REVISTA DO INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO

JOURNAL OF THE SÃO PAULO INSTITUTE OF TROPICAL MEDICINE

CASE REPORT

http://doi.org/10.1590/S1678-9946202264065

Leukocytoclastic vasculitis in a patient with syphilis and HIV coinfection

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ABSTRACT

Leukocytoclastic vasculitis (LCV) is a small vessel vasculitis characterized by an inflammatory infiltrate composed of neutrophils with fibrinoid necrosis and "leukocytoclasia", a term that refers to nuclei disintegration into fragments. LCV is related to multiple conditions including ANCA-associated vasculitis, cryoglobulinemia, IgA vasculitis, infectious and systemic diseases such as rheumatoid arthritis and systemic erythematous lupus (SLE) as well as infections and malignancy. We describe the clinical case of severe systemic vasculitis in a young male patient with secondary syphilis and HIV coinfection manifested by cutaneous and neurological involvement, as well as peripheral necrosis that requires bilateral lower limb amputation. The skin biopsy revealed histopathological changes compatible with endarteritis obliterans and LCV related to treponemal infection. This case highlights the plethora of clinical manifestations of treponemal infection and the diagnostic challenge this poses in current clinical practice.

KEYWORDS: Syphilis. HIV. Vasculitis.

CLINICAL CASE REPORT

A 33-year-old male with prior medical history of human immunodeficiency virus (HIV) infection that was diagnosed 16 years ago, in treatment taking Atazanavir/Ritonavir 300 mg/60 mg qd and Abacavir/Lamivudine 600 mg/300 mg qd, with adequate viral suppression and immunological response (CD4+ 489 cell/uL, viral load <20 copies/mL) at the time of admission. He reported a complaint of skin lesions and progressive decrease of visual acuity and loss of color discrimination for 3 weeks. On initial examination, erythematous papules were observed in the anterior chest and proximal limbs, with some desquamation of skin on the surface. During the ophthalmologic examination, the reduced visual acuity (right eye: 20/60, left eye: 20/50) was confirmed and the fundoscopy revealed a bilateral optic disk edema.

The initial blood tests showed that the complete blood count as well as kidney and liver function were within normal parameters. The syphilis serological tests showed a reactive nontreponemal antibody test (RPR - Rapid Plasma Reagin) with titers of 1:256 dilutions. A positive fluorescent treponemal antibody-absorption test (FTA-ABS) was also obtained which suggested the existence of an active treponemal infection. Lumbar puncture was performed, showing normal cerebrospinal fluid opening pressure and a clear-colorless appearance. The cell count was negative, with normal glucose levels (57 mg/dL, serum glucose 74 mg/dL) and increased protein concentration levels (77.2 mg/dL). The Venereal Disease Research Laboratory (VDRL) in the cerebrospinal fluid

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Received: 4 June 2022

Accepted: 22 August 2022

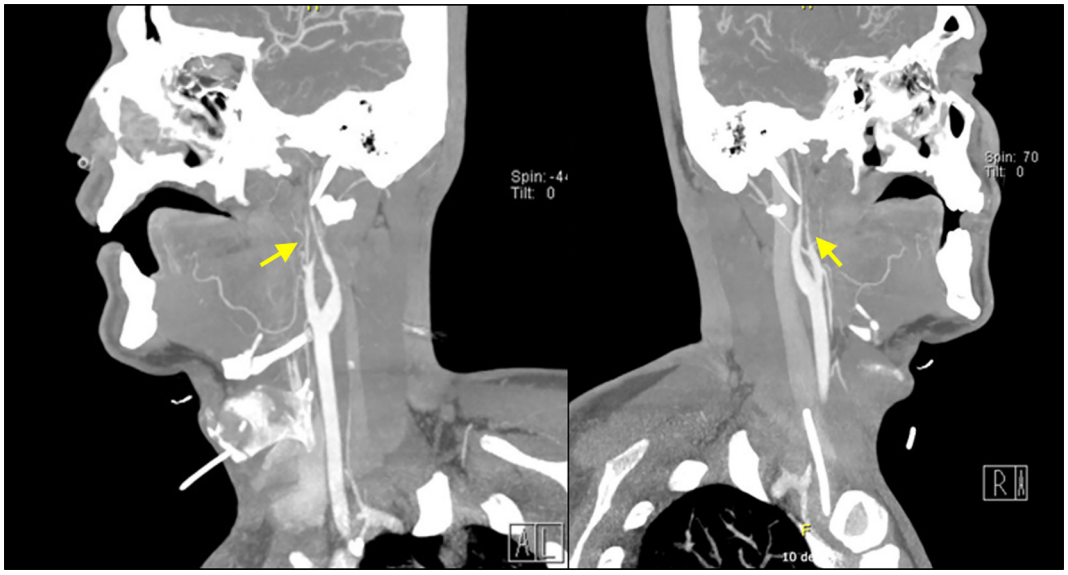

Figure 1 - Cervical angiotomography showing bilateral, symmetrical and concentric internal and external carotid arteries stenosis over 70% (yellow arrows).

was negative followed by a positive FTA-ABS. These results confirmed the active syphilis infection related to neurologic involvement and optic neuritis, so IV Methylprednisolone (250 mg per day) and IV Crystalline Penicillin were given (4 million units every 4 h), according to the national syphilis management guidelines.

Screenings for other infectious diseases including Cytomegalovirus, *Histoplasma capsulatum*, Epstein-Barr virus, *Bartonella* spp, *Toxoplasma* spp, and viral hepatitis were negative. The autoimmune disease assessment included negative reports for antinuclear, anticardiolipin, anti-Beta-2 glycoprotein and anti-double stranded DNA antibodies, as well as normal C3 and C4 serum levels; the cryoglobulins test was also negative.

On day 2 after starting the course of antibiotics, the patient developed a sudden left hemiplegia and right facial palsy consistent with ischemic stroke; the brain CT showed no signs of intracerebral hemorrhage, so thrombolysis was performed using 78 mg of Alteplase, with minimal recovery (NIH Stroke Scale/Score from 13 to 12 points after thrombolysis). The cerebral angiotomography revealed a bilateral, symmetrical and concentric internal carotid stenosis over 70% (Figure 1); the brain MRI showed multiple white matter lesions consistent with acute infractions and the largest lesion was in the right centrum semiovale owing to the patient's neurological deficit. On day 8 after admission, peripheral bluish coloration was observed in the fingers and toes with a decrease in pulse amplitude in the four limbs (Figure 2). The doppler evaluation of lower limbs confirmed bilateral occlusion of posterior tibial, anterior tibial and fibular arteries with halo sign suggestive of large vessel vasculitis.

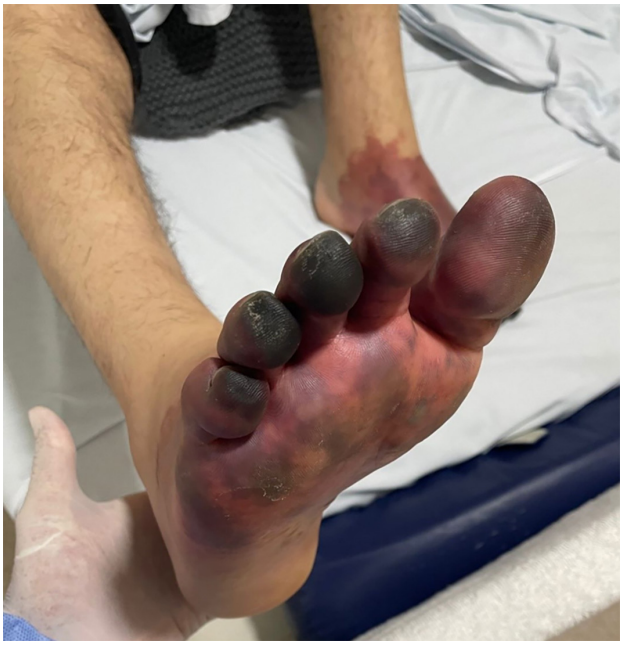

Figure 2 - Violaceous discoloration and necrosis on the distal feet region.

Clinical evolution was torpid with the progression of the bilateral lower limb necrosis, requiring bilateral below-knee amputation. The biopsy of amputated tissue showed a severe compromise of skin and soft tissue small vessels with the thickening of its walls, associated with fibrinoid necrosis, polymorphonuclear infiltration extending to the perivascular zone and nuclear dust. Large and medium size vessels presented endarteritis obliterans with dense plasma cell infiltration (Figure 3); taken together, these histological findings suggested syphilitic vascular and skin affection; unfortunately, the Warthin-Starry stain and

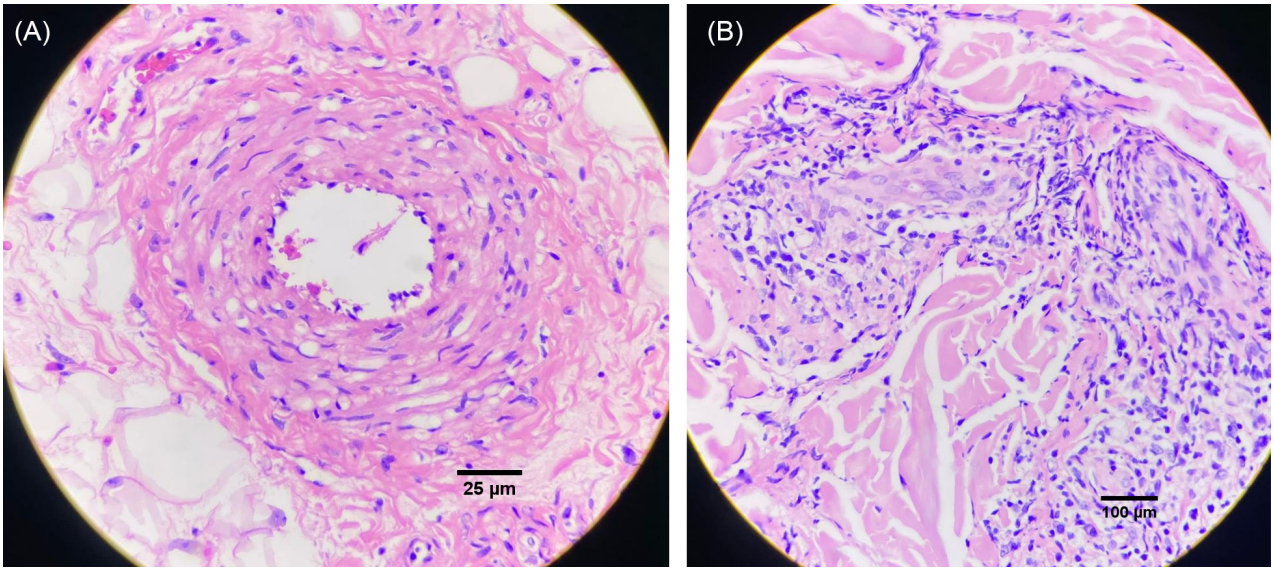

Figure 3 - A) Leukocytoclastic vasculitis with karyorrhexis and fibrinoid necrosis;(B) Diffuse dermal immune infiltrate predominantly composed of plasma cells and histocytes; Cutaneous vasculitis: perivascular infiltrate of polymorphonuclear neutrophils, monocytes and lymphocytes, as well as endarteritis obliterans (Hematoxylin-eosin).

immunohistochemistry using anti-T. pallidum specific antibodies were not available.

After completion of a 14 day-course of penicillin, the clinical improvement was progressive with the disappearance of cutaneous lesions and recovery of visual deficit. The patient was discharged and the follow-up RPR six months after treatment completion was reactive at 1:32 dilutions, demonstrating an eightfold decrease and confirming the serologic cure. The HIV viral load remained durably undetectable during the patient's follow-up period.

DISCUSSION

Syphilis is an infection caused by *Treponema pallidum* subspecies *pallidum*, whose incidence has increased over the years, especially among patients with high-risk sexual behavior[1]. Its causative agent disseminates within days after the infection, with early invasion of distant tissues, including the central nervous system (CNS), which results in a characteristic disease course composed of primary, secondary, latent and tertiary stages. Its variable and subtle manifestations and broad differential diagnosis has earned it the name of "the Great Mimicker", a statement that gains strength in the event of concurrent HIV infection, which alters the natural history of the disease leading to early symptomatic neurosyphilis and multiple unusual presentations[1,2], such as vascular compromise.

Although it is known that syphilis can cause endothelial cell swelling and progress to endarteritis obliterans[1], multiple vessel injury, particularly in association with leukocytoclastic vasculitis (LCV), is exceptional. Potential mechanisms include delayed onset hypersensitivity reactions mediated by IgG, IgA, and/or IgM antibody-antigen complexes and, neutrophil hyperactivation and associated immune disarrangements[3]. Previous HIV infection has been proved to alter the immune response in syphilis infected patients, with increased levels of anti-inflammatory cytokines such as IL-10[4].

LCV is a histopathologic term that describes a form of vasculitis of small vessels which encompasses neutrophilic inflammatory infiltrate and degranulation, a process known as "leukocytoclasia" that can be related to multiple disease processes including autoimmune systemic vasculitides such as Anti-neutrophil Cytoplasmic Antibody (ANCA) associated vasculitis, Behçet's disease, and Cogan's syndrome; other autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, cryoglobulinemia and infection associated vasculitis related to viral (hepatitis B and C) and bacterial (especially endocarditis and meningococcemia) etiologies[5-7].

Although its relationship with infectious diseases has previously been described[8], LCV cases associated with syphilis and HIV coinfection are rare, and few clinical cases have been reported in medical literature[9,10]. Among these, we identified two reports related to HIV coinfection: a syphilitic roseola with histologic features of LCV[11], and a description of LCV as the initial symptom of malignant syphilis in the setting of HIV[12].

CONCLUSION

We report an interesting clinical case given the

uncommon presentation of secondary syphilis as multiple vessel vasculitis with "leukocytoclasia" in skin biopsy and its extreme severity which led to ischemic stroke and necrosis of the lower limbs requiring bilateral below-knee amputation. The thrombotic events represented a diagnostic challenge in view of numerous differential diagnoses including infectious and autoimmune diseases, such as antiphospholipid syndrome. This report acknowledges the vasculitis as a key manifestation of syphilis infection and highlights the importance of early identification of unusual manifestations in patients with HIV coinfection.

AUTHORS' CONTRIBUTIONS

NA and VG wrote the manuscript with support from JMM and LPV; NA and JMM conceived the original idea.

FUNDING

The authors received funding from "Fundacion Cardioinfantil" for the publication fee.

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