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Syphilis in Men Infected with the Human Immunodeficiency Virus

Francisco Rodríguez-Gómez\textsuperscript{1}, Hortencia Cachay\textsuperscript{1}, David Chinchón\textsuperscript{2}, Enrique Jorquera\textsuperscript{3} and Emilio Pujol\textsuperscript{1}

\textsuperscript{1}Internal's Medicine Department, Hospital Juan Ramón Jiménez, Huelva, Spain
\textsuperscript{2}Department of Clinical Pathology
\textsuperscript{3}Department of Dermatology/Hospital Juan Ramón Jiménez

“\textit{He who knows syphilis, knows medicine}”
Sir William Osler

1. Introduction

1.1 Historical perspectives

The origins of syphilis have been discussed for many centuries. Two main theories have been proposed: The new World or Columbian theory and the world or pre-Columbian theory. The Pre-Columbian theory purports that syphilis originated in central Africa and was introduced to Europe prior to the voyage by Columbus (Hudson, 1956). The former holds that syphilis was endemic in the part of the world now known as Haiti and was then acquired and carried to Europe by Columbus in the 1400s (Rothschild, 2005). Bacteriological studies evoke the theory than the syphilis was introduced by Columbus to the Europe (Harper, 2008). In 1495 there was the first syphilis’s epidemic in Europe (Knell, 2004). John Hunter in 1767 inoculated matter from a patient whom believed to have gonorrhea onto the prepuce and glans of a recipient, who traditionally is believed to be himself. Ten days after the inoculation, a chancre appeared, followed by signs of secondary syphilis. (Oriel, 1994).

It is now believed that the donor had both syphilis and gonorrhea, but Hunter was convinced that he had induced syphilis by inoculation of gonorrheal pus. In 1838 Philippe Ricord demonstrated conclusively that syphilis and gonorrhea were separate diseases on over 2500 human inoculations and he was the first to propose a scheme for the categorization of syphilis into primary, secondary, and tertiary stages, which is still used today. In 1905 Schaudinn y Hoffman demonstrated spirochetes in Giemsa-stained smears (Schaudinn, 1905). August von Wassermann devised a serum reaction test for syphilis (Wasermann, 1906). The treatments for syphilis included mercury, organic arsenical compounds (Sartin, 1995). In 1943 Mahoney (Mahoney, 1943) successfully treated the first four cases with penicillin (table 1).

1.2 Etiology

\textit{Treponema Pallidum} is a member of the order \textit{Spirochaetales}, family \textit{Spirochaetaceae}, and genus \textit{Treponema}. The pathogenic species are \textit{T.pallidum} subsp. \textit{pallidum} which causes venereal
A widespread syphilis epidemic had spread throughout Europe (Knell, 2004). John Hunter considered that the disease to Neisseria gonorrhoeae and T. pallidum were the same (Oriel, 1994). Philippe Ricord: first to propose a scheme of syphilis into primary, secondary, and tertiary stages. Bazin: the term lues maligna was first used. Third International Congress of Dermatology: lues maligna was classified as the ulcerative form of secondary syphilis. Neisser and Haslund: classic descriptions of lues maligna. Schaudinn y Hoffman: demonstrated spirochetes in Giemsa-stained smears. (Schaudinn, 1905) Wasermann: first serologic test for syphilis. (Wasermann, 1906) Mahoney: first who successfully treated four cases of syphilis with penicillin. (Mahoney, 1943) Shulkin: first report HIV infected patient with lues maligna.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1495</td>
<td>A widespread syphilis epidemic had spread throughout Europe.</td>
</tr>
<tr>
<td>1767</td>
<td>John Hunter considered the disease to Neisseria gonorrhoeae and T. pallidum were the same.</td>
</tr>
<tr>
<td>1838</td>
<td>Philippe Ricord: first to propose a scheme of syphilis into primary, secondary, and tertiary stages.</td>
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<td>1859</td>
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</tr>
<tr>
<td>1905</td>
<td>Schaudinn y Hoffman: demonstrated spirochetes in Giemsa-stained smears.</td>
</tr>
<tr>
<td>1906</td>
<td>Wasermann: first serologic test for syphilis.</td>
</tr>
<tr>
<td>1943</td>
<td>Mahoney: first who successfully treated four cases of syphilis with penicillin.</td>
</tr>
</tbody>
</table>

**Table 1. Historical aspects of syphilis.**

Syphilis. T. pallidum subsp. endemicum, which causes endemic syphilis (bejel), T. subsp. pertenue which causes yaws, and T. carateum, which is the etiologic agent of pinta (Tramont, 2010). The T. pallidum is a spirochete varying from 0.10 to 0.18 um in diameter and from 6-20 um in length, making it invisible by light microscopy, for the visualization the Dark-field microscopy is generally used (Creigton, 1990). T. pallidum cannot be cultivated in vitro, although limited multiplication can be obtained in tissue cultures (rabbits are the laboratory animals most commonly used for maintaining virulent organism), for this reason is difficult to study and determine its metabolic, physical, and pathogenic features. There were few physiologic studies have previously shown that the organism has limited biosynthetic capabilities, requiring multiple nutrients from the host. (Fraser, 1998). However, genomic sequencing has provided some insights by suggesting functional activities. This consists of a single circular chromosome of approximately 1,138,006 bases pairs, which places it close to the lowest end for the range of the bacteria. Unlike most pathogenic, its genome lacks apparent transposable elements, suggesting that the genome is extremely conserved and stable. This is the likely explanation of why T. pallidum has remained exquisitely sensitive to penicillin for more than 70 years (Tramont, 2010).

**1.3 Epidemiology**

**1.3.1 Transmission of disease**

The primary mode of transmission is by sexual contact and the next common is transfer across the placenta (Singh, 1999). Kissing, blood transfusion, and accidental inoculation have also been reported as routes of transmission but are of minor importance today. The majority of infants with congenital syphilis are in uterus, but the newborn can also be infected by contact with an active genital lesion at the time of delivery (Fiumara, 1975). Today, the acquisition of syphilis through transfused blood or blood products is now rare, at least in the developed world, because of the low incidence of disease, the requirement that all blood donors have a nonreactive non-treponemal blood test, and because T. pallidum cannot survive longer than 24 to 48 hours under the current conditions of blood bank storage (Tramond, 2010).
Accidental direct inoculation can occur by needlestick or during handling of infected clinical material. Syphilis of the fingers is most common in medical personnel (Palfi, 2008).

### 1.3.2 Occurrence of the disease

In USA, prior to the penicillin age, the incidence in 1947 of primary and secondary syphilis was reported at 66.4 cases per 100,000 persons. Rates declined in 1956 to 3.9 cases per 100,000 persons due to availability of penicillin, changes in sexual behaviour, and public health measures (Nakashima, 1996). The most recent epidemic was noted in 1990, with reported rates for primary and secondary syphilis at 20 per 100,000 persons, although no simple factor can explain this trend, and important contributing factor is crack cocaine use and the exchange of illegal drugs for sex (Rolf, 1990) (Fig.1). In USA, the rates fell to 2.1 cases per 100,000 in 2000, rising to 3 cases per 100,000 in 2005 (86% men). Actually the syphilis is a health problem with a prevalence of 12 million cases per year in worldwide (Hook, 2004).

![Fig. 1. Primary and Secondary Syphilis - Reported Rates: United States, 1970-2000 and the Healthy People Year 2010 Objective](image)

Table 2. WHO estimates of number of new cases of Syphilis per year

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia &amp; New Zealand</td>
<td>10 000</td>
</tr>
<tr>
<td>North America</td>
<td>100 000</td>
</tr>
<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>100 000</td>
</tr>
<tr>
<td>Western Europe</td>
<td>140 000</td>
</tr>
<tr>
<td>East Asia &amp; Pacific</td>
<td>240 000</td>
</tr>
<tr>
<td>North Africa &amp; the Middle East</td>
<td>370 000</td>
</tr>
<tr>
<td>Latin America &amp; the Caribbean</td>
<td>3 million</td>
</tr>
<tr>
<td>sub-Saharan Africa</td>
<td>4 million</td>
</tr>
<tr>
<td>South &amp; Southeast Asia</td>
<td>4 million</td>
</tr>
</tbody>
</table>

### 1.3.3 Syphilis, HIV, and men who have sex with men (MSM)

Co-infection with syphilis and HIV is common due shared risk factors related to sexual behavior. In the USA, MSM have consistently represented the greatest single at risk group for HIV acquisition (Zetola, 2007). In Germany the rate is 75% (Ditzen, 2005). In Africa the prevalence of infection for HIV is 21% between MSM in comparation the 1-2% of general population (Wade, 2005). Some researchers have postulated that oral sex may now be more
common among MSM since it is associated with a reduced frequency of HIV transmission; however, syphilitic transmission from oral lesions is highly probably.

1.4 Natural course of untreated syphilis

Descriptions of the natural history of untreated syphilis originate primarily from two large prospective studies and one study retrospective study. Boeck performed a prospective natural history of 1978 patients with early syphilis in 1891. His observations 20 years were then continued by Brusgaars, and this information was later termed the Oslo Study. Between 1949 and 1951, Gjestland undertook a follow up of 1404 of the original 1978 patients. The data were reviewed in 1955 and then reanalyzed in 1964 by Clark and Danbolt (Clark, 1964), the diagnoses were made clinically since neither serologic testing nor microscopy was available when the study began. The results indicate that approximately one-third of the patients developed tertiary manifestations of neurologic, cardiovascular, and gummatous (late benign) syphilis and that the probability of dying due to untreated syphilis was 17% and 8% in females (Table 3).

<table>
<thead>
<tr>
<th>%</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary syphilis</td>
<td>100</td>
</tr>
<tr>
<td>Cured after secondary syphilis</td>
<td>60%</td>
</tr>
<tr>
<td>Tertiary syphilis</td>
<td>28%</td>
</tr>
<tr>
<td>Tertiary syphilis; Late benign syphilis</td>
<td>15% males, 17% females</td>
</tr>
<tr>
<td>Tertiary syphilis; Cardiovascular syphilis</td>
<td>13.6% males, 7.6% females</td>
</tr>
<tr>
<td>Tertiary syphilis; Neurosyphilis</td>
<td>9.4% males, 5.0% females</td>
</tr>
<tr>
<td>Mortality</td>
<td>17% males, 8% females</td>
</tr>
</tbody>
</table>

Table 3. Clinical Manifestations of Untreated Syphilis

Rosahn retrospectively reviewed all autopsies at the Yale University School of Medicine from 1917 to 1941. Of 4000 autopsies of persons, 9.7% had evidence of syphilis, of them 77 patients with untreated syphilis and late anatomic lesions at autopsy (83% had cardiovascular complications, 9% had late benign lesions, and 8% had neurosyphilis (Rosahn, 1947). There was an increased overall mortality in syphilitic compared with nonsyphilitic populations.

1.5 Clinical manifestation

*T. pallidum* penetrates the intact mucous membrane or gains access through abraded skin, it enters the lymphatics and bloodstream and disseminates throughout the body. Clinical lesions appear when a concentration of approximately $10^7$ organisms/mg of tissue is reached (Magnuson, 1956). The incubation period is directly proportional to the size of the inoculums (3-90 days approximately). In untreated cases, syphilis has traditionally been divided into the following stages: incubating, primary, secondary, early latent, late latent and late tertiary syphilis.

1.5.1 Primary syphilis

The classic primary chancre begins at the site of inoculations as a single, occasionally multiple, painless papule. The base is usually smooth; the borders are raised and firm and have a characteristic cartilaginous consistency (Stokes, 1944). The size of the
chancre varies from 0.3 to 3.0 cm, multiples chancres can occur especially in persons who are immunosuppressed as those co-infected with HIV (Chapel, 1978 & Rompalo, 2001). The localization, in men is the penis, more specifically the coronal sulcus and glans. Anorectal chancres are common in homosexual men (Horihan, 2004). In women, the commonest locations of the lesions, in order of decreasing frequency, are the labia majora, labia minora, fourchette, and perineum. Regional lymphadenopathy consisting of moderately enlarged, firm, non-suppurative, painless lymph nodes or satellite buboes usually accompanies the primary lesion (DiCarlo, 1997).

1.5.2 Secondary syphilis
A rash of varying severity is the most common initial presenting symptom. This rash appears on the palms, soles, flanks, and arms and can range from macular to follicular and occasionally to pustular. Additionally up to 7% of patients may experience alopecia characterized by patchy hair loss of the scalp, beard, and lateral eyebrows, with is referred to as a moth-eaten appearance. Patients may also experience sore throats due to inflammatory involvement of the pharynx or the tonsils. Condyloma lata are found 5-22% of patients. Although the incidence of these effects is rare, syphilis can cause renal, ophthalmologic, hepatic, bone, and joint disease.

1.5.3 Latent (early and late) syphilis
Latent syphilis is a stage in which patients are seroreactive but asymptomatic. It occurs between the disappearance of secondary syphilis symptoms and the appearance of tertiary syphilis manifestations or therapeutic cure. About 90% of first relapses occur within 1 year, its defined early latent syphilis, and late latent syphilis is defined as occurring after 1 year (Gjestland, 1955).

1.5.4 Tertiary syphilis
Tertiary syphilis describes a broad range of manifestations but most commonly includes cardiovascular, gummatous, and/or neurological effects. Together, approximately 15% to 40% of individuals who are not treated will develop tertiary manifestations, with men at increased risk compared with women. Cardiovascular complications are the most common of the effects and typically present within 10 to 30 years of infection. They often involve the aortic arch and can lead to angina from coronary ostitis, aortic regurgitation, or aortic aneurysm. Gummas can present in any organ and can lead to complications, including ulcers of the skin, collapse of the palate or nasal septum, or organomegaly. It can develop any time after a year of infection, but incidence peaks at approximately 15 years.

1.6 Syphilis and HIV
The coinfection have shown no distinctive or unique clinical presentation or pathologic manifestations from those without concurrent HIV infection, they are at an increased risk to manifest a more protracted and malignant course, more constitutional symptoms, greater organ involvement, atypical and florid skin rashes, multiple genital ulcers in the 70% of patients (Rompalo, 2010), 25% presented concomitant chancre during the secondary stage (Hutchinson, 1994), and a significant predisposition to develop symptomatic neurosyphilis (Tramont, 2010).
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<table>
<thead>
<tr>
<th>Stage of syphilis</th>
<th>Clinical manifestations</th>
<th>Percentage of cases</th>
<th>Incubation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Chancre, regional lymphadenopathy</td>
<td>3 wk (3-90)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>Rash, condiloma latum, lymphadenopathy&lt;br&gt;Constitutional symptoms(fever, malaise, weight loss)&lt;br&gt;Mouth and throat (mucous patches, erosions, ulcer)&lt;br&gt;Genital lesions (chancre, condyloma latum, mucous patch)&lt;br&gt;Central nervous system&lt;br&gt;Asymptomatic&lt;br&gt;Symptomatic</td>
<td>90%&lt;br&gt;70%&lt;br&gt;35%&lt;br&gt;20%&lt;br&gt;8-40%</td>
<td>2-12 wk&lt;br&gt;2 wk-6 mos</td>
</tr>
<tr>
<td>Latent</td>
<td>Asymptomatic</td>
<td>Early,&lt;1 yr; late,&gt;1yr</td>
<td></td>
</tr>
<tr>
<td>Tertiary. Cardiovascular Syphilis</td>
<td>Aortic aneurisma, aortic regurgitation, coronary artery ostial stenosis</td>
<td>10-30 yr</td>
<td></td>
</tr>
<tr>
<td>Tertiary. Late neurosyphilis. Asymptomatic</td>
<td>Asymptomatic</td>
<td>31%&lt;br&gt;&lt;2 yr</td>
<td></td>
</tr>
<tr>
<td>Tertiary. Late neurosyphilis. Acute syphilitic meningitis</td>
<td>Headache, meningeal irritation, confusion</td>
<td>1-2%&lt;br&gt;&lt;2 yr</td>
<td></td>
</tr>
<tr>
<td>Tertiary. Late neurosyphilis. Meningovascular</td>
<td>Hemiplejia, seizures, aphasia.</td>
<td>10%&lt;br&gt;5-7 yr</td>
<td></td>
</tr>
<tr>
<td>Tertiary. Late neurosyphilis. General paresis</td>
<td>Changes in personality, affect, sensorium, intellect, insight, and judgment. Hiperactive reflexes, speech disturbances, Argyll Robertson pupils.</td>
<td>10-20 yr</td>
<td></td>
</tr>
<tr>
<td>Tertiary. Gummatous Syphilis.</td>
<td>Monocytic infiltrates with tissue destruction of any organ</td>
<td>15%&lt;br&gt;1-46 yr&lt;br&gt;(most cases 15 yr)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Clinical phases of syphilis

1.6.1 Syphilis and HIV transmission
The two diseases can affect each other in a number ways. Studies epidemiologist showed that the syphilis increasing the likelihood of acquisition of HIV (Buchacz, 2004, Reynolds, 2006, Fleming 1999).
The acquisition and transmission of each other but syphilis also upregulates CCR5 coreceptor expression (Sellati, 2000) and causes local immune activation, thereby further increasing likelihood of acquisition of HIV, the stimulation of syphilis infected patient immune system might induce replication of the virus (Quinn TC, 2000), decrease CD4 T cell counts and induce lymphocyte and CD4 apoptosis (Buchacz, 2004). The pathogenic interaction between HIV and *T. pallidum* leading both to an immunodeficiency state may reduce the immunologic response to treponemal infection through a decrease in CMI, macrophage functional defects, and possibly immunomodulation of the humoral immunity response. Functional immunologic abnormalities may impair the host defense against syphilis, leading to more aggressive forms. The serologic tests for syphilis may be modified, often resulting in extremely high titers (11% HIV-infected persons have a biologic false-positive serologic test result) and a failure to decrease in response to adequate treatment unless successfully treated with HAART.

<table>
<thead>
<tr>
<th>Genital ulcers can increase HIV transmission</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>T. pallidum</em> induce the expression of CCR5 on macrophages in syphilitic lesions</td>
<td>Setalli, 2000</td>
</tr>
<tr>
<td><em>T. pallidum</em> decreased CD4 T-cell counts and increased HIV viral load</td>
<td>Buchacz, 2004</td>
</tr>
<tr>
<td>Syphilis increased HIV transmission 2-to9-fold</td>
<td>Chesson, 2003</td>
</tr>
<tr>
<td>First six months after exposure of syphilis, represent the of greatest risk for HIV infection</td>
<td>Reynolds, 2006</td>
</tr>
</tbody>
</table>

Table 5. Syphilis and HIV transmission.

1.6.1 Clinical features of syphilis in HIV-infected patients
The majority of patients coinfected with HIV and syphilis have a primary syphilis similar to the population without HIV. However sometimes can show multiples chancres, larger and deeper and that heals more slowly (Hutchinson, 1994). The primary and secondary period overlap in 75% of cases (Rompalo, 2001). The signs of secondary syphilis can develop and succeed while chancres are still present. The rash may be more widespread and condylomata lata lesions more common than in patients without HIV. Unusual cutaneous manifestations, particularly the malignant lues are not uncommon in HIV patients. Acute syphilitic meningitis, ocular manifestations and losing hearing are more common in HIV patients (Tramont, 2005). The progression of tertiary syphilis is faster in HIV patients (Hutchinson, 1994)

1.6.2 Diagnosis of syphilis in HIV-infected patients
1.6.2.1 Identification of *T. pallidum* (Lesion-Based Testing)
Direct fluorescent antibody test (DFA): A direct fluorescent antibody test can be performed on lesion exudate or tissue specimen. There are no differences in test performance characteristics among HIV-infected and non-infected patients.
Primary stage  
- Multiple chancres  
- Chancres larger, deeper, and resolve more slowly  
- Atypical chancres appearing as abrasions or fissures  

Secondary stage  
- Coincident chancres with signs of secondary syphilis  
- Duration of rash may be slightly longer, and rash may be widespread  
- Atypical skin rashes, including papular, nodular, ulceronudular (lues maligna)  
- Reports of ocular syphilis, mainly uveitis.  
- Retinitis, papillitis, and cranial nerve abnormalities II, III, or V in association with syphilitic meningitis.  

Tertiary syphilis; Late benign syphilis  
- Several reports of gummas  
- One case of rapid progression to gumma within several months of a chancre  
- Located in multiple organ systems including the brain  

Tertiary syphilis; Cardiovascular syphilis  
- Rare cases of rapidly developing aortitis reported  

Tertiary syphilis; Neurosyphilis  
- Progression to neurologic syphilis despite treatment of early syphilis  
- Reports of rapid progression to neurologic syphilis without long latency  
- Cases in patients with both normal and low CD4 counts  
- Clinical features include asymptomatic disease, meningitis, cranial nerve deficits, optic neuritis, myelitis, stroke, cerebral gummas  


### 1.6.2.2 Serology

The serology in patients co-infected syphilis and HIV are similar; however there are least different in the serology but very important in the diagnostic (Table 7).

### 2. Case report and discussion

#### 2.1 Case report

A 42-year-old homosexual man with chronic infection for HIV from 2003, in stadium A2 without antiretroviral therapy consulted at the outpatient infection department at Juan Ramon Jimenez Hospital for fever of 38.5 º C of three weeks of evolution, which the patient...
False positive non-treponemal antibody test (RPR/VDRL). In one study, 4% of HIV-infected patients tested had false-positive RPR results. 

Seroreactivity may be delayed or absent in HIV-infected patients. Rare cases have been reported of biopsy-proven secondary syphilis in HIV-infected patients with negative serology. 

Higher mean serologic serum non-treponemal antibody levels than non-HIV-infected 

Serum non-treponemal antibody levels may decline more slowly after treatment in HIV-infected patients than non-infected patients 

Pro-zone reaction more commonly in HIV-infected persons 

Table 7. Considerations for serology in HIV-infected patients.

| False positive non-treponemal antibody test (RPR/VDRL). In one study, 4% of HIV-infected patients tested had false-positive RPR results | Rompalo, 1992 |
| Seroreactivity may be delayed or absent in HIV-infected patients. Rare cases have been reported of biopsy-proven secondary syphilis in HIV-infected patients with negative serology. | Tikjob, 1991 |
| Higher mean serologic serum non-treponemal antibody levels than non-HIV-infected | Rolfs, 1997 |
| Serum non-treponemal antibody levels may decline more slowly after treatment in HIV-infected patients than non-infected patients | Rolfs, 1997, Yinnon 1996. |
| Pro-zone reaction more commonly in HIV-infected persons | Schöfer, 1996 |

relates to a "boil" perianal weeks before the beginning of the fever. On examination lymph nodes were palpable in the cervical, axillary and inguinal regions and skins lesions consisted of multiple erythematous present in his face, neck, trunk and extremities.

One week after came back by persistence of the fever and pain of the throat. The laboratory studies reveal the following: Hemogramme, glucose, urea, creatinine and ions were normal, GPT 71 U/l, GOT 50U/l, GGT 212 U/l, phosphatase alkaline 149 U/l. His CD4 cell count was 315/mm3 and his HIV viral load of 102.718 copies/ml. The Acid-fast bacilli stains, bacterial, fungal cultures and Lowenstein's culture in urine were all negative. The abdominal ultrasound scan was normal. Before the persistence of the clinic in absence of diagnosis the hospitable for continue the study.

On examination, the patient was fever of 39 º C with stable vital signs. In mucous oral was presented whitish plates, didn't show ulcerative lesions or thrush (fig.1), skins lesions in different stages in trunk (fig. 2, panel A,B), face and neck, consisting of stains, papules, pustules with center necrotic and ulcerative scabs. He had and inguinal lymph node of 1-2 cm, and cardiac, lung and abdominal examinations are benign. Neurologically, the patient was grossly intact without focal deficits.

The C reactive-protein was 3,9 mg/dl and the erythrocyte sedimentation rate was 99 mm/hour. There were realized bacterial, fungal, mycobacterial culture and the blood detection of the antigen criptococe were normal. The Chest x-ray film was normal and the tomography thorax-abdominal didn't observe lesions in lung and in abdomen showed moderate enlargement hepatoesplenomegalgy and lymphadenopathy in retroperitoneo, chains external iliacas and inguinal approximately of 1,5 cm.

The histological examination of the ganglionar biopsy showed reaction granulomatous giants cells without necrotic debris (fig. 3, panel A), didn't observe acid-fast bacilli fast and the fungal culture was negative. The skin biopsy punch revelead infiltrated lymphocytes, histiocytes with extensive areas of necrosis and debris, (fig. 3, panel B), the culture of this one (conventional, fungi and mycobacterial) was negative. Warthin-Starpy’s stain was negative in both samples.
Fig. 2. Mucous patches confused with oral candidiasis.

Fig. 3. Noduloulcerative lesions of the trunk. Disseminated ulceronodular rash is affecting the trunk and abdomen (A) and back (B). The lesions are papules, pustules, pustules with necrosis central and ulcerated.
Treatment began with nistatine for the muguet. The presence of long fever, skin lesions, hepatoesplenomegaly and ganglionar affection with noncaseating granuloma, suspected infection for Bartonella beginning treatment with azitromicina (500 mg c/ 24 hours) with fever and decrease of the size of the inguinal lymphadenopathy. The serology's bartonella was negative <1/256 (IFI). The information together with the persistence of the fever and the skins lesions in a patient HIV forced us to reject the diagnosis of malignant Syphilis. The cerebrospinal fluid was without cell (VDRL negative). Empirical treatment began with injection of intramuscular benzathine penicillin (2.4 million UI) in only dose, the fever defervesced over the next 24 hours, receiving in ambulatory regime two additional doses weekly. He didn't present Jarish-Herxheimer's reaction. There began antiretroviral treatment of high efficiency based on tenofovir 300mg with 200 mg of emtricitabina and efavirenz 600mg every 24 hours. He was discharged from the hospital with this therapy.

It was checked 10 days later in consultation being afebril and asymptomatic. The oral lesion had disappeared and the skins lesions ones were showing clear improvement. The syphilis serology showed a positive RPR titer 1/32, the immunoglobulin G was positive and the immunoglobulin M negative. The liver function test was normal three months after of the beginning the therapy. To six months RPR titer had descended to 1/4. The rash approximately coincided months before with inconsistent condom use and several new sexual relationships.

Fig. 4. A) Biopsy lymph node: Nodular growth without central necrosis with lymphoid and plasma cell, (H/E, original x 126). B) Biopsy skin: small base with moderately dense perivascular lymphocitic infiltrate and deep dermis (H&E, original x 252).

2.2 Discussion
2.2.1 Definition
Lues maligna was first described by Bazin (1859) and Dubuc (1864), who applied this term based on the bizarre clinical features and progressive course of this variant of syphilis.
During some decades, there was controversy about whether lues maligna was a severe variant of secondary syphilis or an early manifestation of tertiary syphilis; a question clarified by Haslund and Neisser in 1896-1897. In contrast to tertiary syphilis, the lesions of lues maligna are multiple, have a round or oval configuration, with no tendency to central healing, and exhibit a lamellated, brown-black rupioid crust. Moreover, the early onset of necrotic ulcers in the disease is in contrast to the later occurring gummas of tertiary syphilis. Neisser identified five clinical features of malignant syphilis:

- Short incubation period
- Constitutional symptoms are pronounced
- The skin and frequently the mucous membranes of the mouth and nose present multiple irregularity distributed lesions consisting of large pustules, ulcers, and rupioid ecthymatous lesions
- The patient may have characteristics of the milder forms of the disease such as mucous membrane buccal patches, etc.

The skin lesions:
- Pleomorphic
- Papulopustules, beginning ulceration, deep ulceration, ulcers covered with crusts, healing lesions
- Typically round or oval with a granulating base, and a lamellated, brown-black rupioid crust
- The surrounding skin is little affected, showing only minimal erythema.

Table 8. Criteria required for malignant lues diagnosis (Neisser, 1896).

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<th>Criteria</th>
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<td>Compatible gross and microscopic morphology</td>
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<td>A high titer serologic test for syphilis</td>
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<tr>
<td>Herxheimer reaction</td>
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<td><strong>Dramatic response to antibiotic therapy</strong></td>
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### 2.2.2 Risks factors for malignant lues

The risks factors for malignant lues are: constitutional symptoms. MSM, sex, syphilis previous. Shulkin proposed the HIV and the presence of opportunistic infections (Shulkin, 1988).

### 2.2.3 Incidence

The incidence of malignant lues in the cases of series were 0.36% (Haslund, 1987) in the age pre-HIV and 7.3% after of the co-infection (Schofer, 1996).

### 2.2.4 Cases of ulceronodular syphilis in HIV patients

Shulkin published in 1988 the first case of malignant lues in British language. We checked the characteristics epidemiologist, diagnostic, evolutions and treatments in patients with co-infection ulceronodular syphilis-HIV from 1988 until 2010 (British and Spanish languages) including our case.
The total cases were 28 patients with mean age 33 years (R:18-61). There were twenty men and eight women. The risk factor most important was MSM in 45% of cases. The followed features are described in the next table.

2.2.5 Serology
The serology in patients with malignant syphilis is similar that the patients co-infected with syphilis-HIV presented high titles of non-treponemal antibody.

2.2.6 Treatment
The penicillin is the treatment of election. In the secondary syphilis (ulceronodular syphilis) the recommendation is only one dosis of Benzathine PCN 2.4 million UI, however there are other authors than recommended to additional two dosis of penicillin every one week to the initial treatment.

3. Conclusion
In the last years there was an increased of cases of syphilis malign in relation with co-infection HIV. Early and targeted recognition and treatment of both diseases is essential to deterring continued trends in incidence and prevalence of this disease.

4. References


Sellati TJ, Wilkinson DA, Sheffield JS, Koup RA, Radolf JD, Norgard MV. Virulent Treponema pallidum, lipoprotein, and synthetic lipopeptides induce CCR5 on human monocytes and enhance their susceptibility to infection by human immunodeficiency virus type 1. J Infect Dis 2000;181:283-293.
Syphilis. New York Department of Health AIDS Institute: www. hivguidelines.org
Recent Translational Research in HIV/AIDS


The collective efforts of HIV/AIDS research scientists from over 16 countries in the world are included in the book. This 27-chapter Open Access book well covers HIV/AIDS translational researches on pathogenesis, diagnosis, treatment, prevention, and also those beyond conventional fields. These are by no means inclusive, but they do offer a good foundation for the development of clinical patient care. The translational model forms the basis for progressing HIV/AIDS clinical research. When linked to the care of the patients, translational researches should result in a direct benefit for HIV/AIDS patients.

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