

Purpura fulminans–like lesions in antiphospholipid syndrome with endothelial C3 deposition



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INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies (aPL) associated with thrombosis or pregnancy morbidity. These antibodies include lupus anticoagulant (LA), anticardiolipin antibody (ACL), and anti- β 2-glycoprotein antibody (anti- β 2GPI). APS can be either primary or secondary to autoimmune diseases, mainly to systemic lupus erythematosus, but it can also be associated with other autoimmune, malignant, or drug-induced diseases.¹

The condition affects the skin in 70% of cases, producing a variety of skin lesions.² Livedo reticularis is the most frequently observed lesion; other types of lesions include ulcerations, digital gangrene, subungual splinter hemorrhages, superficial venous thrombosis, thrombocytopenic purpura, pseudovasculitic manifestations, and primary anetoderma. Disseminated cutaneous necrosis with dermal vascular thrombosis³ have been described on rare occasions. We present a case of extensive disseminated cutaneous necrosis. The C3 endothelial deposits observed in thrombotic vessels support the hypothesis of complement activation as a primary phenomenon in the development of cutaneous thrombosis.

CASE REPORT

A 49-year-old healthy woman was admitted to the hospital because of a painful rapidly progressive skin

Abbreviations used:

ACL:	anticardiolipin antibody
anti- β 2GPI:	anti- β 2-glycoprotein antibody
aPL:	antiphospholipid antibodies
APS:	antiphospholipid syndrome
DIF:	direct immunofluorescent
LA:	lupus anticoagulant

lesion. Her clinical history was otherwise unremarkable. The patient was not taking any medication. She had no history of smoking, drinking, thrombosis, or fetal loss. She had 2 normal gestations delivered by cesarean section. There were no constitutional symptoms.

On physical examination, she had purpura fulminans–like lesions on her legs, arms and the abdomen (Fig 1). Clinically, they began as non-blanchable, painful, distal purpuric lesions with an indurated halo, which evolved into bullae that became hemorrhagic and turned into necrotic scars. There were no oral lesions or lymphadenopathy. At this point, we started treatment with empirical intravenous ceftriaxone and doxycycline to cover a possible infectious cause, and a skin biopsy was performed.

The laboratory examination found microcytic anemia (hemoglobin 8.7 g/dL; normal value, 12.5–16 g/dL) and an increased level of C-reactive protein (21 mg/dL; normal value, 0–0.5). Leukocyte and platelet values were normal. The results showed

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Fig 1. Purpura fulminans-like lesions. Hemorrhagic bullae and necrotic scars were observed. The lesions were delimited to monitor their growth.

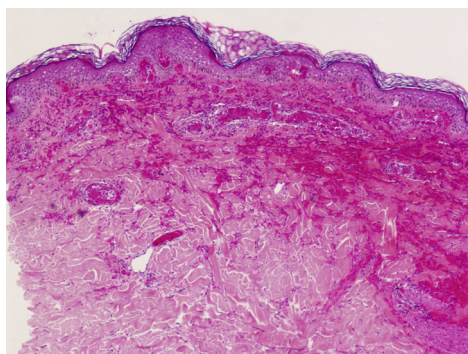


Fig 2. Vascular thromboses in small arterioles and capillaries of the dermis. Hemorrhages and eosinophilic necrosis of the epidermis were observed. (Hematoxylin-eosin stain; original magnification, $\times 10$.)

antinuclear antibody titer 1:80 and LA 3.06 (normal value, 0.6-1.2). Anti- $\beta 2$ GPI and ACL were also positive, but cryoglobulins and cryofibrinogens were normal. Anti-dsDNA antibody, cANCA, p-ANCA, SS-A, SS-B and C3 and C4 levels were normal. The blood levels of protein C, protein S, factor V and anti-thrombin III, and the prothrombin time were within the normal ranges, but partial thromboplastin times (51 seconds; normal value, 25.1-36.5 seconds) as well as D-dimer (5250 ng/mL; normal value, 0-232) were elevated.

Several blood cultures and all serologic tests were negative, including *Treponema pallidum*, *Rickettsia spp*, *Coxiella burnetii*, *Borrelia burgdorferi*, measles virus, rubella virus, Epstein-Barr virus, Dengue virus, Zika virus, *Hantavirus*, and Crimean-Congo fever virus. A total body computed tomography scan was requested to rule out the presence of an internal neoplasm was without significant findings.

Skin biopsies found extensive thrombosis of small-sized vessels and red blood cell extravasation (Figs 2 and 3). The involved vessels were surrounded by a sparse inflammatory infiltrate. Direct immunofluorescent (DIF) testing revealed C3 deposits on the

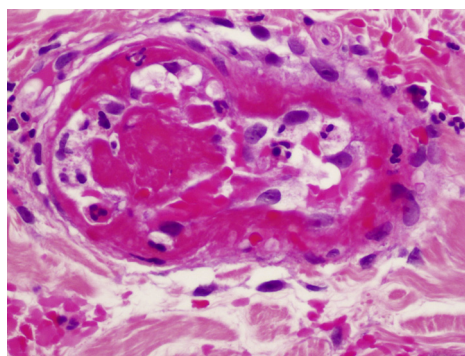


Fig 3. Vascular thromboses in small arterioles and capillaries of the dermis. Affected vessels were surrounded by a sparse inflammatory infiltrate. (Hematoxylin-eosin stain; original magnification, $\times 40$.)

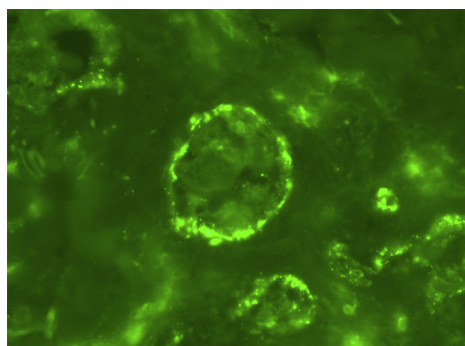


Fig 4. Complement C3 deposits in thrombotic vessels wall were revealed in DIF testing.

walls of the affected vessels (Fig 4), suggesting the influence of humorally mediated vascular injuries in the pathogenesis of the cutaneous lesions.

Primary APS was diagnosed after infectious, malignant, drug, and autoimmune causes were ruled out. We started treatment with methylprednisolone pulse at 1 g/d during 3 days and low-molecular-weight heparin at anticoagulant doses. The hemorrhagic bullae and necrotic scars healed with residual hyperpigmentation.

DISCUSSION

APS is the most common cause of acquired thrombophilia. APS causes cutaneous or systemic vessel occlusion owing to aPL and circulating anti-phospholipids that damage endothelial cells upon binding to exposed phospholipids and interfering with normal procoagulant protection, leading to thrombosis.⁴ LA is the most specific test, whereas ACL is the most sensitive test for APS diagnosis. In the presence of LA, partial thromboplastin times are prolonged, and they are not normalized when the patient's plasma is mixed with the plasma of a healthy person. Anti- $\beta 2$ GPI are also used and have

recently been included in the classification criteria. In addition, the Venereal Disease Research Laboratory tests may show positive results.¹

The histopathology of skin lesions shows noninflammatory thrombosis of dermal vessels. Multiple deep biopsies are often required to show vascular thrombi with partial or complete obstruction of the small or medium-sized arteries located at the dermo-hypodermal junction. True vasculitis is not a constant feature of the disorder, and inflammatory infiltrates are scarce.⁵ Deposits of C5b-9 within the cutaneous vasculature in DIF test have been described.⁶ However, in our case, complement C3 deposits were observed on the walls of the blood vessels. Complement C3 activation is required for APS-induced fetal loss in a murine model. The use of a C3 inhibitor blocks fetal loss and growth retardation. Furthermore, mice deficient in complement C3 are resistant to fetal injury induced by aPL antibodies.⁷ This physiopathologic mechanism has not yet been demonstrated in humans.

The treatment is based on the patient's clinical history and risks. However, anticoagulation is the mainstay of the management of APS.⁸ Anticoagulation and antiplatelet drugs are administered in low-risk patients, and high-dose systemic steroids with anticoagulation, intravenous gamma-globulin, and plasma are administered in high-risk patients.² Therapy for dermatologic manifestations remains

empirical and no treatment is systematically effective. Widespread cutaneous necrosis is considered a major thrombotic event requiring long-term anticoagulation treatment.⁸

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