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Granuloma Inguinale

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ABSTRACT

Granuloma ingunale (GI) or donovanosis is a genital ulcer disease caused by the Calymmatobacterium granulomatis. It is a Gram-negative, facultative, obligate intracellular and pleomorphic bacterium. This bacterium has phylogenetically closed to and placed within the Klebsiella genus. Clinically, the disease is commonly characterized as painless, slowly progressive ulcerative lesions on the genitals or perineum without regional lymphadenopathy. The lesions are highly vascular and bleed easily on contact Extragenital lesions may occur but are rare and more common in newborns from mothers with GI genital lesions. This disease is often neglected, therefore it is often misdiagnosed and inaccurate therapy. Treatment time is 3 weeks or until clinical cure has been achieved for all proposed regimens. It often occurs both in men and women of reproductive age (20-40 years). This article consists of several theoretical references that have been viewed to have a better understanding of GI.

1. Introduction

Granuloma inguinale (GI) is a chronic, progressive sexually transmitted infection (STI) caused by the bacterium Klebsiella granulomatis (known as Calymmatobacterium granulomatis) with a predilection for the genital region.[1] However, this organism was reclassified as Klebsiella granulomatis comb nov. This disease is also known as genital serpiginous ulceration, genital lupoid ulceration, granuloma pudendal ulceration, granuloma genito-inguinal, granuloma genito-inguinal venereum, infective granuloma, tropic inguinal granuloma, chronic venereal wound, and granuloma sclerosis. Marmell and Santora's study recommended the name of GI disease to be donovanosis and many researchers agreed with the nomenclature.[2] According to the Centers for Disease Control and Prevention (CDC), the etiology of GI is an infection of the Klebsiella granulomatis organism which is an intracellular Gram-negative pain.[3]

The first GI case report presented by McLeod, Professor of Surgery at the Medical Faculty of Calcutta in 1882, found a group of patients with clinical manifestations of serpiginous ulceration and incomplete cyclical formation of the scrotal region and male penis, as well as chronic elephantiasis of the clitoral region and female labia. These organisms are difficult to cultivate, and this has led to a debate among researchers about definitive etiology.[2]

Donovan's study in India, the discovery of GI has resulted in Donovan bodies 1.5 x 0.7 µm in macrophages and epithelial cells of the stratum Malpighi.[2,4] Donovan bodies are a form of Klebsiella

granulomatis organisms that are found in the cytoplasm. mononuclear phagocytes, thus giving a purple appearance on Wright's stain.[5] The research of Aragao and Vianna in 1913 proved the successful identification of the cultivation of Calymmatobacterium granulomatis bacteria with a pleomorphic form of genital ulcer lesions.[2,4] Lagergard, et al. succeeded in identifying the causative agent of GI as Klebsiella granulomatis with characteristics of Gram-negative bacteria in the form of pleomorphic, bacilli, elliptical enveloped capsule and predominantly intracellular, especially in macrophages or monocytes.[5]

Cornwall and Peck, in 1925, conducted a cultivation test of organisms that were injected into guinea pigs and subsequently showed granulomatous lesions such as GI at the injection site. In 1926 McIntosh also experimented with the transmission of organisms from one individual to the next. Greenblat, et al in 1929 managed to transmit the disease to human volunteer subjects using material derived from the pseudobubo of GI patients, but were unable to breed these organisms in embryonic chorioallantois chicken.[2]

Cultivation experiments did not yield optimal results before about 1943. Anderson's study reported the isolation of GI-causing organisms in the yolk sac of chicken embryos and proposed a new genus Donovania with granulomatis species. Further studies on Donovania granulomatis cultivation media do not give satisfactory results. The success of this organism growth was achieved by using beef heart infusion media for the agar and yolk sac of chicken embryos, then transferred to tryptose beef heart infusion broth and modified Levinthal's stock broth. Positive skin reactions occur in humans after injection of bacterial antigen from the infected vitellin sac, but the success of cultivation of this organism is influenced by contamination.[2]

Research on GIs is progressing slowly, although significant progress has been made. About 1962, no cultivation tests were reported. Kharsany et al, and Carter reported successful cultivation of GI-responsible organisms using monocyte media from the co-culture system and single-cell hepatitis 2 monolayers. The molecular characteristics of pathogenic organisms started to be investigated after the Polymerase Chain Reaction (PCR) assay was developed. Another study by Carter, et al identified DNA sequencing for 16S rRNA and its genes showing that Calymmatobacterium granulomatis was 99% identical to Klebsiella pneumonia and Klebsiella thnoscleromatis.[2]

A study by Carter and Kharsany et al published the results of the molecular-based phylogenetic of Calymmatobacterium granulomatis organisms and proposed the determination of Klebsiella granulomatis comb nov as the organism causing GI.[1]

Epidemiology

Endemic cases of GIs are most commonly found in countries with tropical to subtropical climates. This disease is more common in populations with low economic status, poor personal hygiene, active sexual activity and more often occurs at the age of 20 to 40 years with the same ratio of men and women.[6] The incidence of GI has decreased and is rarely found, but there are still reports of GI cases in endemic areas, including Papua New Guinea, India, Brazil, Australia, and South Africa.[7]

The complete eradication of GI was accomplished, especially the indigenous population, in Australia in 1998. This program involves designated clinical officers who collaborate clinical protocols, carry out health promotion activities, validate epidemiological data, ensure laboratory control and assist in the follow-up of existing cases.[2] Australian government publication data reported a decrease in the incidence of GI with an initial data of 117 cases in 1994 to 12 cases in 2000.[8] Endemic areas in India, including the city of Orissa, Andhra Pradesh, Tamill Danu and recently there were reports of six new GI cases with a history of use of Antiretroviral Therapy (ARV) in central India.[7] Muller and Kalaratne's 2020 study in South Africa, reported a decrease in the incidence of genital ulcers due to GI during the 2007-2018 period, namely 19 cases out of a total sample of 974.[9] According to O'Farrel's previous 1993 study in South Africa, a total of 171 patients were exposed to GI in one year.[10]

Goldberg put forward the hypothesis that the transmission of GI disease through contamination or autoinoculation of feces can be a medium for transmission to the skin and trials of the isolation of organisms using fecal media have been carried out, but there are no further reports that support this hypothesis.[2] Some researchers claim that GI transmission is not through sex, but Carter's research in 1947 produced arguments to support GI as a sexually transmitted disease. These arguments include: the patient had a history of sexual intercourse before the lesion appeared, an increased incidence of GI in the age group with high sexual activity, lesions especially in the cervix, lesions in the anus were found mainly in the homosexual group and there was an outbreak in the group of commercial sex workers. children are associated with transmission from adults and sexual violence.[8] Magalhaes, et al GI transmission was reported due to sexual abuse among 11-year-old girls in Brazil.[6] It has also been reported in neonates born to mothers with lesions of the large granulomatous vulva.[2] This is in line with the study of Govender and Ahmed et al. Reported the incidence of GI in neonates with manifestations of mastoiditis to meningitis who were born vaginally with mothers with GI lesions.[11,12] Infected neonates from their mothers should be cleaned carefully. It is often neglected because of its limited prevalence in certain geographical areas and its rare incidence. Consequently, the pathogenesis and epidemiology of GI are not fully understood and further studies are required.[4]

Biology and pathogenesis

Skin or mucous tissue injury due to minor trauma (the most common cause of sexual intercourse) provides an optimal environment for inoculating bacteria. The initial GI manifestation is a painless indurated papule that gradually develops into an irregular, serpiginous and progressive ulcer. Characteristics of granulomatous ulcers with a red base such as flesh, painless, easily bleeding when touched, accompanied by secondary infection.[13] If neglected, it causes multiple kissing lesions to become progressive ulcers, scarring, and depigmentation.[1,13]

Goldzieher and Peck in 1926 were the first researchers to successfully identify histologically in the GI lesion tissue, found large mononuclear cells, swollen and contained Donovan bodies. Pund and Greenblatt found large mononuclear cells ranging in diameter from 25 to 90 μm consisting of intracytoplasmic cysts with images of deeply stained bodies on hematoxylin-eosin and dieterle silver-impregnation stains.[2]

Based on electron microscopy examination, Klebsiella granulomatis has a typical morphology of Gram-negative bacteria covered with three layers of walls, round or oval-elliptical shape, 900 nm wide and 1700 nm long without flagella.[15] Donovan bodies have different morphological features, namely coccus, coccobacillus, and bacilli.[2,15] It is pathognomonic in GI.[14] Filiform or vesicular protrusions can be seen on the cell wall, other surface structures such as fimbriae and bacteriophage are not found.[2]

Clinical features

The average GI incubation period is 2-3 weeks, with an estimated 1-360 days. In vivo inoculation assays indicated that granulomatous lesions occurred on the 50th day following inoculation.[2,15] The initial manifestation of GI is in the form of well-defined papules or subcutaneous nodules that develop into ulceration.[16] Ingunale granuloma is divided into 4 types of clinical forms, the first is the ulcerogranulomatous type which is the most common form, the vascularization increases so that it appears beefy-red ulcers that bleed easily when touched and are painless (Figure 1). Second, the hypertrophic or verrucous type, the lesion is raised with irregular margins resembling a walnut-like appearance or condyloma acuminata (Figure 2). The three types are necrotic, deep foul-smelling ulcers which cause tissue destruction and there is a gray exudate (Figure 3).[15,17,18] Fourth, the sclerotic type with dry lesions in the form of extensive fibrosis and scarring. rare and different from other types, Gram stain examination is rare for Donovan bodies (Figure 4).[15, 17,18,19]

The most common predisposition for GI lesions is genitalia (90%) and inguinal (10%). Extragenital lesions account for 6% of cases.[20] Several cases of extragenital lesions have been reported, including lips, gums, cheeks, palate, and pharynx.[19,20] Extragenital lesions are associated with primary genital disease but are still controversial.[2] Study of Ahmed, et al reported cases of extragenital GI in infants aged 8 months, in the form of ulcerogranulomatous lesions of the intraparotid and cervical lymph nodes without primary genital lesions.[14] O'Farrel, et al reported that GI lesions found in infants and children can show clinical manifestations and atypical locations.[20] Squamous cell carcinoma (SCC) of the penis can resemble any form of GI lesion, histopathologic biopsy is needed if antibiotics do not respond to improvement.[18] In women, GI clinical manifestations can mimic cervical carcinoma and ovaries.[21]

Lymphadenopathy is not a typical GI manifestation, possibly the result of secondary infection and expansion of the inguinal subcutaneous granuloma (pseudobubo). Massive swelling of the genitalia can give clinical manifestations of elephantiasis. Disseminated GI is rare, secondary spread can affect the liver or bones and is commonly associated with pregnancy and cervical lesions.[18] The main predilections in males are the prepuce, coronary sulcus, frenulum, and glans penis, whereas women can affect the labium minor and fourchette.[17]

Diagnosis

The diagnosis is made based on history, physical examination, supporting examinations in the form of Gram stain, biopsy, and organism culture. In the history, patients usually ignore genital lesions in the form of skin protrusions or painless sores that develop into progressive ulcers.[22] Patients who have a history of sexual intercourse with multiple partners, but it is still controversial.[15] In contrast to infants and children, there are infant case reports of babies with GI in the ear after vaginal delivery in mothers with GI.[22]

Ulcerogranulomatous lesions of the donovanosis have a distinctive aspect and can be easily distinguished from other sexually transmitted diseases that cause genital ulcers. However, in cases of primary syphilis (chancres), secondary syphilis (condyloma lata), chancroid, and large herpetic ulcers can be suspected as GI.[2] In the GI there is no lymphadenopathy, but pseudobubo can be found. The histopathologic examination makes it possible to distinguish different types of differential diagnosis, in particular, the GI type ulcerogranulomatous that resembles the clinical picture of various genital ulcers.[3]

Direct tissue swab examination is the main method of diagnosing GI, this examination is fast and has high reliability.[2,18] Sampling of specimens using sterile cotton swabs on lesions, then using Giemsa, Leishman, and Papanicolaou staining techniques. Procedure for specimen collection; If there is necrotic tissue it should be removed slowly, then using a sterile cotton swab in a circular motion and gently pressing to get the deepest lesion and rubbed on the slide. Dry and fix using bunsen fire and stain as recommended.[2] Avoid taking specimens on the surface of the lesion to avoid debris and other bacterial contamination.[2] The expected results are the discovery of Donovan bodies, 1-2 x 0.50.07 µm, pleomorphic forms of coccus, coccobacillus, Gram-negative bacilli in the cytoplasm of mononuclear cells, histiocytes, and macrophages (Figure 5a-b).[2,17,18] The immature or encapsulated form will show a safety pin surrounded by halos or whitish areas due to the presence of bipolar chromatin density. The mature or capsulated form has a truncated, well-defined, high-density shape surrounded by a pink halo. Immature and mature forms can be found in a vacuole, sometimes forming a palisade at the periphery of the cytoplasm.[2,17]

Histopathologic examination of infected tissue can use the Hematoxylin-Eosin, Giemsa, or Silver staining technique which aims to find groups of intracellular Donovan bodies in macrophages, plasma cells, polymorphonuclear cells, lymphocytes, and dendritic cells. Recommendations for histopathological specimens include certain GI lesions and certain healthy tissues.[17,18] Pund and Greenblatt described five histopathological features in diagnosing GI, including

massive cellular infiltrates consisting of plasma cells, diffuse polymorphonuclear cells, epithelial proliferation at the edges of the lesion, and found infiltrates in large mononuclear cells which are a pathognomonic sign.[23] This is consistent with the Ornelas, et al in the histopathological results found Donovan bodies intrahistiocytes originating from ulcerogranulomatous type GI lesion tissue (Figure 6).[23] A study by Jain, et al recommended the use of a semi-thin section (~ 1 nanometer) to increase the sensitivity of histopathologic detection. Besides, thionine azure II fuchsin staining can also increase the sensitivity of host cells and causative organisms.[2,15]

Currently, PCR testing for GI is still under development and is only available for research. PCR testing is not commercially available.[15] Indirect immunofluorescent serologic assays have been developed with promising results, but their sensitivity is low.[10] This serologic test is not reliable or routinely performed because of the scarcity of antigenic material required for the examination.[1,15] Serological examination is not the main basis for diagnosing GI.[15]

Anderson's research in 1943, conducted a test for the culture of organisms causing GI using chicken egg embryo media and Goldberg's 1962 on cell medium free of stool samples from GI sufferers. Neither of them succeeded in growing the desired bacteria.[2] The monocyte co-culture system examination was reported to be successful in several three samples compared with free cell media. Hep-2 cell monolayers media culture examination techniques have similar results compared to Chlamydia modified media so that it becomes an alternative and routine examination in supporting GI diagnosis.[1] To date, successful culture examinations have been reported using monocyte co-culture system media and Hep-2 cell monolayers.[1,15]

Monocyte co-culture system examination procedure, monocyte cells obtained directly from the donor via peripheral venous blood collection, serum separation using a centrifuge Histopaque 1077 (Sigma chemicals, St. Louis) at a rate of 1640 RPMI. The serum is rinsed with Hank's solution and added with L-glutamine. The collection of cells was collected in a glass vial and deposited for 1 hour, at 37^{o}C and 5% CO2. Specimens were obtained from a patient's genital ulcer suspected to be GI.[15]

Differential diagnosis of GI

Clinically, the GI-like appearance of genital ulcers can be caused by sexually transmitted and non-sexually transmitted diseases. Clinical features and symptoms, such as pain-free, beefy-red appearance and kissing lesions can make it difficult for experts to diagnose. Several diseases that can mimic the GI are listed in Table 1.[15]

Management and therapy

Granuloma inguinale (GI) is a bacterial infection that can be treated in the pre-antibiotic era. Antimony compounds have been used successfully for primary infections but have limited efficacy for treating recurrence and reinfection.[2]

The first antibiotic effective for GI was streptomycin in 1947. In India, streptomycin has been used extensively and effectively for large GI lesions, the disadvantage of which is injection drug administration. Chloramphenicol has been used in Papua New Guinea, cotrimoxazole in India and South Africa, and thiamphenicol in Brazil. Recovery has also been achieved with tetracyclines, although resistance has been reported. Norfloxacin, ciprofloxacin, and high-dose ceftriaxone have also been reported to be effective.[2] Guidelines for GI therapy according to the United Kingdom National Guideline in 2018 are shown in Table 2.[18]

In patients with a history of sexual intercourse in the previous six months, a thorough physical examination is performed for further identification. Monitor GI lesion repair until the lesions are completely cleared. Patients are educated that GI is a disease condition that can be treated and cured if the choice of antibiotic is adequate. Other STI screening tests are also needed.[18]

Complication

The most common complications of GI include

pseudoelephantiasis (more women than men), lymph node obstruction, phimosis, genital destruction, and obstruction of the vaginal orifice, meatus urethra, or anus. Several investigators reported squamous cell carcinoma (SCC) as a rare complication with an incidence rate of 0.25% of cases. The mean duration of the transformation of the GI to malignancy ranges from one to five years GI ulcers can be co-infected with other STIs. In similar cases, it is advisable to provide therapy for both conditions with a syndromic approach. Patients should be followed up until complete healing is achieved.[2]

Inguinale granuloma and hiv infection

In developing countries, STIs manifested by genital ulcers have a significant risk factor for getting HIV. In the population in Durban, South Africa the proportion of men (63%) exposed to GI with HIV increased significantly with the chronicity of ulcer lesions.[2] This is similar to the case report of Sardana., Et al. In 2008 that individuals with a history of genital ulcers had a 4-7 fold risk of contracting HIV due to post-sexual transmission.[25]

Until now, the guidelines for GI therapy and management in HIV are unclear GI therapy with HIV coinfection requires modification of the duration of intensive antibiotic administration compared to GI individuals without HIV.[25] The mean duration of a cure for HIV-positive GI patients in Mumbai was 26 days compared to 17 days for HIV-negative patients According to the CDC, therapy of HIV-positive GI patients is not different from HIV-negative, but it is necessary to consider the addition of aminoglycoside drugs. Until now, there are no data on the efficacy of using azithromycin for GI patients with HIV positive. Male patients who have not been circumcised are advised to routinely maintain preputial hygiene.[3,25]

Prevention and control

Granuloma ingunale is one of the most easily recognized causes of genital ulcers in endemic areas. This disease is limited to a specific geographic location. Local elimination and global eradication are realistic. The high rate of HIV transmission through genital ulcers requires more attention. A program needs to be implemented to inform the existence of various communities that are susceptible to GI infection and require an assessment of the sufferer's local habits and beliefs. Communities in GI endemic countries such as Papua New Guinea, India, South Africa, Brazil, and Australia are different, but they have similarities that are relevant for GI control. Most of the individuals with GI in this community are in a condition of loss of social status, low socioeconomic status, and poor personal genital hygiene.[2]

In large surveys for case identification or mass, campaign therapy is not recommended even though the prevalence of GI in most endemic areas is low. Mass therapy in cases identified from house visits in Goilala, Papua New Guinea was successfully carried out to control the local epidemic in 1950. This strategy is gaining more attention as a measure of HIV prevention in the country if GIs are still found.2 The stigma against GI patients makes them as avoided as leprosy patients. Many sufferers feel humiliated, guilty and ashamed and even want to commit suicide. Greenblatt paints an emotional picture of this disease that "If GI disease does not understand and is not treated properly because of disgust, then only a few clinics and doctors will do therapy".[2]

In developing countries, GI patient visits are increasing at STI clinics after treatment at primary health care and receiving various types of failed therapies. GI patients require long-term antibiotic consumption and a rational explanation of the conditions they will experience in the long term. This should be done by officers selected to work with STI patients and be able to provide attention to individuals with a sympathetic, non-judgmental approach. Continuous education is needed for health workers regarding GI in endemic areas and to raise public awareness about the importance of genital ulcers which is a proven risk factor for the spread of HIV. Expanding access to azithromycin is a major step and this contributes to overcoming drug compliance problems experienced by other previously used drugs.[2]

In treating GI patients, it requires the role of medical

treatment as the elimination of causative organisms and a management approach. Before knowing the causes and effective treatment for GI disease, many sufferers experience psychological problems in the form of hopelessness to suicidal thoughts. The explanation of the disease and the assurance of treatment are essential to eliminate the patient's fear and the patient's desire for contemporary therapy as opposed to the causative organism.[10]

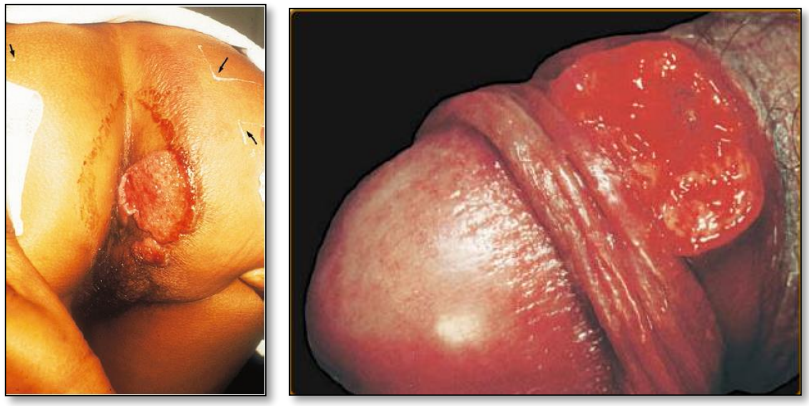

Figure 1. Ulcerogranulomatous.[15,17]

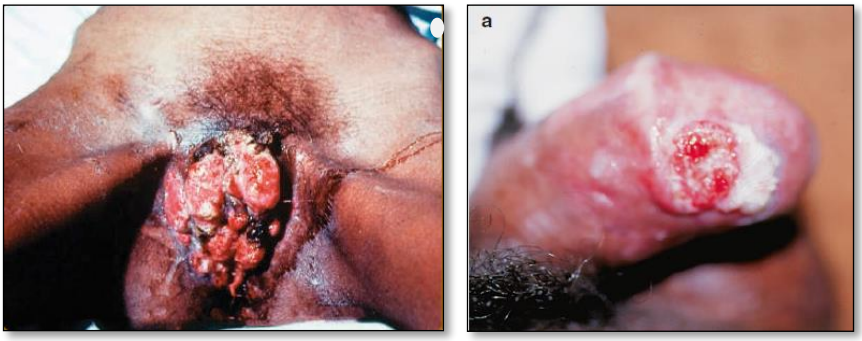

Figure 2. Hypertrophic or verrucous.[15,17]

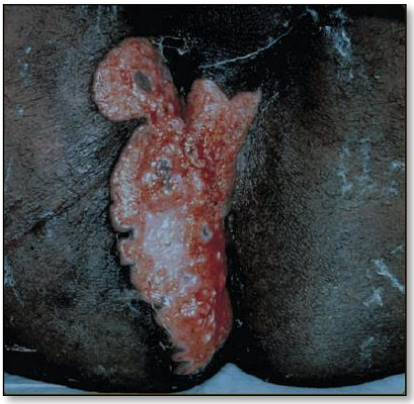

Figure3. Necrotic.[15]

Figure 4. Sclerotic.[19]

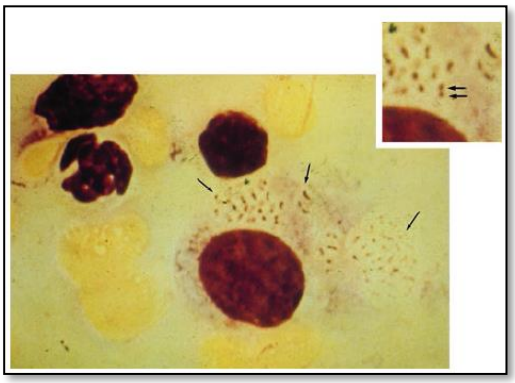

Figure 5a. Giemsa stain.
( ) *Donovan bodies.*[17]

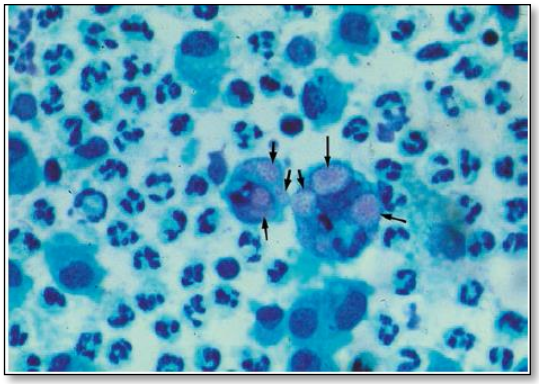

Figure 5b. Papanicolaou stain.
( ) *Donovan bodies.*[17]

Table 1. Differential diagnosis of GI.[15]

Differential diagnosis	**Clinical feature**
Genitalia ulcer	
Primer primer	Chancre: painless, punch-out, ulcer with a clean base (non-purulent), the edge of the induration and is felt firm or hard
Secondary syphilis	Condyloma lata: pale, white to gray, humped plaque looks wet but very rarely becomes an ulcer
Lymphogranuloma venereum	Initial symptoms are asymptomatic, painful papules or pustules or ulcers; then bubo arises
Chancroid	Very painful, yellowish, the skin around erythema with lymphadenopathy
Condyloma acuminata	White, grayish, humped papules to cauliflower-like lesions
Chronic necrotic lesions	
Squamous cell carcinoma	Ulcers bleed easily. Chronic ulcers that do not respond to long-term antibiotics should be considered as lesions in carcinoma
Amubiasis	Very painful ulcers with or without urinary tract disorders
Chronic herpes simplex in immunocompromised patients	Chronic ulcers that never improve with predominance of granulation tissue with varicose growth

Table 2. Guidelines of GI.[18]

Recommended therapy
(The duration of therapy is three weeks or until the lesions are completely healed)
- Azithromycin 1 gram every week or 500 mg orally **(1B)**
Alternative therapy
- cotrimoxazole 160/800 mg divided into 2 doses orally per day **(1B)**
- Doxycycline 100 mg orally every day **(1C)**
- Erythromycin 500 mg divided into 4 doses orally every day **(1C)**
- Gentamicin 1 mg/kg divided into 3 doses parenterally **(1C)**
Therapy in pregnancy

- Erythromycin 500 mg divided into 4 doses orally every day **(1C)** - Azithromycin 1 gram every week orally **(1D)**
Therapy in children - Azithromycin 20 mg/kg every day orally **(1D)** - Prophylactic considerations for vaginal newborns with a history of maternal genital ulcers: Azithromycin 20 mg/kg daily for 3 days orally **(1C)**

2. Conclusion

Granuloma ingunale is an STI disease that is easily recognized in endemic areas but can be neglected in non-endemic areas. GI disease can pose a burden of morbidity and mortality, especially in developing countries with limited resources, such as reducing the quality of life, reproductive health, and indirectly playing a role in facilitating the sexual transmission of HIV infection and its impact on individual and national economies. Appropriate antibiotic treatment can prevent sequelae and morbidity. GI vaccines are currently not available.

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