CASE REPORT

Rare association of cutaneous vasculitis, IgA nephropathy and antiphospholipid antibody syndrome with tuberculous lymphadenitis

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INTRODUCTION

Mycobacterium tuberculosis infections can be associated with several immune mechanisms. Some of these mechanisms, such as vasculitis associated with tuberculosis, are rare and can challenge dermatologists when making differential diagnoses. The association between pulmonary tuberculosis (Tb) and vasculitis was first described by Parish and Rhodes (1) in 1967. These associations fall into three main types: pulmonary Tb/cutaneous leukocytoclastic vasculitis (CLV), pulmonary Tb/Henoch-Schönlein purpura (HSP) and pulmonary Tb/vasculitis secondary to rifampicin (2-7). The existence of circulating immune complexes in pulmonary Tb has been demonstrated, and the levels of these complexes are related to disease activity. The mechanism of vascular damage is attributed to immune complexes rather than to direct damage caused by *M. tuberculosis* (8,9). Another differential diagnosis is CLV due to rifampicin therapy (7). In cases of Tb-related vasculitis, skin lesions usually improve following the administration of a specific Tb treatment; an anti-inflammatory therapy is not required (2-5,10). Immune complexes are also responsible for renal injury, which is associated with increased levels of immunoglobulins (mainly IgA against the A-60 antigen of *M. tuberculosis*), and mesangial deposition, which leads to the activation of the alternative complement and lecithin pathways, resulting in glomerular damage (IgA nephropathy) (11). Finally, Tb is associated with the development of anti-phospholipid antibody syndrome (APS) by inducing the production of autoantibodies (18,19). The association of tuberculous lymphadenitis, CLV, IgA nephropathy and APS in a single patient has not been reported yet.

CASE DESCRIPTION

A 45-year-old woman from Ribeirão Preto (northeastern region of São Paulo State, Brazil) presented to our clinic with painful necrotic lesions on both feet, mainly on the toes, which had recently increased in number and size. She had a history of headaches and seizures, an ischemic stroke five years earlier (resulting in facial motor sequelae) and five pregnancies, which consisted of four normal deliveries and one abortion at 22 years of age. On examination, there were cervical adenomegalies with bulky and coalescing lymph nodes (the largest measuring 3 cm in diameter) and crusted lesions on the dorsal feet and tips of the toes with purulent exudates and interdigital maceration (Figure 1). The peripheral sensitivity test yielded normal results. Laboratory tests showed hypochromic anemia with microcytosis (hemoglobin: 11.0 g/dL; NR: 12.0-15.5 g/dL), increased inflammatory activity (ESR: 30 mm/1st hour; NR: $<$10 mm/1st hour; C-reactive protein: 3.46 mg/dL; NR: up to 0.5 mg/dL; alpha1-acid glycoprotein: 156 mg/dL; NR: 50-120 mg/dL), increased levels of immunoglobulins (IgA: 1,070 mg/dL; NR: 134-297 mg/dl; IgG: 1,900 mg/dL; NR: 770-1,510 mg/dl; IgM: 222 mg/dL; NR: 67-208 mg/dl), positive autoantibodies (antinucleolar antibody (ANA)-positive 1:100 with nucleolar pattern; lupus anticoagulant (PIL and dRVVT)-positive; anticardiolipin IgG: 14.9 GPL/mL (weak positive); NR: up to 14.0 GPL/ml; p-ANCA-positive), urinary disorders (microscopic hematuria: 25-30 RBCs/field; NR: 3-5 RBCs/field; urinary erythrocytes: 90% total dysmorphic cells, 19% acanthocytes; NR: up 4% acanthocytes; proteinuria: 255 mg/24 h; NR: up to 150 mg/24 h), and intradermal reaction test positive for Tb (PPD: 45 mm with necrosis). Cervical, thoracic and abdominal computed tomographies showed cervical adenomegaly (up to 1.8 cm in length) with central necrosis, a left axillary 2.3-cm lymph node, and several retroperitoneal lymph nodes (up to 0.9 cm in length). A cranial MRI showed a cerebral infarction on the left parietal region and lacunar infarctions in the region of capsular nuclei. Histopathology showed the following: (1) cervical lymph node - chronic granulomatous lymphadenitis with caseous necrosis; (2) fifth left toe - focal granulomatous in addition to leukocytoclastic vasculitis and direct immunofluorescence (DIF) strongly positive for anti-fibrinogen serum (3+) on capillary walls; and (3) renal biopsy - focal and segmental sclerosis with mild focal and chronic tubulointerstitial damage, characterized by mesangial deposition of IgA on DIF, which may correspond to primary IgA nephropathy (Berger's Disease) or Henoch-Schönlein purpura (Figure 2).

No potential conflict of interest was reported.

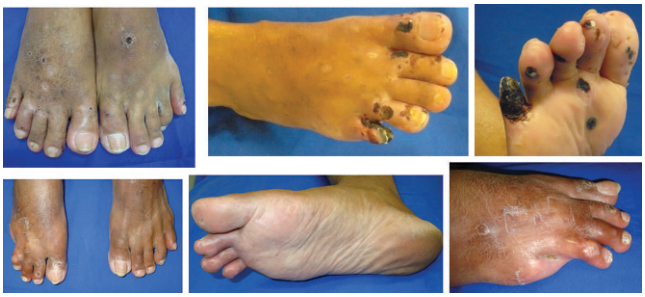

Figure 1 - Clinical presentation of a patient with cutaneous vasculitis. The upper figures show progressive necrotic lesions on the dorsal feet, mainly on the toes. The lower figures show the amputation of the left fifth toe and the improvement of vasculitic skin lesions following RIPE treatment.

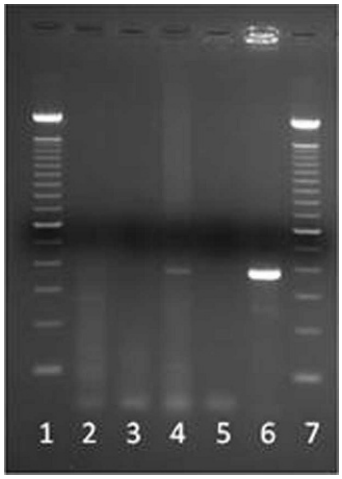

Figure 3 - 2% agarose gel. PCR was performed with specific primers for *Mycobacterium* sp. (17), whose amplicon is 383 bp. Columns: 1 and 7, 100-bp marker; 2, negative control (without DNA); 3, paraffin biopsy of skin vasculitis; 4, paraffin sample of a cervical lymph node; 5, culture of *M. avium* complex; and 6, culture of *M. tuberculosis*. PCR was positive for *M. tuberculosis* culture and the cervical lymph node (site of infection) and negative for the skin (hypersensitivity vasculitis).

PCR with DNA that was extracted from paraffin blocks of lymph node and skin biopsies confirmed *Mycobacterium* sp. only in the lymph node (Figure 3). The final diagnosis consisted of Tb lymphadenitis, CLV, primary IgA nephropathy and APS. Ciprofloxacin (500 mg) was prescribed twice per day for ten days, and Fluconazole (150 mg) was prescribed once per week for eight weeks for the secondary infection and interdigital maceration on the feet. Thereafter, aspirin (200 mg daily) and warfarin (for anticoagulation) were prescribed. The patient was evaluated by physicians in the Departments of Neurology, Ophthalmology, Nephrology and Infectious Diseases. Tb treatment was initiated with RIPE (rifampicin, isoniazid, pyrazinamide and ethambutol). Because an adverse drug reaction to pyrazinamide was observed, administration of this medication was suspended. Because of the worsening necrosis on her toes, the patient's left fifth toe was amputated with no complications. The patient finished the Tb treatment, which was followed by weight recovery, normalization of lymph node size, absence of new vasculitic lesions and significant improvement of previous skin lesions. ANA and PIL were negative, but glomerular hematuria and proteinuria remained positive.

DISCUSSION

There are few reported cases of an association between Tb and CLV (nine cases) and Tb and IgA nephropathy (six cases) (2-6,13,14). Only 10% of CLV cases are attributed to

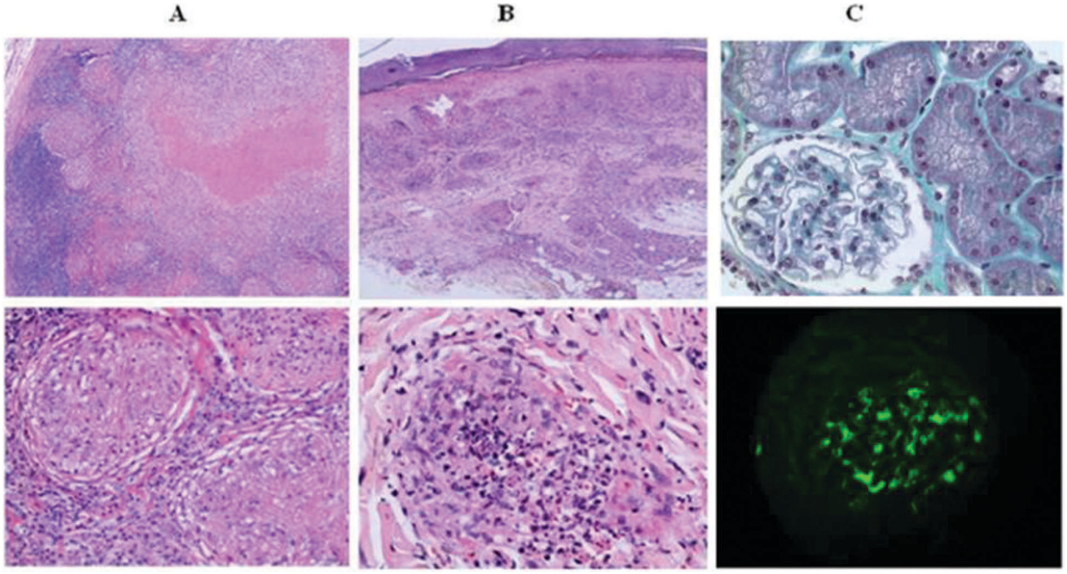

Figure 2 - Histopathology of lymph node (A), skin (B) and kidney (C) biopsies. A. Chronic granulomatous lymphadenitis with caseous necrosis without microorganisms (magnification: 20x and 40x) B. Leukocytoclastic and focal granulomatous vasculitis (objectives: 20x and 40x) C. Renal biopsy contained 13 glomeruli, 12 normal and one with a focal segmental lesion. DIF showed diffuse and global mesangial deposits of IgA (objective: 40x).

drugs and infections, and 61% are considered idiopathic cases. Considering the existence of circulating immune complexes in pulmonary Tb and the relationship between immune complex levels and disease activity, the damage mechanism that has been proposed for this type of vasculitis is the deposition of immune complexes that are formed by antibodies against antigens of the bacterium on the vascular wall rather than direct aggression by the bacterium (8,9). Up to 56% of Tb patients have circulating immune complexes, and there is evidence of increased immunoglobulin levels in these patients, mainly IgA and IgG, as was observed in our patient. These immunoglobulins are produced against the A-60 antigen of the mycobacterium, leading to the formation of immune complexes (11).

Another differential diagnosis is the onset of vasculitis following rifampicin therapy, as demonstrated in some case reports, where CLV occurred due to this medication (7). However, our patient had skin lesions before using this drug. In cases of Tb-related vasculitis, skin lesions improve with RIPE treatment alone; no specific anti-inflammatory therapy is required (2-7,10,15).

In 1985, Cohen and Rosenstein (12) described a case of an association between Tb and IgA nephropathy in which renal involvement improved after Tb treatment. In this case, HSP needed to be considered. HSP is a type of systemic vasculitis that is more common in children, and both renal involvement, defined as IgA nephropathy, and palpable purpura appear in 50% of cases (6,13,14). Some specialists defend the theory that Berger's disease is a restricted form of HSP, and there have been five reported cases of HSP associated with Tb. However, our patient presented with CLV with anti-fibrinogen, not IgA, deposition in the capillary walls, which rules out a diagnosis of HSP.

In addition, PCR with primers specific to *Mycobacterium* (17) was performed in cervical lymph node and skin samples, which confirmed the etiology of *Mycobacterium* sp. in the lymph node sample but not in the skin sample. The DNA that was extracted from the paraffin skin sample was amplified with keratin primers, confirming its integrity (data not shown). These results strongly suggest a hypersensitivity form of CLV.

None of the case reports of Tb associated with CLV or Tb associated with IgA nephropathy in the literature included descriptions of positive autoantibodies. In our patient, ANA, p-ANCA and lupus anticoagulant (PIL and dRVVT) tests were positive, and there was a prior medical history of ischemic stroke (confirmed by MRI). These findings reinforce the diagnosis of an autoimmune disease and lead us to a diagnosis of APS secondary to Tb.

The production of anti-phospholipid antibodies (aPLs) could have either an autoimmune or infectious origin. The latter origin does not involve anti-β2-glycoprotein I (anti-β2GPI) activity and usually does not cause thrombosis. However, there have been recently described cases of lepromatous leprosy patients with genetically determined anti-β2GPI activity followed by thrombosis (18). By inducing a specific cellular immune response and secondary antibody production (as noted by the strong positive PPD and increased immunoglobulin levels), tuberculosis stimulates the production of autoantibodies (including aPLs) and procoagulant factors, such as plasma fibrinogen (factor I), factor VIII and D-dimers. Thus, *M. tuberculosis* can be considered an etiologic factor in aPL production and the triggering of APS (19).

In the literature, there is a single report of concomitant CLV, Sweet syndrome, cutaneous polyarteritis nodosa and cervical adenopathy caused by *M. fortuitum* (20). The association of Tb, focal granulomatous, CLV and IgA nephropathy in a single patient has not been reported. This case is complex, demonstrating rare manifestations of an endemic disease in Brazil, and serves as a warning to dermatologists to be cautious in the differential diagnosis of patients with vasculitic presentations.

AUTHOR CONTRIBUTIONS

Bueno Filho R contributed to the writing, literature review, data interpretation, and data and picture collection and was clinically responsible for the patient. Cordeiro AP contributed to the collection of pictures and data and was clinically responsible for the patient. Almeida FT was involved in data collection and was responsible for the PCR experiment. Shaletich C was involved in the review and data interpretation processes. Costa RS was involved in the review, data interpretation, and writing processes. Roselino AM was involved in the review, writing, and data interpretation processes and was the coordinator of the Granulomatous Skin Diseases Clinic and coordinator of the Biomolecular Laboratory of Dermatology.

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