

# Lues maligna in an HIV-infected patient

## Lues maligna em um paciente com infecção pelo HIV

Luiz Fernando Cabral Passoni<sup>1</sup>, Jacqueline Anita de Menezes<sup>1</sup>, Sayonara Rocha Ribeiro<sup>1</sup>  
and Érica Coutinho O. Sampaio<sup>1</sup>

### ABSTRACT

We report such a case of malignant syphilis in a 42-year-old HIV-infected man, co-infected with hepatitis B virus, who presented neurolues and the classical skin lesions of lues maligna. The serum VDRL titer, which was 1:64 at presentation, increased to 1:2,048 three months after successful therapy with penicillin, decreasing 15 months later to 1:8.

**Key-words:** Malignant syphilis. Lues maligna. Neurolues. HIV infection.

### RESUMO

Descrevemos um caso de sífilis maligna em um paciente de 42 anos com infecção pelo HIV e pelo vírus da hepatite B. O paciente, com lesões cutâneas clássicas de lues maligna e VDRL positivo no soro e no líquido, teve uma resposta excelente ao tratamento com penicilina cristalina. O VDRL sérico, que no diagnóstico era de 1:64, aumentou três meses depois para 1:2.048 e diminuiu para 1:8 após 15 meses.

**Palavras-chaves:** Sífilis maligna. Lues maligna. Neurolues. Infecção HIV.

Lues maligna is a rare ulcerative form of secondary syphilis characterized by papulopustular skin lesions that rapidly enlarge and evolve into round or oval ulcers with sharp borders, centrally covered by a dark, sometimes rupioid crust<sup>6</sup>. Lesions in various stages of development confer a pleomorphic picture. Mucous membranes of the mouth and nose may be involved, and prodromes of fever, headache, and myalgia are common<sup>6 14</sup>. Although its incidence had been decreasing since the beginning of the 20<sup>th</sup> Century, the number of reported cases has increased after 1988, most occurring in patients with HIV infection. We describe a case of malignant syphilis in an HIV-infected patient, the third diagnosed at the Infectious Diseases Department of the *Hospital dos Servidores do Estado*, Rio de Janeiro, Brazil, from 1986-2002. Previously, in April 1989 and January 1993, respectively, a 43-year-old bisexual man and a 44-year-old homosexual man presented with lues maligna as their first manifestation of HIV-infection<sup>12</sup>.

### CASE REPORT

In June 1999, a 42-year-old homosexual male presented with a two-week history of multiple erythematous papules on

his face, trunk and extremities, which progressed to pustules and crusted ulcers. All lesions were painless and he denied having any systemic symptoms.

He was advised that he was HIV-positive in June 1995, when he was seen for evaluation of spleen enlargement and anemia. At that time, laboratory investigations revealed a positive serology for both HIV (ELISA and Western-Blot) and HTLV I/II infection. Serology for hepatitis B showed the presence of HBsAg and HBcAb, whereas serology for hepatitis C was negative. A liver biopsy was refused and he was lost to follow-up until June 1996, when he sought medical assistance presenting clinical features of liver failure and hypersplenism. Six months later his CD4<sup>+</sup> cell count was 242/mm<sup>3</sup> (20%), but he refused to use antiretroviral drugs, which were begun only in May 1998. At that time, his CD4<sup>+</sup> cell count was 404/mm<sup>3</sup> (34%) and his HIV viral load 5,800 copies/ml (nucleic acid sequence based amplification, NASBA). Six weeks after starting stavudine and lamivudine, CD4<sup>+</sup> count increased to 494/mm<sup>3</sup> (59%) and viral load dropped to undetectable levels (<400 copies/ml). He had been taking the medicines regularly until two months before the appearance of the skin lesions, when he discontinued the antivirals.

On examination the patient appeared underweight. He was pale and afebrile. Skin lesions consisted of multiple erythematous

1. Serviço de Doenças Infecciosas e Parasitárias do Hospital dos Servidores do Estado, Rio de Janeiro, RJ, Brasil.

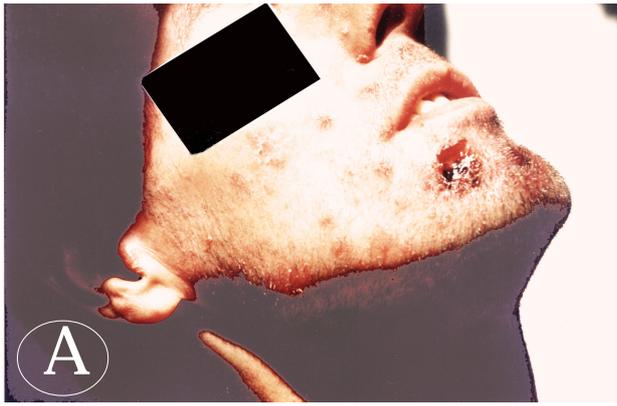
**Address to:** Dr. Luiz Fernando Cabral Passoni. R. Mal Mascarenhas de Moraes 191/1007, Copacabana, 22030-040 Rio de Janeiro, RJ, Brasil.

Tel: 55 21 2518-1594

e-mail: lfpassoni@ig.com.br

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**Figure 1 - Multiple skin lesions of lues maligna in an HIV-infected patient: A) papulopustular lesions and necrotic ulcers over the face; B and C) trunk; D and E) extremities.**

plaques and nodules, some with a necrotic center, and ulcers covered by a dark brown crust, present in his face, trunk, and extremities, including palms and soles (Figure 1). A large fetid rupioid crusted ulcer was observed on his jaw. No mucosal lesions were seen. He had cervical lymphadenopathy, splenomegaly, and gynecomastia. The remainder of the physical examination was normal, including the neurologic system.

**Laboratory investigations revealed.** Hemoglobin, 10.1g/dL; leukocytes, 3,000/mm<sup>3</sup> (58% granulocytes and 32% lymphocytes); platelets, 63,000/mm<sup>3</sup>; erythrocyte sedimentation rate, 103mm/hr. Levels of serum AST, ALT, bilirubin, and alkaline phosphatase were normal. Syphilis serology showed a VDRL titer of 1:64 and a positive *Treponema pallidum* hemagglutination (TPHA). Chest x-ray film was normal. The cerebrospinal fluid examination showed: 2 cells/mm<sup>3</sup>; protein 45mg/dl; glucose 50mg/dl; VDRL 1:1; and TPHA positive.

Treatment was started with intravenous aqueous crystalline penicillin G 18 MU per day, preceded by a single dose of prednisone 60 mg. On the sixth day of treatment he had fever with rigors that defervesced over the next 36 hours. Blood cultures were negative. It was assumed to be a late Jarisch-Herxheimer reaction. The response to penicillin was excellent and he was discharged from hospital after 14 days of treatment.

Three months after completion of therapy, he had gained 3kg, and was taking the antiretrovirals regularly. All skin lesions were healed, though some with residual scars. His CD4<sup>+</sup> cell count was 297/mm<sup>3</sup> (41%) and HIV viral load was 670 copies/ml (2.8 log). VDRL test showed a titer of 1:2,048. The patient denied maintaining sexual relationships since hospital discharge. No specific treatment was provided. At 15 and 35 months later, the VDRL was 1:8.

## DISCUSSION

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<sup>14</sup>. 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 1896-1997<sup>14</sup>. 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<sup>6</sup>. The criteria for diagnosis of lues maligna listed by Fisher *et al*<sup>6</sup> include strongly positive serological test results, a severe Herxheimer reaction, and an excellent response to antibiotic therapy. In the past, serological anergia was one of the characteristic features of the disease, a concept no longer supported<sup>10, 22</sup>. Even taking into account the extensive clinical differential diagnosis of lues maligna, which includes pyoderma gangrenosum, vasculitis, lymphoma, leishmaniasis, leprosy, yaws, and mycobacterial or fungal infections, no other disease process could explain both the

morphology of the lesions and the rapid involution with treatment<sup>6</sup>.

Our case showed the classical clinical picture of lues maligna, and had an excellent response to penicillin. A Jarisch-Herxheimer reaction occurred late in the course of therapy, probably due to the use of prednisone preceding the first penicillin dose<sup>21</sup>. The patient had a serologic response not previously described in malignant syphilis occurring in HIV-infected patients, or that is, the VDRL titer, which was 1:64 at presentation, increased to 1:2,048 three months after successful treatment. Gregori *et al*<sup>7</sup> reported an HIV-infected patient with lues maligna – described as tertiary syphilis with lesions of early and advanced secondary syphilis – in whom the rapid plasma reagin (RPR) titer was 1:256 at presentation, raised to 1:8,192 one week later (before therapy), and decreased to 1:32 eight weeks after successful treatment. Since a polyclonal antibody response is documented in some HIV-infected individuals, patients co-infected with HIV and *T. pallidum* may have a serological response with very high titers, which is common, or present persistently high titers despite antibiotic therapy<sup>20</sup>. Thus, high serological titers after treatment should not be viewed as therapy failure, but as a possible phenomenon. Even considering that falsely rising titers occur in individuals with previously treated syphilis, reinfection with *T. pallidum* should not be discarded.

The first cases of lues maligna in HIV-infected individuals were reported in 1987 by Rosenheim *et al*<sup>3</sup>, and in 1988 by Armignacco *et al*, Schröter *et al*<sup>7</sup>, and Shulkin *et al*<sup>8</sup>. Since then, the number of case reports has increased, which might be related to better recognition or reporting<sup>15</sup>. However, it seems to represent an actual increase in the occurrence of this type of syphilis<sup>45</sup>. In a German multicenter retrospective survey of 11,368 HIV-infected patients, active syphilis was reported in 151 (1.3%) patients, 11 (7.3%) of whom presented with malignant syphilis<sup>16</sup>. In Chandigarh, India, lues maligna was reported in 2/55 patients with syphilis diagnosed from 1990 to 1999: one of three HIV-infected patients presented with lues maligna<sup>8</sup>. In Rio de Janeiro, at the Infectious Diseases Department of the *Hospital dos Servidores do Estado*, lues maligna was diagnosed in three HIV-infected individuals from 1986 to 2002, a finding that contrasts with a previous report of lues maligna occurring in 3/3,253 patients with acquired syphilis diagnosed at the Dermatology and Venereology Department of our Institution between 1948 and 1972<sup>14</sup>. All those reports reinforce the hypothesis that HIV-infected individuals are at risk for developing malignant syphilis.

It is still unclear why only a few *T. pallidum*-infected patients develop lues maligna. The progressive and destructive course of this type of syphilis might be due to an immunocompromised status of the host, a more virulent strain of *T. pallidum*, or even an excessive immune response<sup>2</sup>. However, it appears unlikely that there are *T. pallidum* strains of different virulence<sup>10</sup>, and an immune complex mediated mechanism is apparently not involved in the disease process<sup>9</sup>. Cell-mediated immunity seems to play an important role in the pathogenesis of syphilis, but the CD4<sup>+</sup> cell count is not the only determinant factor for the occurrence of lues maligna, since it has been reported in HIV-infected patients with a CD4<sup>+</sup> cell count of 24/mm<sup>3</sup><sup>17</sup> as well as in patients with

1,200 CD4<sup>+</sup> cells/mm<sup>3</sup><sup>4</sup>. Qualitative or functional defects of both cell-mediated and humoral immunity are probably involved in the pathogenesis of malignant syphilis: the pathogenic interaction between HIV and *Treponema pallidum* both leading to an immunodeficiency state may reduce the immunologic response to treponemal infection through a decrease in cell-mediated immunity, macrophage functional defects, and possibly immunomodulation of the humoral immunity response<sup>19</sup>. The local immune response to *T. pallidum* may be critical to the development of clinical manifestations as well as to the clearance of spirochetes from infected tissues. However, relatively little is known about the local immune responses to *T. pallidum* in skin and other body sites, and virtually nothing is known about the subpopulations of immune cells in the lesions of patients with syphilis co-infected with HIV<sup>11</sup>.

Although the clinical manifestations and the course of syphilis may be altered in the presence of HIV infection, most HIV-infected patients with syphilis have typical disease manifestations. Clinical features of syphilis are protean, and the diagnosis of lues maligna should be considered in all HIV-infected individuals with ulceronodular skin lesions<sup>3 22</sup>. This approach might avoid unnecessary efforts or more complex investigations of other diseases occurring in these patients. As Witkowsky and Parish<sup>22</sup> emphasized, a simple serologic test for syphilis can bring a case to a speedier and less costly conclusion.

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