

## LYMPHOGRANULOMA VENEREUM: A REVIEW OF LITERATURE.

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### ABSTRACT

Lymphogranuloma venereum (LGV) is a systemic STD caused by *Chlamydia trachomatis* serotypes L1, L2 and L3. The disease is endemic in parts of Africa, Asia, South America and the Caribbean but rare in Western countries where the disease occurs mainly in sporadic form. Large outbreaks occurred recently in Europe and America mostly among men who have sex with men (MSM). The clinical course of the disease is stratified into primary, secondary and late stages but the presentation may be atypical particularly when coexisting with HIV and may result in diagnostic confusion. We present here a review of literature on LGV.

**KEY WORDS:** Lymphogranuloma, Venereum, Literature, Review

### INTRODUCTION AND EPIDEMIOLOGY

Lymphogranuloma venereum (LGV) is a systemic STD caused by *Chlamydia trachomatis* serotypes L1, L2 and L3. LGV is endemic in parts of Africa, Asia, South America and the Caribbean but rare in Western countries where the disease occurs mainly in sporadic form (1). Large outbreaks of LGV occurred recently in Europe and America mostly among men who have sex with men (MSM) (2, 3, 4, 5). This has prompted the US Centers for Disease Control and Prevention to alert health care providers in industrialized countries about the possibility and implications of such an outbreak (2). Preliminary evaluation of the outbreak determined that all of the patients were white, concurrent STDs were prevalent, and the majority of patients were HIV-positive and had participated in casual sex gatherings and had had unprotected anal sex within the 12 months

before onset of symptoms (5). Only 1 patient presented with the classic symptoms of LGV (inguinal adenopathy and genital ulcer). Most of the infected men presented with gastrointestinal symptoms (bloody proctitis with anal discharge and constipation). In all cases, LGV was associated with the presence of high-titre *C. trachomatis* antibodies in sera. LGV is believed to predispose to HIV infection (2). Whether HIV predisposes to LGV is still being debated. HIV infected persons with LGV have more extensive disease and require longer treatment duration with the same drugs used for HIV negative individuals (2). We present here a review of literature on LGV.

### The causative agent

Chlamydiae as a group are obligate intracellular parasites (1, 6). Three biovars are recognized until recently when an additional biovar was described

(6). *C. trachomatis*, one of the biovars consist of at least 15 serovars: A, B, Ba, C-k, L<sub>1</sub>, L<sub>2</sub> and L<sub>3</sub>. This classification is based on antigenic composition, intracellular inclusion types, disease production and susceptibility to sulfonamides (1, 6). Major outer membrane proteins (MOMP) and LPS are the antigenic components used in typing chlamydiae. Serovars Da, Ia and L2a have also been described (1, 6).

Chlamydiae are prokaryotes. They exhibits morphologic and structural similarity to gram negative bacterial including a tri-laminar outer membrane which contains lipopolysaccharides and several membrane proteins that are functionally and structurally analogous to proteins found in *Escherichia coli* (7, 8, ). They lack the classic peptidoglycan layer although their genome contains all the genes necessary for its synthesis.

Chlamydiae exhibit a biphasic life cycle consisting of alternating phases known as elementary body (EB) and reticulate body (RB). EB is the infective particle and upon entry into host cell develop into RB from which many EBs will be formed and eventually released from the host cell. Factors governing this transformation are not known but relative concentration of cyclic nucleotides (cAMP and cGMP) is important (1).

The EB and RB differ in metabolic activity, their size, structure of their nucleus and cell membrane. EB is metabolically inert, smaller in size, has electron denser nucleus and extensive disulfide cross-linking between cystein residues both within and between outer membrane proteins compared with RB (1, 6).

### **Pathogenesis**

Following exposure to infective particle, the EB enters squamocolumnar epithelial cells by a

receptor mediated endocytosis via a clathrin coated pits (1, 9). Other mechanisms like pinocytosis via non-coated pits can also be used (1, 6). Lysosomal fusion is inhibited by undefined mechanism with EB residing within intracytoplasmic membrane bound vesicle called inclusion body where it transforms to RB from which more EB are subsequently released with host cell rupture (1).

Unlike the more common *C. trachomatis* serotypes A-K, which tend to be confined to columnar epithelial cells in the genital tract and eye, LGV serotypes predominantly infect monocytes and macrophages and pass through the epithelial surface to regional lymph nodes getting disseminated to other body parts (2). *Chlamydia trachomatis* inhibits apoptosis in the infected cells until developmental cycle is completed- a crucial determinant of survival (4, 10).

The mechanism by which *C. trachomatis* induces inflammatory tissue destruction are poorly understood. They are known to produce effectors like cytokines, phosphatases and kinases that influence eukaryotic cell signaling (1). The characteristic histology is that of granuloma formation with development of small abscesses that may become necrotic or coalesce into suppurative foci (1).

### **CLINICAL FEATURES**

The clinical course of LGV can be divided into 3 stages: the primary, secondary and the late stages.

#### *The primary stage*

The primary stage presents with a small, painless papule or herpeticiform ulcer, typically seen on the penis, vulva or rectum, after an incubation period of 3-30 days. *C. trachomatis* cannot infect squamous epithelial cells and thus, when primary

lesion occurs on external genitalia or vagina, the organism probably gained entry through minor laceration or abrasions. The lesions may not be noticed by infected people (1, 7).

#### *The secondary stage*

The secondary stage usually presents some day to weeks later with painful, unilateral lymph nodes in the inguinal or ano-rectal region. The lymphadenopathy is bilateral in 1/3 of cases (11). When unilateral femoral and inguinal lymphadenopathy occurs, the "groove sign" which is characteristic of LGV is seen being a groove separating the two groups of lymph nodes (1, 6). Proctitis is a common presentation of LGV in women and since lymph vessels from the rectum, cervix and vagina tend to drain to the retroperitoneal area, there is often retroperitoneal lymphadenopathy in women whereas men present more often with unilateral, enlarged, painful inguinal nodes (1, 2). MSM more commonly present with proctitis, proctocolitis or enteritis that results from direct inoculation in the anal region and these forms the disease may be associated with retroperitoneal lymphadenopathy (2, 3, 4). Other groups of lymph nodes that may be affected are the deep iliac and obturator (12).

Initially the lymph nodes are discrete and tender with overlying erythema but because of extensive paradenitis, inflammatory cells spread beyond the lymph nodes to the surrounding tissue, forming an inflammatory mass (1, 6). Abscesses develop within coalesce masses forming a bubo that may rupture spontaneously with the development of loculated abscesses, fistula or sinuses. Only about one third of the abscesses rupture (1). Rupture relieves pain and the associated fever, and the sinus may continue to drain thick yellowish pus for several weeks or months before resolving.

Healing leaves scarring and relapse occurs in 20% of untreated cases (1).

Other systemic manifestations associated with this stage apart from fever include headache, myalgia, meningismus and arthritis (1, 2, 6).

#### *The late stage*

Chronic untreated LGV can lead to lymphatic obstruction, resulting in elephantitis of the genitalia in either sex. Rectal involvement can lead to the formation of strictures and fistulas, which may require surgery to correct (1, 2, 3, 4, 5, 6).

#### **CLINICAL MANAGEMENT:**

The diagnosis of LGV is made primarily on the basis of clinical findings but laboratory investigations including microscopy, serologic tests, antigen detection tests, culture or nucleic acid testing are necessary to confirm clinical assessment (1, 6).

#### *Clinical Assessment*

The differential diagnosis of sexually acquired ulceration with or without accompanying inguinal adenopathy includes chancroid, herpes, syphilis, donovanosis (granuloma inguinale) and lymphoma (13).

LGV manifesting as inguinal lymphadenopathy can be distinguished from genital herpes by the presence of multiple painful ulcers at the site of primary herpes infection in contrast to painless lesion of LGV. Also, lymphadenopathy is frequently bilateral in herpes unlike LGV.

Syphilitic infection is suggested by a primary lesion with indurated margins (chancre) and bilateral, non-tender inguinal lymphadenopathy.

Large, multiple and extremely tender ulcers with associated lymphadenopathy suggest chancroid.

The pseudo-bubo which occurs in granuloma inguinale is nodules in the skin and subcutaneous

tissue with lymph node involvement arising from secondary bacterial infection (11).

### ***Specimens***

Several specimen types could be taken depending on the site and nature of infection, and type of test to be done. Pus aspirates from buboes give high yield on culture (1). Fluctuant nodes should be aspirated through healthy skin. Incision and drainage or excision of nodes may delay healing. Biopsy particularly of uterine tube for diagnosis is considered a research tool. Other specimens include epithelial scrapings, swabs, blood, stool, urine and CSF. Swabs could be of different material types but should be on plastic or metal support, wooden materials are toxic to cell culture.

Specimen for culture must be maintained at 4°C and inoculated within 24 hours otherwise stored frozen at -70°C until inoculation. A useful transport medium has 0.2 mol/L sucrose in 0.02M phosphate buffer, pH 7.0-7.2 with 5% fetal calf serum (14).

### ***Microscopy and Staining***

Direct Microscopic examination by cytological method is not sensitive. Direct fluorescent antibody testing can be used to examine endocervical and urethral specimens. The technique is fast but needs verification by other method.

Microscopy is also useful in reading cultures for identification of intra-cytoplasmic inclusions. Giemsa, Macchiavellos and Gimenez stains or (indirect) fluorescent antibody testing (FAT) may be used. Iodine can also demonstrate glycogen granules. FAT is the most sensitive and specific (1).

### ***Culture***

The causative agent of LGV grows well in a variety of cell lines. Commonly used cell lines are McCoy cells and HeLa cells. Cell lines are monolayer and are grown on cover slips in shell vials or on the surface of multi-well cell culture dishes containing cyclohexamine. Incubation is for 40-72 hours following which microscopy is used to examine culture (15).

### ***Serology***

Being non-specific, serology is used to complement other tests. CFT is available and titres greater than or equal to 1:64 is supportive of LGV. Micro-IF test is more sensitive and can detect IgM antibodies (6).

### ***Direct Antigen Detection***

This could be by EIA or FAT. Both are fast and reasonably sensitive and specific though not effective as culture. MOMP (species specific) and LPS (genus specific) antigens are targeted (14).

### ***Nucleic acid tests***

This could be by Hybridization or PCR. Hybridization identifies rRNA with sensitivity in the range of EIA. PCR is the most recent of diagnostic techniques with sensitivity, specificity and predictive value all approaching 100% (1, 14).

### ***Histology***

The characteristic histology is that of granuloma formation with development of small abscesses that may become necrotic or coalesce into suppurative foci. Similar histological features can be found in cat-scratch disease and inflammatory bowel diseases (1, 2).

### **Treatment**

Recommended regimens of treatment of LGV include 100 mg of doxycycline taken orally twice a day for 14–21 days, or 500 mg of erythromycin taken orally 4 times a day for 14–21 days (1, 2). Sulfonamides though active in-vitro does not produce bacteriological cure (1). Other useful drugs include minocycline, chloramphenicol, and rifampicin (16).

Sex partners who had contact with the patient within 30 days of the patient's onset of symptoms should be given either 1 g of azithromycin in a single dose or 100 mg of doxycycline twice daily for 7 days (Post exposure prophylaxis) (1, 2, 3).

Surgical aspiration, through healthy skin, of buboes is important to prevent rupture and sinus formation. Strictures may also require surgery (1).

### **Control and Prevention**

Barrier methods, such as condoms, provide good protection against transmission. The use of vaginal sponges containing the spermicide nonoxynol 9, which has antichlamydia activity, is also advocated (1). Counseling on delaying the age of first sexual intercourse is an important attitudinal change that must be induced. Central to control measure is identification and treatment of affected persons. Patients must be investigated for other STDs and treated appropriately (17).

### **CONCLUSION**

LGV is a sexually transmitted disease with recent outbreak amongst MSM and atypical feature when coexisting with HIV infection. High index of suspicion is required for this disease with the current HIV pandemic. Proper treatment must be instituted if affected persons must escape late sequelae of the disease and not being a risk to the community at large.

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