



CLINICAL AND EVOLUTIVE FEATURES IN SYPHILIS - HIV COINFECTION

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Keywords: syphilis, HIV, infection

Abstract: Syphilis is a systemic infection caused by *Treponema Pallidum* spirochete, which is considered to be the main sexually transmitted disease. The genital ulcerations and local inflammation found in syphilis are favouring factors involved in transmitting the HIV infection. Recent data suggests that individuals suffering from other sexually transmitted diseases are 3 to 5 times more exposed to developing HIV infection. On the other hand, simultaneous HIV infection may worsen the syphilis evolution. In the light of this data we present the case of a patient with syphilis-HIV coinfection recently diagnosed and we will summarize the clinical and evolutive features of the syphilis-HIV coinfection.

INTRODUCTION

Syphilis - a sexually transmitted disease (STD) is a systemic infection caused by the *Treponema Pallidum* spirochaete. Worldwide, every year, a number of 20 million new cases of syphilis is reported, of which the most are found in the „Third World” countries. In the last 2 decades, a growth in syphilis’ incidence has been noted, especially among men who have sex with men (MSM).(1)

Untreated syphilis has 3 evolutive stages, with different prognosis and therapeutic approaches. The luetic infection may be transmitted not only sexually, but also transplacental, during birth, or through contact with infected blood. Therefore, the national health programmes have included test screenings of luetic infection in certain periods of life: in pregnant women- during the first and last pregnancy trimesters, at birth and marriage.

Primary syphilis is characterized by the presence of specific luetic chancre, which is rough, localised at the entrance site, often with a tendency of spontaneous heal and the presence of local adenopathy with particular features. The aspect of it being compared with “mother hen with chicken”.

In secondary syphilis there is an erythematous papular generalized rash, without pruritus, which sometimes resolves spontaneously. The lesions involve the mucosae and skin annexes but they may also involve the internal organs (liver, heart, and so on). General symptoms (headache that exacerbates during night - painkiller resistant, fever, fatigue, worsening of patient’s condition) appear in ¼ of the cases.

Tertiary syphilis appears in approximately 16% of untreated cases. In this stage, on the patient’s skin the syphilides may have a nodular aspect and specifically syphilitic gumma may appear. Organ damage is also reported (bone lesions, nervous system and heart damage, and so on).

Lues, like other sexually transmitted diseases (STD) that manifest clinically through genital ulcerations, may be more frequently associated with the HIV infection. Among the factors

that increase the risk of acquiring HIV infection in patients with syphilis we mention: the impairment of muco-cutaneous barrier (ulceration), increased number of macrophages and T cells with HIV receptors, increased production of cytokines by the lipoprotein stimulated macrophages.(2)

General overview. Sexually transmitted diseases are generally considered to be an important favouring factor in HIV infection. Certain studies have showed that in a certain number of HIV-positive patients, no matter if heterosexual or homosexual, the HIV infection is associated with other sexually transmitted diseases. There are thought to be 3 types of sexual behaviours with increased risk of acquiring HIV, syphilis or syphilis-HIV coinfection:

- **Sexual promiscuity** – in the “Third World” countries it was noted that about 63% of HIV infected patients are also infected with other STD. The lack of appropriate hygiene favours genital infection in uncircumcised men who frequently have balano-preputial infections and penile microulcerations that allow the virus to enter easily. On the other hand, in drug addicted HIV positive patients, associate venereal diseases are identified at about 15% of the cases.(3)
- **Homosexuality** - since 1983 Metroka et al. noticed that from 90 studied patients the majority already had gonococcal infections, syphilis, candidiasis and genital herpes.(4) Mintz and Drew analysed a larger group of homosexuals regarding previous sexually transmitted infections and they identified that the most frequent in their medical history were gonococcal infections (38,4%), nongonococcal urethritis (24%), syphilis (13,5%) and anal herpes (9,4%). (5)
- **Prostitution** – plays an important role in spreading STD in Western Europe and America, but also in developing countries. During the last decade it has been noticed that the frequency of HIV infection in prostitutes trebled. Low-class prostitutes are often infected with various sexually

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Article received on 18.08.2020 and accepted for publication on 02.12.2020

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transmitted diseases including HIV due to the fact that most of them do not use any barrier protection measures.(6) It has been also noticed that the majority of HIV positive prostitutes had genital ulcerations with increased risk of passing the infection to their sexual partners.(3)

Recent data suggests that patients with other STD are 3 to 5 times more exposed to the HIV infection. Some authors claim that even the presence of genital lesions makes the immunodeficiency virus inoculate 10 times easier comparing to persons without any lesions.(3)

Genital lesions caused by STD work in two ways. So through abundant genital secretion including those from ulcers-sick persons pass the infectious agent more easily to the healthy partner. Also, uninfected persons that have genital lesions (fissures, ulcerations) create better conditions to acquire more easily the infection from their sexual partner. The frequency of HIV infection in patients who have other sexually transmitted diseases is bigger in males (6,3% of cases) compared to females (3% of cases). (3) On the other hand, syphilis-HIV coinfection is capable of worsening the progression of syphilis.

In HIV positive patients the clinical picture of sexually transmitted diseases is often altered. Therefore, these diseases may present unusual clinical aspects, and the clinical progress is often atypical. Clinical studies show that the therapeutic response at certain treatment patterns (Ceftriaxone, Quinolone) is weaker in patients coinfecting with *Haemophilus Ducreyi* and HIV and the ulcerations persist longer. The resistance at treatment in these cases is not due to the resistance to tested antibiotics, but to the immunosuppression, the altering of pharmacokinetics, and mostly due to the lack of circumcision.(7)

Genital herpes in HIV positive patients is manifested through deep ulcerations with difficult healing, frequent relapse and poor response to classical antiviral treatment.(8,9) The infection with Human Papilloma Virus (HPV) in HIV positive patients is often recurrent and has an increased resistance to applied treatments (Podophyllin, cryotherapy, imiquimod, and so on).(10) It is also considered that female patients, HIV positive and infected with HPV, have a bigger transforming rate of dysplastic cervix lesions in cancer, comparing to general population.(11)

Johns et al. described some cases of syphilis - AIDS coinfection where the evolution to severe forms of neurosyphilis happened very quickly, within 1-3 years. (12) In the same group of patient's seronegative secondary syphilis cases were reported, the diagnosis being established through ultramicroscopy. There were also some cases of syphilis treated with Benzathine Penicillin in regular dosage, whose serology was not modified under treatment, developing neurosyphilis some years later.(12)

Therefore, the HIV infection in syphilis or other STD confirmed patients is capable of modifying substantially the clinical aspect, but also the response to therapy, and by extension the course of the disease to more severe forms in a short time.

CASE REPORT

We report the case of a 40-year old male patient who was admitted to Dermato-Venerology Clinic for the appearance for 1 month of an erythematous papular scaly rash, disseminated and some of the lesions having a necrotic center. From the onset the patient was also subfebrile and complained of joint pain of the feet and knees for which various investigations were conducted without identifying the etiology of the febrile syndrome.

When admitted, multiple erythematous papular scaly lesions of lenticular shape were noticed, which were infiltrative, well-defined, round-shaped, with a tendency of uniting,

persistent, covered with thin white scales. Some of them centrally ulcerated and covered with necrotic tissue, disseminated on the torso, lower and upper limbs (figure no 1), scrotum (figure no. 2) and palmoplantar (figure no. 3).

Figure no. 1. Persistent infiltrative erythematous papular lesions, localized on the upper limbs



Figure no. 2. Erythematous scaly lesions localized on the scrotum, with tendency of uniting, asymptomatic



The general physical examination revealed: malaise, fever (38,7°C), inguinal and occipital bilateral lymphadenopathy, with lymph nodes of about 1cm, firm, mobile, slightly painful, knee and tibio-tarsal bilateral joint pain.

Figure no. 3. Plantar syphilides, at admission



Conducted investigations showed positive luetic and HIV serology (RPR - 1/128, TPHA - 1/10.210, HIV positive in ELISA and confirmed in Western Blot, viremia - 284.5 copies/ml). The epidemiological investigation revealed that patient had one random unprotected sexual contact, 2 months before.

Furthermore, normochromic normocytic anemia stands out (hemoglobin=10.3 g/dl) with lymphocytopenia. The T CD4 lymphocytes were below normal range, 258/mm³ (normally over 400/mm³), and T CD8 lymphocytes were normal (832/mm³), with CD4/CD8 sub unitary ratio, of 0.31.

Corroborating the anamnestic, epidemiologic, clinical and paraclinical data, we established the following diagnosis:

1. Secondary syphilis
2. Acquired immunodeficiency syndrome
3. Anemia.

The treatment of syphilis was 2 million IU of

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Penicillin/ day. In the first day after beginning the treatment the patient developed Herxheimer reaction (39°C) due to the destruction of a huge number of spirochetes, together with their elimination into the bloodstream, that was treated with antipyretics. When discharged, 5 days later, the patient was afebrile, with diminished lymphadenopathies and complete remission of joint pain. He was recommended to continue with Benzathine Penicillin - 2.400.000 IU/week intramuscular, for 5 weeks, with luetic serology monitoring every 3 months during the first year. At the same time, for HIV infection, specific therapy by the Infectious disease specialist with Emtricitabine/Tenofovir, Dolutegravir was initiated.

DISCUSSIONS

Sexually transmitted diseases, including syphilis are associated with an increased risk of HIV infection in heterosexual people but especially in MSM. Literature data claims that favouring factors in transmission of HIV infection are genital ulcerations and local inflammation, identified in syphilis patients.(13)

The immune system plays an essential role in protecting against syphilis. Immunosuppression found in the HIV infection limits the body's defence capacity against *Treponema Pallidum*, worsening the natural course of luetic infection and exacerbating the clinical features of it.

Clinical reports suggest that in HIV positive patients, the clinical features of syphilis may be more often atypical (14), more severe, with quicker evolution to late stages, of neurosyphilis. It was also noted that there is a poor efficiency of standard therapy of syphilis, in HIV-positive patients.

In syphilis-HIV coinfection, the penicillin or derived penicillin drugs dosage recommended as necessary are higher and extended on longer periods of time comparing to simple luetic infection. The atypical clinical aspect, lacking the typical features can sometimes delay the diagnosis and the initiation of treatment, making the syphilis evolve to the malignant form, with severe neurological complications.

Early malignant syphilis represents a form of recent syphilis, but with symptoms that are specific to the secondary or late latent lues. It manifests itself through severe general symptoms: continuous fever (38 - 39°C), important fatigue, anorexia, sweating, anemia, weight loss. The rash consists of typical second stage syphilides (erythematous papular or erythematous papular with pustules) with rapid extension. Other times the clinical aspect of lesions is mainly nodular or with granulomas (made out of lymphocytes, plasmocytes and neutrophils). In evolution, the lesions become necrotic, with adherent necrosis, difficult to detach, resulting in extended ulcerations, sometimes mutilating. The ulcers can be covered with adherent thick scabs. Without treatment, the early malignant syphilis lesions disappear slowly, leaving scars and leucomelanodermic aspect. After a period of variable latency, a new eruptive episode may occur. The rhythm is of about 2-3 relapses/year, repeating for some years. This form is encountered in immunosuppressed patients, including the case of syphilis-HIV coinfection.(15)

In these cases, sometimes the serological reactions for syphilis may be negative, especially at those in AIDS stage, making the diagnosis even more difficult.(16) Also, the evolution towards neurosyphilis is quicker (3) and ocular complications like uveitis, iridocyclitis, chorioretinitis, optic retrobulbar neuritis may appear more frequently.

In our case, the presence of necrotic center of the erythematous papular disseminated lesions, associating general persistent symptoms, resistant to antipyretic therapy raised the suspicion of syphilis and of an immunosuppression through HIV infection, this fact being confirmed by serological reactions.

The lesions from lues are histopathologically vasculitic-like lesions. The more severe aspect of the lesions with tendency to central necrosis suggested an associated worsening factor.

The HIV infection prognosis is influenced by the number of T CD4 lymphocytes, viral load in the blood, patient's age and the presence of another comorbidities.(17) Starting as early as possible the antiretroviral therapy after the detection of HIV infection helps delaying the AIDS onset.

In cases of untreated lues, without HIV coinfection, neurosyphilis may appear after 10-15 years from the infection time. Neurological symptoms may appear at about 8% of the secondary syphilis cases. Johns et al. and Hobbs et al. showed that associating HIV - syphilis infections modifies significantly its course.(12,18) So, the number of neurosyphilis cases is increasing, with new cases being reported in young people, despite receiving appropriate Penicillin treatment. Out of all the HIV positive patients, it is thought that 55% of neurosyphilis cases appear in persons having HIV, and 45% in patients in AIDS stage. In HIV positive patients, neurosyphilis has various clinical aspects, from general progressive paralysis to meningovascular neurosyphilis, meningitis and tabes dorsalis.(18)

Considering the severe allure of clinical presentation and the possibility of a quick evolution of syphilis to complications, in HIV positive patients the Penicillin dosage is much higher, only with intravenous administration, during long periods of time. In case of allergic reaction to Penicillin, another treatment option for this patients category would be Ceftriaxone, which could prevent evolving towards neurosyphilis.(3)

In all HIV positive patients is recommended to perform lumbar puncture determining the luetic serology from the cerebrospinal fluid. If positive, the patient is treated according to the neurosyphilis scheme.(3)

Jordan et al. demonstrated that in patients with AIDS and neurosyphilis sometimes even the serological reactions for lues from the cerebrospinal fluid can be negative.(19)

During the last decade we notice an increase of HIV infection incidence alongside with that of syphilis. Therefore, the World Health Organisation recommends that in all syphilis patients, the HIV detection serology should be performed as well.(3)

CONCLUSIONS

- In HIV seropositive patients the natural course of luetic infection is worsened, with the exacerbation of clinical features, with more severe skin lesions, necrotic, and increased chance for quicker progression to neurosyphilis.
- In our case, the unfavourable prognosis factors consisted of the syphilis - HIV association, low T CD4 lymphocytes level (258/mm³) and high viral load (284,5 copies/ml).
- The HIV coinfection determined, in our case, the altering of the clinical aspect of skin lesions, having a necrotic aspect, being disseminated and presenting persistent general manifestations, resistant to symptomatic treatment.

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