual intercourse, such as the parasite *Sarcoptes scabiei*, the scabies agent. A serologic test of syphilis will always be useful in these cases.

Systemic illnesses also cause genital ulcerations. For instance, Berçet's disease, herpetiform Dermatitis, gangrenous Pyodermitis, multiform Erythema and steady Erythema. A story of similar recurrent lesions, in the same anatomic location - usually gland and foreskin, and associated with recent assumption of medicine is very likely to cause fixed drug eruption. Cyclines, cotrimoxazol, and, less frequently, barbiturics, are frequently responsible for such eruptions.

Treatment

Antibiotics that are active against all the agents that cause GU's has not yet been found. In the countries where etiological diagnosis is not available, the syndromatic approach is advisable. Under these circumstances a therapeutic attitude towards a GU will be viewed covering, simultaneously, the agents responsible for the more frequent ulcerous diseases, e.g. syphilis and chancroid. The cost of medicaments is a major factor to be considered in the choice of the therapeutic schemes, especially in developing countries.

T. pallidum is sensitive to benzathine penicillin, in a single 2,4 MU IM dose. In HIV-seropositive individuals, it is convenient to repeat the dose weekly with up to 3 injections. In case of allergy to betalactamics, a few a cycline can also be used, namely Doxycycline 100mg or Minocycline 100mg twice a day for 15 days, or Tetracycline HCL 500mg 4 times a day for 15 days, or Erythromycin 500mg 4 times a day, for 15 days, particularly in women who are pregnant or breast-feeding, when they are allergic to penicillin.

H. ducreyi responds to various antimicrobials, some of which in a single dose. However, in the past few decades the bacterium has developed resistance to sulfanamide, penicillin and tetracycline through the acquisition of plasmids that code for resistance to these drugs. Various treatment can be currently recommended. Single dose treatment is advantageous because it prevents addictive problems. The cost, however, is an important consideration in developing countries, where chancroid prevails. Any of the following therapeutic schemes can be used:

1. Erythromycin (base or estearate), 500mg 3 times a day for 7 days.
2. Azithromycin, 1g in a single oral dose.
3. Ciprofloxacin, 500 mg in a single daily oral dose, 3 days. Ciprofloxacin is contraindicated for women who are breast-feeding, children and adolescents below 17 years of age.
4. Ceftriaxone, 250 mg IM in a single dose.
5. Spectinomycin, 2g IM in a single dose.
6. Cotrimoxazole, 80/460mg, 2 pills twice a day, for 10 days.

Concomitant infection with HIV increases the probability of therapeutic failure in a single dose treatment, a more prolonged treatment being preferable.

C. trachomatis, responsible for LGV, responds well to the cyclines, which continue to be the drug at choice. Thus, one can use Doxycycline 100mg or Minocycline 100mg twice a day, for 14 days, or Tetracycline 500mg 4 times a day for 14 days. Alternatively, Erythromycin (base or estearate) 500mg 4 times a day, for 14 days.

Fluctuating buboes in the case of LGV and Chancroid (when present) must be aspirated with a large diameter needle. Repeated aspirations may be necessary, the procedure must be carried out through the normal adjoining skin, to avoid the formation of fistulas. A persisting bubo with fluctuation after therapy has begun, does not mean unsuccessful treatment.

In cases of Donovanosis, *Calymmatobacterium granulomatis* is sensitive to Erythromycin (estearate) 500mg or Tetracycline 500mg 4 times a day, or Doxycycline 100mg twice a day, for 2-3 weeks, until the lesions have regressed completely. In serious cases any of the scheme above can be supplemented with Streptomycin 1g IM twice a day, for 10 days. Penicillin is inefficient and Ampicillin shows inconsistent results.

Genital herpes, caused by the Herpes Simplex Virus type 2 or type 1, does not have a definitive treatment; that is, there is no virucide that eliminates the virus from the body. Therefore the most important aspect in the treatment of genital herpes may be giving correct information and guidance, about the condition, to the patient. That means they need to know how the virus is transmitted, the behavior of the virus in the body and its relationship with the host, as well as the signs and symptoms of the disease, particularly learning to recognize the prodromic signals. Another objective of counseling is to calm the patient, seeing as stress is one of the factors that incur relapses. Another aspect to be considered in counseling, has to do with the sexual partner (s).

Currently, there are medicines on the market which, in spite of their inability to eliminate the virus, and thus preventing relapses, have a powerful inhibiting effect on the DNA polymerase (an enzyme), thus stopping replication and viral multiplication. When administered early, it has the following results: reduction of the sickness period, reduction of symptoms such as pain, reduction of the duration of viral shedding, and less new lesions.

Aciclovir was the first generation of antiviral drugs of this class, and is recommended under certain conditions: in the primary infection (particularly in the acute form), in the frequent recurrences, and most of all in the cases associated with HIV infections. The administration doses are as follows:

Primary infection:

- Acute: 5mg/kg IV in 60 min. 3 times a day, for 10 days;
- Not acute: 200mg oral 5 times a day for 10 days;

Recurrences:

- Non-frequent and moderately acute: 200mg oral 5 times a day for 5 days.
- Frequent: 400mg oral twice a day;
- HIV infection associated: 200mg 5 times a day, for 10 days.

A second generation of anti-herpetic drugs is available on the market: Valaciclovir and Famciclovir, both with identical effectiveness to Aciclovir, although they have the advantage of greater bioavailability, therefore being able to be administered a lot less frequently than Aciclovir.

Valaciclovir is used in the 1000mg dose twice a day for 10 days for the herpetic primary infection, and 500mg twice a day for 5 days in the treatment of relapses; in suppressive treatment, a 500mg daily dose of Valaciclovir must be administered.

To achieve higher effectiveness with any of these drugs, the treatment must begin as soon as possible, preferably in the first 12 hours the symptoms have begun.

Many individuals with genital herpes do not need Aciclovir because:

- The lesions regress spontaneously
- These drugs are excessively expensive.

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