Leukocytoclastic vasculitis: another condition that mimics syphilis *

Vasculite leucocitoclástica: mais uma "imitação" da sífilis

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Abstract: Syphilis, a disease that in the past was associated with significant morbidity and lethality rates, has resurged in recent years principally as a consequence of changes in risk behavior. An epidemiological group that is commonly affected is the HIV-infected population. The characteristics of the disease and its progression may differ in these patients. The present report describes a case of an HIV-positive male patient, who developed florid secondary syphilis: in addition to syphilitic roseola, he also presented with bilateral panuveitis and involvement of the central nervous system. Investigation revealed the prozone phenomenon and histological examination of the skin lesions showed the presence of leukocytoclastic vasculitis. This finding is extremely rare and few cases have been documented.
Keywords: Histology; Syphilis; Syphilis serodiagnosis; HIV; Vasculitis

Resumo: A sífilis, doença de importante morbiletalidade no passado, tem ressurgido nos últimos anos, graças, sobretudo, às alterações nos comportamentos de risco. Um grupo epidemiológico, frequentemente, acometido é a população com infecção pelo HIV: estes pacientes podem apresentar características peculiares nas manifestações e evolução da doença. Relatamos o caso de um paciente masculino, HIV-positivo, que desenvolveu um quadro florido de secundarismo: além da roséola sifilítica, apresentou pan-uveíte bilateral e acometimento do sistema nervoso central. A investigação, apresentou fenomeno pro-zona e no estudo histologico, mostrou a presenca de vasculite leucocitoclastica achado este extremamente raro e pouco documentado.
Palavras-chave: Histologia; Sífilis; Sorodiagnóstico da sífilis; HIV; Vasculite

INTRODUCTION

Syphilis was a disease of significant importance in the past, with morbidity and lethality rates that in the fifteenth and sixteenth centuries led it to be likened to one of the horsemen of the apocalypse. [1] Since its clinical presentation is extremely variable and it may mimic other diseases, it was dubbed "the great imitator". [2] Following the discovery of penicillin and the post-war period of the twentieth century, the incidence of syphilis decreased significantly, principally in Europe and in the United States, suggesting that the disease could be eradicated. Nevertheless, there has been a resurgence of syphilis in recent years, principally in association with migration, changes in risk behavior and a reduction in the practice of safe sex, predominantly in the group of men who have sex with men (MSM). [3,4] This latter group has been found to comprise approximately 65% of the cases of primary and secondary syphilis in some population samples. [2,5] Another important characteristic of the current syphilis epidemic is its effect on the HIV-positive population, since the two diseases affect the same risk groups. [6]

HIV-infection may alter the presentation of syphilis, the primary form presenting with milder symptoms and the more common and more aggressive secondary form that involves a greater risk of neurological and ophthalmological impairment. [6] There is a greater likelihood of false-negative serology results compared to the HIV-negative population, both in the primary and in the secondary forms of the disease. In AIDS patients there is also a greater association with the prozone effect in nontreponemal tests. [6,7]

Approved by the Editorial Board and accepted for publication on 15.03.2010.
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Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial funding: None / *Suporte financeiro: Nenhum*

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The present report describes the case of an HIV-positive MSM patient who, in addition to developing florid secondary syphilis, was also found to have certain singular characteristics at analysis: the prozone phenomenon and a finding of leukocytoclastic vasculitis at histological evaluation of syphilitic roseola, an extremely rare and seldom reported finding.

CASE REPORT

JAC, a 37-year old male, who had been human immunodeficiency virus (HIV)-positive for 11 years and had been receiving antiretroviral treatment for four years (zidovudine, lamivudine and efavirenz), with a current CD4 lymphocyte count of 444 cells/mm^3 and a viral load of <400 copies/mm^3, presented with influenza-like symptoms including nasal congestion, sneezing and coughing, albeit without fever, over the previous month. He developed eye inflammation and a bilateral reduction in visual acuity. He reported having had sexual intercourse with men, not using condoms regularly and having had an anal lesion four months previously, which had healed. For the previous 8 days, he had had a skin rash, which led him to seek medical care at the emergency room. At admission, an ophthalmological evaluation was performed, resulting in a diagnosis of bilateral panuveitis and papilledema (Figure 1). Based on this latter finding, computed tomography of the brain was performed, revealing a diffuse cerebral edema. Lumbar puncture for cerebrospinal fluid (CSF) analysis was carried out, showing normal pressure, a clear, colorless appearance both prior to and following centrifugation, cell counts of 60 cells/mm^3, 68% lymphocytes, 11% monocytes and 15% neutrophils, 2 red blood cells; normal glucose (67 mg/dl) and increased protein levels (57.2 mg/dl). The only additional laboratory test with abnormalities was the erythrocyte sedimentation rate (ESR) (100 mm/hour), with full blood count, liver and kidney function tests and electrolytes all being within normal levels. Samples were collected for serology (syphilis, cytomegalovirus [CMV], herpes simplex and Epstein-Barr virus [EBV]). The patient was admitted to the infectious diseases ward and dermatological evaluation was requested for his skin condition. At physical examination, the patient was found to have evanescent pink macules on his upper trunk and upper limb joints (Figure 2), patchy alopecia on his scalp (Figure 3) and cervical, retroauricular, epitrochlear, axillary and inguinal lymph node enlargement. Serology results were negative for VDRL, both in serum and in CSF. Considering this finding and at the request of the infectious diseases team, a skin biopsy of the macule on the patient's back was performed. It was also suggested that the serum should be diluted prior to performing a further VDRL in view of a possible prozone phenomenon.

Histological evaluation showed some areas with vessel-wall necrosis, infiltrated by polymorphonuclears surrounded by nuclear dust with no other abnormalities. In addition to these findings that characterize leukocytoclastic vasculitis, the analysis of other sections showed an abundant infiltration of plasmocytes, typical of syphilis (Figures 4 and 5). Puncture/aspiration of the cervical lymph node was also performed and showed reactive lymphoid hyperplasia with a follicular pattern.

Following dilution of the serum, a subsequent VDRL tested positive, with titers of 1/256. Treponema pallidum hemagglutination assay (TPHA) was also positive. A diagnosis of secondary syphilis was thus reached and the patient was treated with intravenous ceftriaxone (2 grams/day for 14 days). At follow-up, VDRL titers fell to 1/16 and 1/1 after 3 and 9 months, respectively.

DISCUSSION

Syphilis presents with different characteristics when it affects patients who are co-infected with HIV.

Figure 1: Eye inflammation: ophthalmological evaluation revealed bilateral panuveitis

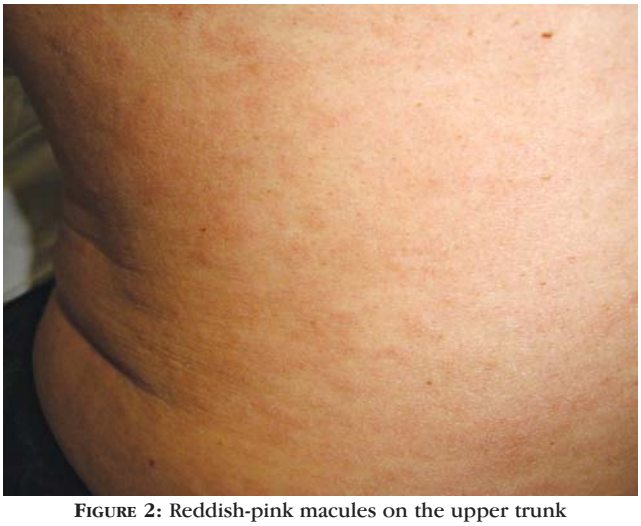

Figure 2: Reddish-pink macules on the upper trunk

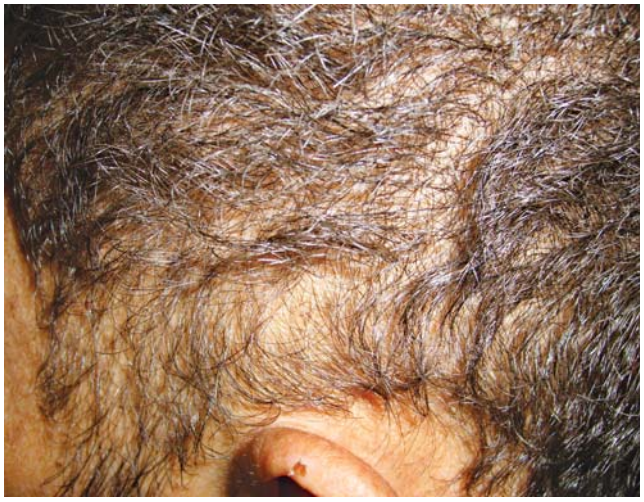

FIGURE 3: Patchy alopecia

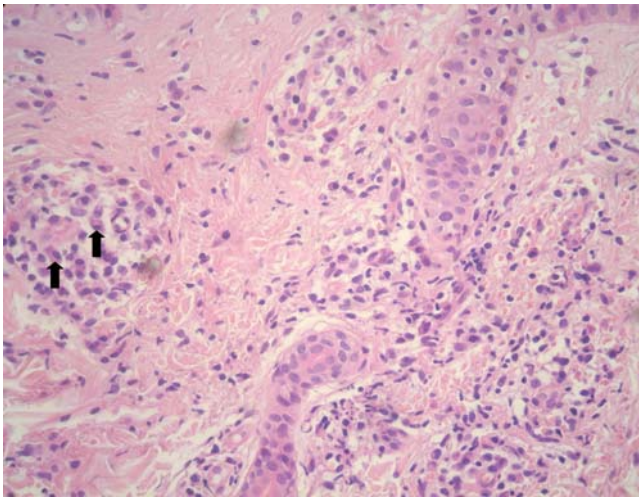

FIGURE 5: On the left, note the presence of plasmocytes (arrows) in the vessel wall infiltration, characterizing syphilis. On the right, leukocytoclastic vasculitis and leukocyte diapedesis. Hematoxylin-eosin, magnification 100x

In the primary disease, these patients may present with more than one chancre in up to 70% of cases and concomitance of primary and secondary lesions affects a quarter of these cases. [7] Although these patients may present with atypical and aggressive forms of the disease, these represent a minority of cases.

Uveitis is the most common ophthalmological manifestation of the disease and may be present at any stage of syphilis. [6] Anterior uveitis is the most common form and is unilateral in 56% of cases. [8] Other forms in which syphilis may affect the eyes include optic neuritis and arterial and venous occlusion. In HIV-positive patients, manifestations are more severe and progress faster. Panuveitis is more common than anterior uveitis alone and the presence of papillitis or optic neuritis may be indicative of a concomitant disease of the central nervous system (CNS).

If the CNS is affected by syphilis, CSF lymphocytic pleocytosis may be found. Nevertheless, the HIV infection alone may lead to CFS pleocytosis, thus making the correct diagnosis of neurosyphilis more difficult in this population of patients. [2] In a third of HIV-positive patients with early syphilis, the CNS has been invaded by treponema irrespective of the immunological status of the patient. [7] Therefore, the CNS may be affected right from the early post-primary to the late stages of the disease, with the peak incidence at 12-18 months after the primary infection. [6] Co-infection by HIV accelerates and alters the clinical course of neurosyphilis. Although involvement may occur irrespective of CD4+ lymphocyte count, the risk of developing neurosyphilis is three times higher in individuals with fewer than 350 cells/mm^3. Nontreponemal tests may also be negative in the CSF evaluation; however, this is rare, with persistence of positive antibodies despite effective treatment being more commonly described. [6]

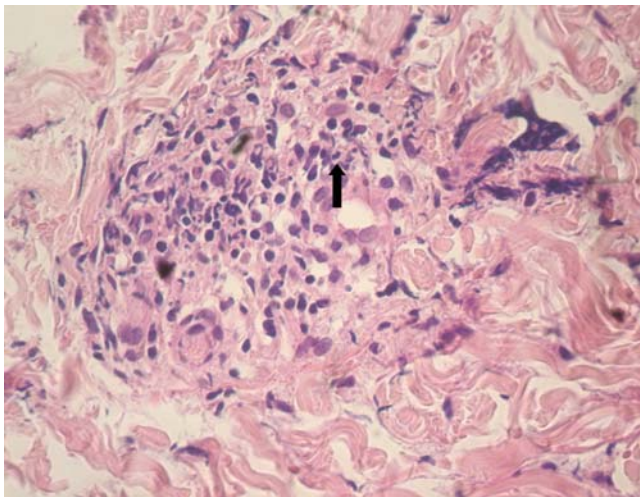

FIGURE 4: Presence of degenerated neutrophiles (arrow) and cell debris (leukocytoclasia) surrounding a vessel and affecting the vessel wall (invading endothelial cells) (hematoxylin-eosin, magnification 400x)

The prozone phenomenon is identified when a serological test is false-negative due to the presence of blocking antibodies or very high titers of specific antibodies or both. This occurs in around 2% of cases; however, in HIV-positive patients, this figure increases to approximately 7%. [9] Dilution of the serum, as performed in the present case, renders the test positive.

Secondary syphilis is characterized by systemic signs and symptoms (micropolyadenopathy, fever, malaise, cephalea, odynophagia, arthralgia and anorexia) in addition to skin eruptions. Syphilitic roseola is one of the earliest manifestations of the disease and consists of the eruption of reddish-pink ellipsoid macules, typically located on the lateral surfaces of the trunk; however, they may be found on the thighs, buttocks and upper limbs. Other forms of macular lesions (syphilitic leukomelanoderma), papulous lesions (lenticular, lichenoid, nummular, condy-

loma planus), nodular-ulcerative lesions (malignant syphilis), diffuse, patchy alopecia, ungual lesions (paronychia, syphilitic onychia) may be found in secondary syphilis; therefore, patients may present with quite different clinical conditions. [2,8]

Irrespective of the type of lesion present in cases of secondary syphilis, the histological findings are essentially identical. What differentiates them is the intensity of these characteristics: the macular, initial forms of secondary syphilis present with more subtle findings compared to the papular lesions. On the other hand, the pustulous and nodular-ulcerative forms are associated with exacerbated alterations. [1] The most common histological findings are plasmocytes and lymphocytes around the vessels, the endothelium of which presents proliferation and edema. Nevertheless, these findings may vary, even in HIV-negative patients.

Leukocytoclastic vasculitis is a necrotizing, small-vessel vasculitis. The necrotic wall of the vessel is infiltrated by polymorphonuclear leukocytes and nuclear dust may be seen surrounding it. It is a histopathological expression of various diseases such as Henoch-Schönlein purpura or cryoglobulinemia, or of drug hypersensitivity. It has already been reported in cases of syphilis; however, these are rare and are more commonly associated with types of skin lesion other than roseola. [10-13] Taytan et al. reported a case of a 45-day old infant with a recent diagnosis of congenital syphilis, who presented with nephrotic syndrome and skin lesions (purplish papules and vesicular hemorrhages on the palms of the hands and soles of the feet), which histopathology revealed to be leukocytoclastic vasculitis. [10] Another recent publication by Chao et al. reported the case of a 46 year old, HIV-negative male patient with multiple, painless ulcers on the glans penis. Biopsy showed only leukocytoclastic vasculitis. Untreated, the patient progressed to the secondary form of the disease and tested positive in serology, thus confirming a diagnosis of syphilis. [11]

CONCLUSION

The wide gamut of possible skin manifestations in secondary syphilis, principally in the HIV-positive patient, together with the possibility of false-negative serology, makes skin biopsy essential for diagnosis in these circumstances. Nevertheless, as the "great imitator", syphilis may reserve surprises either in its clinical presentation or in supplementary investigation. It is important to emphasize that multiple management and knowledge of the various facets of syphilis permits rapid diagnosis and immediate treatment for the patient. ❑

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How to cite this article/*Como citar este artigo*: Furlan FC, Oliveira APV, Yoshioka MCN, Enokihara MMSS, Michalany NS, Porro AM. Leukocytoclastic vasculitis: another condition that mimics syphilis. An Bras Dermatol. 2010;85(5):676-9.