Amputation of Digits or Limbs in Patients with Antiphospholipid Syndrome

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Objective: To describe the characteristics of patients with peripheral vascular disease leading to amputation of digits or limbs encountered in patients with the antiphospholipid syndrome (APS).

Methods: Twenty-one cases derived from several geographical centers (Brazil, Serbia, Italy, Israel, United Kingdom, and South Africa) are presented. The major clinical, serological, and histopathological data (where available) of this cohort are described, documented, and analyzed.

Results: Patients were suffering mainly from systemic lupus erythematosus (9 patients) or primary APS (8 patients). Peripheral vascular occlusions occurred during the course of the catastrophic APS in 5 patients. The vascular occlusions occurred both early and very late in the course of the disease (time after APS diagnosis, 0-38 years). Vasculitis was present in 7 patients and 5 demonstrated the typical antiphospholipid antibody (aPL)—vasculopathy with complicating bland thrombosis. Myocardial infarctions had occurred in 4 patients but it was not possible to determine whether they suffered from premature atherosclerotic disease or whether the infarctions were aPL-related. The appearance of *livedo reticularis* preceding the arterial thrombosis was noted in 9 patients. Cryoglobulinemia was detected in only 1 patient.

Conclusions: Peripheral vascular disease leading to amputation of digits or limbs is a severe complication encountered in patients with APS. In the absence of histopathology, it may be difficult to distinguish whether concomitant atherosclerotic occlusions, vasculitis, or aPL-related thrombosis of peripheral vessels is the main cause of the vascular ischemia. Treatment should, therefore, include full anticoagulation as well as corticosteroids and immunosuppression in these patients.

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Gangrene leading to amputation of digits or limbs is 1 of the most devastating complications occurring in patients with antiphospholipid antibodies (aPL). Patients with this complication may have other features of the simple/classic antiphospholipid syndrome (APS), either primary APS or associated with systemic lupus erythematosus (SLE)/"lupus-like" disease. Rarely, it may be a feature of the catastrophic APS. Other possible etiologies resulting in the necessity for such radical treatment are coincidental atherosclerotic disease or vasculitis (1,2). The latter 2 conditions are not uncommon in patients with SLE and premature atherosclerotic disease is now thought to be 1 of the major complications of longstanding SLE. It may frequently be difficult to distinguish as to which of the underlying pathologies may be responsible for the vascular occlusions (particularly in the presence of aPL) and, in the absence of histopathology, clinicians must be guided purely by the clinical presentation.

In this article, we present 21 cases of gangrene of digits or limbs accompanied by elevations of aPL who required

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Abbreviations	
aCL	Anticardiolipin antibodies
ANA	Antinuclear antibodies
ANCA	Antineutrophil cytoplasmic antibodies
aPL	Antiphospholipid antibodies
APS	Antiphospholipid syndrome
ARDS	Acute respiratory distress syndrome
ß2GPI	ß2-glycoprotein I
DVT	Deep vein thrombosis
ENA	Extractable nuclear antigens
FFP	Fresh frozen plasma
HELLP	Hemolysis, elevated liver enzymes, low platelet count
LAC	Lupus anticoagulant
MI	Myocardial infarction
MRI	Magnetic resonance imaging
PAPS	Primary antiphospholipid syndrome
PE	Pulmonary embolism
IV	Intravenous
SLE	Systemic lupus erythematosus
TIA	Transient ischemic attack
TMA	Thrombotic microangiopathy
VDRL	Venereal Disease Research Laboratory

amputations and highlight the importance of this complication in patients with APS.

MATERIALS AND METHODS

Twenty-one cases with gangrene of digits or limbs accompanied by elevations of aPL and requiring amputations were collected from several centers of different countries, including Brazil, Serbia, Italy, South Africa, United Kingdom, United States, and Israel. Important features of their clinical histories and pertinent investigations were documented. Immunological testing was performed by local laboratories according to accepted international methodologies. Five representative case histories are described in detail.

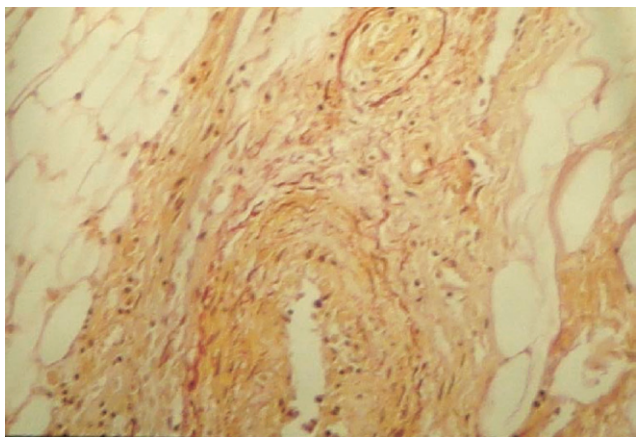

Figure 1 Inflammatory infiltrate with mononuclear cells in the media and intima.

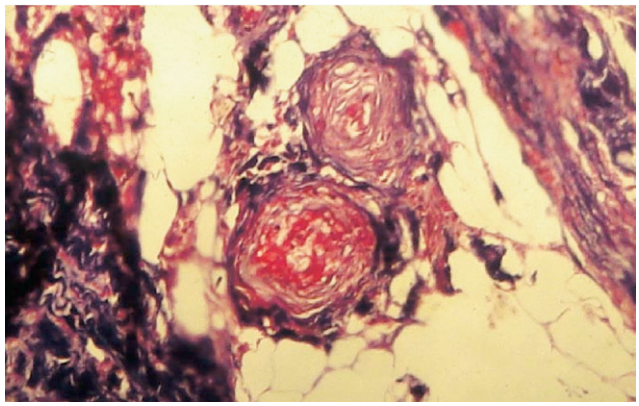

Figure 2 Areas of fibrinoid necrosis and fragmentation of the internal elastica lamina. An organized thrombus is present.

CASE HISTORIES

Case 4

In August 1989, a 25-year-old white Brazilian woman presented with polyarthralgias, lymphadenopathy, splenomegaly, low-grade fever, *livedo reticularis* and Raynaud's phenomenon. She had no personal or familiar history of vaso-occlusive disease and/or dyslipidemia. She had never been pregnant, used estrogens, or smoked. The left posterior tibial pulse was not palpable and a small digital occlusion of the left toe was present. She had Coombs-positive hemolytic anemia, lymphopenia, positive antinuclear antibodies (ANA) (1:640), positive Venereal Disease Research Laboratory (VDRL) test (1/16), positive lupus anticoagulant (LAC), and positive IgG and IgM anticardiolipin antibody (aCL) (30 GPL and 42 MPL, respectively).

Three months later, she suddenly developed intermittent claudication of her right leg, which was progressive until a sudden complete occlusion of the right femoral artery, confirmed by arteriography, occurred. An embolectomy was performed, but there was no success in preserving the arterial lumen and, after some hours, the vessel was again completely occluded. An above-the-knee amputation was performed. Histopathology disclosed an inflammatory infiltrate with mononuclear cells in the media and intima (Fig. 1) with areas of fibrinoid necrosis and fragmentation of the internal elastica lamina (Fig. 2). There was also an organized thrombus present. Treatment included anticoagulation, 100 mg/d aspirin, and 1 mg/kg/d of prednisone combined with azathioprine. She had a good clinical course following the amputation and during the next 15 years she developed only minor articular pain. She was maintained on low-dose prednisone and anticoagulation as well as low-dose aspirin, and no other vascular events have occurred.

Case 7

A 47-year-old black Brazilian woman presented in 1999 with the sudden onset of gangrene of the left 3rd toe and