Gangrene of the auricle as the first sign of antiphospholipid antibody syndrome

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ABSTRACT

Antiphospholipid syndrome (APS), more common in females, manifests clinically as thrombosis and/or recurrent fetal loss. Hemolytic autoimmune anemia and neurological, cardiac and cutaneous manifestations are common. This is the case report of a male patient whose first manifestation of the disease was gangrene of the auricle. The diagnosis of APS was established by biopsy of the lower limb skin, which showed thrombotic vasculopathy with no evidence of vasculitis. This is one of the two major criteria, which, along with a minor criterion, establishes the diagnosis of APS. Possible differential diagnoses are discussed. The importance of the biopsy in the APS diagnosis of this male patient is emphasized.

Keywords: antiphospholipid antibodies, thrombosis, anticardiolipin antibodies, systemic lupus erythematosus.

INTRODUCTION

Antiphospholipid antibody syndrome (APS) is the most common acquired thrombophilia. Clinical manifestations are heterogeneous and reflect the presence of thrombosis in arterial or venous vessels of any caliber and in any organ or system, developing abruptly or insidiously.

The diagnosis is made through the association of clinical and laboratory criteria. The clinical criteria are thrombosis (arterial, venous, or vasculopathy) or history of obstetric morbidity or mortality (three or more fetal losses on the first trimester, one or more fetal deaths or preterm birth due to placental insufficiency). The laboratory criteria are positive titers of lupus anticoagulant antibody, moderate to high titers of anticardiolipin IgG or IgM, and moderate to high titers of β2-glycoprotein I.[1,2]

Clinical findings are diverse and may comprise hematological, renal, neurological, cardiac, and dermatological changes, and even a poor prognosis condition – catastrophic APS.[2,3] It is more commonly found in females and in association with autoimmune diseases. We report a case of primary APS with gangrene of the auricle as the initial symptom.

CASE REPORT

The patient is a 28-year-old male, who has Graves' disease and has been stable for three years on propylthiouracil. He presented to the emergency room complaining of cyanosis and pain on his nose and auricle for one day. On physical examination, he had petechiae on his tongue, palate, and limbs, accompanied by cyanosis on his nose and outer ears. After 12 hours, the cyanotic areas progressed to gangrene (Figure 1). The patient remained normotensive, with no neurological changes. After excluding meningococcal disease and endocarditis, propylthiouracil was discontinued, and pulse therapy with methylprednisolone (1 g/day) for three consecutive days was started. The cutaneous lesions stabilized. Then, oral prednisone (60 mg/day) and topic lugol's solution were maintained.

The following laboratory tests were performed: complete blood count (Hb 11.5; Hct 33.9; leukocytes 4,500; platelets

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44,000); urinalysis (negative proteinuria; leukocytes 1,000; RBC 1,000); negative serologies for hepatitis B, hepatitis C, and HIV; normal levels of ALT, AST, fibrinogen, C3, C4 and CH50; negative C-ANCA and P-ANCA; negative cryoglobulins; negative anti-Ro; negative antinuclear factor and rheumatoid factor. Because of the difficulty in establishing a diagnosis, skin biopsy was performed in the area of erythematous macules in the right lower limb. The result was thrombotic vasculopathy, suggestive of APS (Figure 2).

The diagnostic hypothesis of APS was confirmed by the following findings: positive anticardiolipin IgM titers (55 MPL UI/mL); negative anticardiolipin IgG titers; and positive lupus anticoagulant titers. Once established the diagnosis, the following were introduced: chloroquine diphosphate, 4 mg/kg/day; anticoagulant dose of subcutaneous low-molecular-weight heparin; and oral acetylsalicylic acid (ASA), 100 mg/day.

The cutaneous lesions of nose and left auricle improved. However, a small gangrenous area persisted on the right auricle, with partial loss of the cartilage (Figure 1).

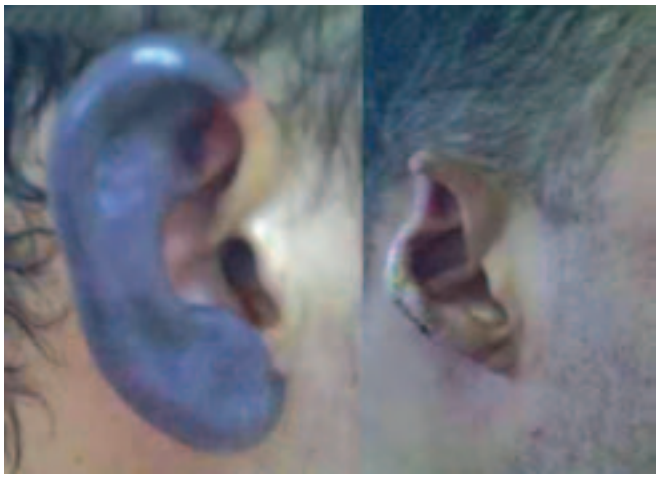

Figure 1
Right ear before and after treatment, with partial cartilage loss.

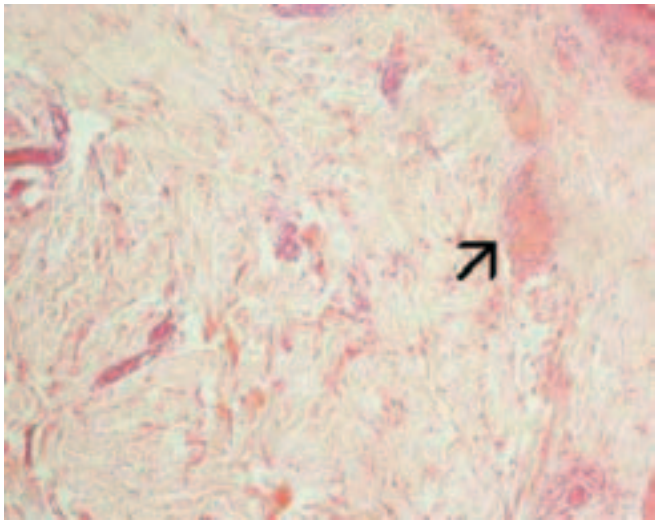

Figure 2
Skin biopsy showing thrombosed vessels (arrow) and absence of perivascular inflammatory infiltrate.

DISCUSSION

During hospitalization, several diagnostic hypotheses, such as propylthiouracil-induced vasculitis, Wegener's granulomatosis, relapsing polychondritis, and antiphospholipid antibody syndrome, were raised.

Propylthiouracil-induced vasculitis may occur at any time during its use,[4] and the report of its manifestations have ranged from skin lesions to renal and pulmonary alterations.[5] Most patients with propylthiouracil-induced vasculitis have positive ANCA titers.[5] The accumulation of propylthiouracil metabolites inside neutrophils has been suggested to make myeloperoxidase, as well as other enzymes present in neutrophil granules, immunogenic. Thus, other neutrophils would be activated, causing the release of enzymes and the production of free radicals and cytokines, leading to vascular damage.[6,7]

Wegener's granulomatosis is defined as vasculitis with formation of inflammatory granulomas and necrosis of medium- and small-caliber vessels.[8] The complete form involves face, lungs, and kidneys.[4] Eighty to ninety per cent of the patients have positive C-ANCA titers. Histopathological exam shows leukocytoclastic vasculitis with necrosis and perivascular inflammatory granuloma.

Clinical findings comprise perforation of the nasal septum, saddle nose, hearing loss, subglottic stenosis, orbital pseudotumor, scleritis, episcleritis, and uveitis. The lungs show nodular infiltrate or cavitations, which may lead to hemoptysis.[8] The kidneys show rapidly progressive glomerulonephritis. Over 75% of the patients will have renal lesion during the course of disease, which initially manifests as proteinuria and hematuria.[4] The skin may show nodules, palpable purpura, vesiculobullous lesions, papules, ulcers, and digital infarcts.[8]

Relapsing polychondritis is an immune system-mediated disease associated with the inflammation of cartilaginous structures and other connective tissues, such as in the ear, nose, joints, and respiratory tract. The clinical findings may comprise chondritis of the auricle, reduced hearing, nasal chondritis, nose deformities, laryngotracheal involvement, ocular inflammation, arthritis, skin involvement, and vasculitis. No specific laboratory change occurs. The diagnosis is made

through clinical findings, tissue biopsy being rarely required. The treatment is performed with corticosteroids, and methotrexate may be associated.[9]

APS, also known as Hughes syndrome, was defined in the late 1980s.[4] It affects 1% to 6% of the population. Thrombosis is the major manifestation and may occur even in patients with thrombocytopenia (40%–50% of the patients). Thrombosis tends to occur especially in the venous circulation of the lower limbs and in the cerebral arterial circulation.

Cutaneous manifestation may be the first one in 41% of the patients, *livedo reticularis* being the most frequent lesion. It is a persistent mottled reticulated lesion of purplish, reddish or bluish color. It is irreversible with rewarming and may affect the trunk, arms or legs.[10] Other lesions associated with the APS are digital gangrene, ulcers of the lower limbs, pseudovasculitis, cutaneous necrosis with painful purpuric lesions that progress to blackish bullous plaques in the limbs, head (nose, ears) or buttocks.[11]

Livedoid vasculitis is a rare disease described in 1967 by Bard and Winkelmann. It is characterized by painful purpuric lesions in the lower limbs that often ulcerate. The ulcers have a chronic and recurrent course and get worse in summer and winter. They may result in atrophic, white and irregular scars with telangiectasia and livedoid hyperpigmentation of perilesional hemosiderin. Its pathogenesis is still unknown, but, in some patients, it is associated with coagulation changes or inflammatory diseases.[12]

APS diagnosis is made through the association of clinical and laboratory criteria.[8] The treatment involves prophylactic measures and anticoagulation, which may be performed with warfarin or heparin, often associated with ASA.

In patients with platelet count under 50,000, the use of ASA or anticoagulants is contraindicated, and prednisone or immunoglobulin may be used until the platelet count normalizes. Chloroquine and hydroxychloroquine have a proved antiplatelet and antithrombotic effect on patients with systemic lupus erythematosus, and a probable preventive role in APS patients as well.[4]

Of the differential diagnoses presented, relapsing polychondritis was eliminated as a diagnostic hypothesis due to the gangrene of the auricle. Wegener's granulomatosis and propylthiouracil-induced vasculitis were also discarded as causes of vasculopathy, especially after the skin biopsy result, which showed neither vasculitis nor leukocytoclasia.

The patient had a rather unexpected evolution, with marked improvement of the skin lesions after methylprednisolone pulse therapy followed by prednisone (60 mg/day) associated with chloroquine diphosphate and heparin. Acetylsalicylic acid was not used at the initial phase of hospitalization because of thrombocytopenia. Propylthiouracil was discontinued, and thyroidectomy was programmed.

CONCLUSION

Skin biopsy was critical to the diagnosis. The clinical findings and thrombotic vasculopathy found on the histopathological study, in association with the high anticardiolipin titers and the presence of lupus anticoagulant antibodies, established the diagnosis of APS.

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