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Morphological Expression of Antiphospholipid Syndrome

Mary Gantcheva

Department of Dermatology, Medical Faculty, Sofia

We reviewed the histopathological findings of skin lesions of 18 patients with Antiphospholipid syndrome. The cutaneous manifestations were as follows: livedo reticularis, pseudovasculitis lesions, livedoid vasculitis-like ulcers, thrombophlebitis, cutaneous gangrene and necrosis. Investigating these different skin markers of the disease we were searching for a specific finding, which could be typical for the disease. However, a constant and characteristic feature was occlusive vasculopathy, leading to vascular thrombosis of dermal and subcutaneous vessels. It was demonstrated in all specimens from these quite different skin lesions.

Key words: Antiphospholipid syndrome, Livedo reticularis, Livedo vasculitis, morphology, histopathology.

Introduction

Antiphospholipid syndrome (APS) is a relatively "young" syndrome and a multisystem disease. Clinically it is characterized by venous and arterial thromboses, recurrent fetal losses, accompanied by moderate thrombocytopenia in the presence of positive lupus anticoagulant (LA), elevated anticardiolipin antibodies (aCL), or both of them. Patients suffering from this syndrome have to undergo one clinical test plus one laboratory test during the course of the disease. Laboratory findings produced by two consecutive blood analyses at 3 month intervals should confirm the clinical picture.

APS may arise as a primary disease in patients who have no clinical or laboratory evidence of another pathologic condition: primary APS, or may be associated with other diseases: secondary APS. Secondary APS is often associated with systemic lupus erythematosus. However, APS may develop in the context of autoimmune diseases, malignancies, drug induced and infectious diseases. LA recognize lipid-bound (human) prothrombin [1]. In this way they inhibit the phospholipid-dependent coagulation reactions [2]. ACL are directed towards β2-Glycoprotein I (β2-GPI) bound to an anionic lipid surface [3]. They are detected by solid phase ELISA or by radioimmunoassay systems employing cardiolipine as coated antigen.

The skin lesions of APS are quite heterogenous. The most characteristic clinical sign is a persistent cyanotic mottling of the skin, affecting the extremities and the

trunk which is known as livedo reticularis. Vasculitic lesions, skin infarcts, ulcerations of different types, thrombophlebities, peripheral gangrene and widespread necrosis are other dermatological aspects of the disease [4].

We reviewed the histopathological findings of different skin lesions in 18 patients with APS, hoping to find a specific morphological feature.

Materials and Methods

We have studied the histopathological findings in 18 patients with APS, diagnosed according to clinical and laboratory criteria. Patients with the skin manifestation of livedo reticularis were four. Their skin biopsies were performed on either the "holes" of the netlike pattern (i.e., the clinically apparent normal skin in the center of the circle segments) or on the "net" itself (i.e., the discolored red or bluish peripherial border segments). Five patients presented pseudovasculitis lesions: macules, nodules and purpura. Edema and erythema were the signs of thrombophlebitis in two cases. The biopsies from these seven patients were performed from the lesions. Five specimens were taken from the edge of the livedoid vasculitis-like ulcers located on the lower portion of the legs, from the edge of gangrenous lesions located on the finger and on a toe in two other cases. All the histological findings were studied of hematoxylin-eosin staining.

Results

On the peripheral discoloured segments only dermal vessels hyperplasia was present. The biopsies from the centers of the circles were normal or show signs of occlusion-microthrombus in dermal capillaries without vasculitis (Fig. 1). Biopsy from vasculitis-like lesions (subcutaneous nodule) demonstrated thrombosed medium-size vessel surrounded by many small vessels (Fig. 2). Histopathological findings of macula on fingers that clinically were in early stages of development showed hemorrhage and prominent dermal edema. Thromboses were seen in both arteries and veins through-

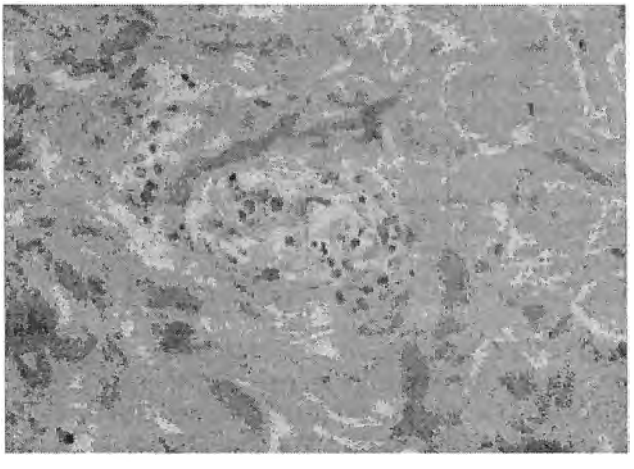

Fig. 1. Microthrombus in dermal vessel. × 300

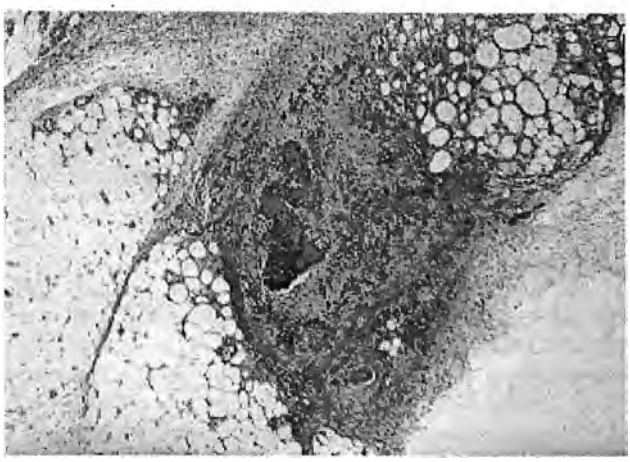

Fig. 2. Mediumsized vessel with thrombosis surrounded by many small vessels. × 150

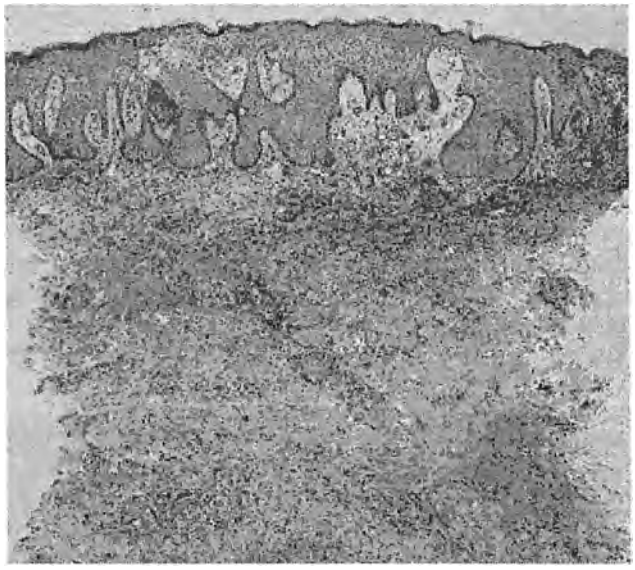

Fig. 3. Prominent dermal edema with disruption of the epidermis from derma. Extensive hemorrhage in papillary derma with thrombosis in vessel. × 15

out the dermis and into the subcutaneous fat (Fig. 3). Lesions that have been present for days showing vascular thrombosis with reactive vascular proliferation and a mild inflammatory infiltrate (Fig. 4). Histological findings from less acute lesions were with thrombosis and fibrinoid deposits in vessels lumens. There were erythrocyte extravasations in fresh lesions and prominent lymphoplasmocytic infiltrate in whole derma (Fig. 5). The specimens from skin gangrene showed non-inflammatory throm-

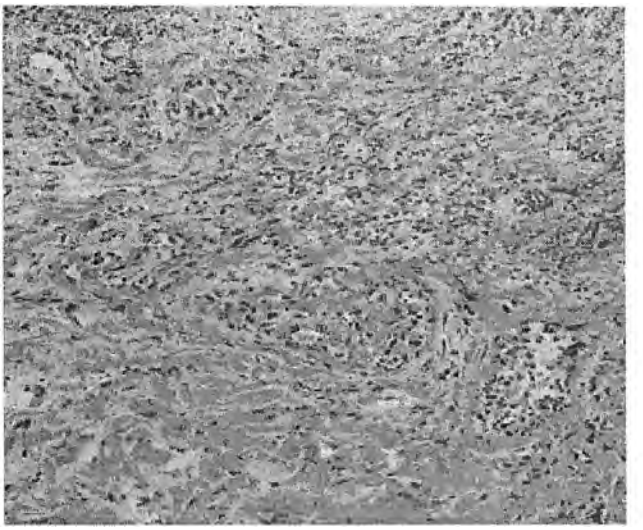

Fig. 4. Thrombosis in the vessels with reactive endothelial proliferation and edema of the endothelial cells. Extensive erythrocyte extravasation. × 150

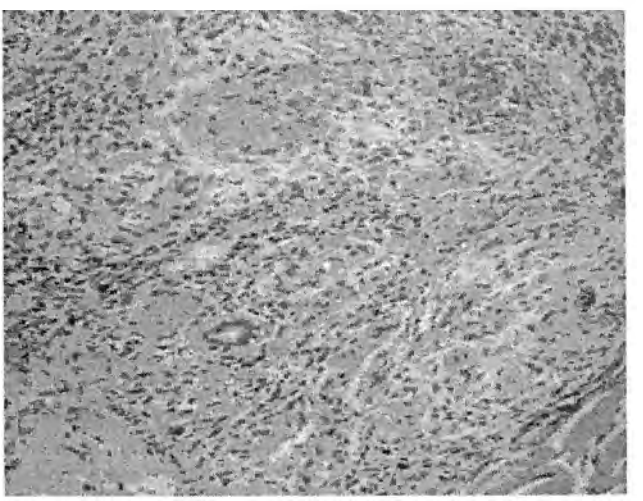

Fig. 5. Thrombosis and fibrin deposits in vessel lumens, erythrocyte extravasation, lymphocytic infiltrate. × 150

bosis of small dermal vessels surrounded by collagen necrosis. In one of the thrombophlebitic biopsy thrombosis was associated with vascular lymphocytic inflammation. Hyalinizing segmental vasculitis with fibrinoid deposits around vessels and thrombosis within were seen in biopsies performed from livedoid vasculitis-like ulcers (Fig. 6). There were no evidence of leucocytoclasia in all five cases.

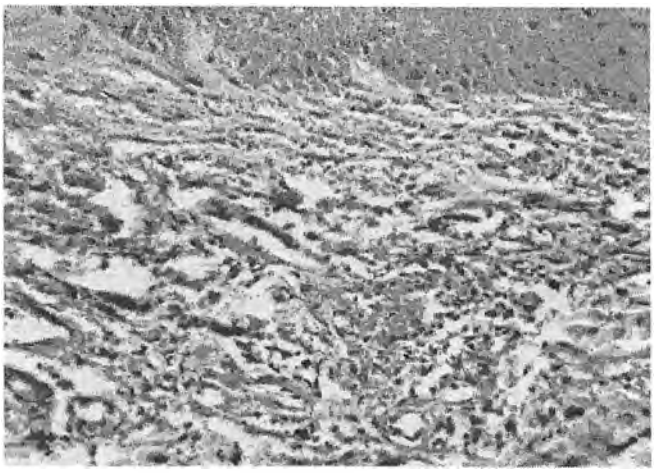

Fig. 6. Hyper and parakeratosis, acantosis, swollen endotel and hyalinization of the vessels, fibrinoid deposits in the lumen vessels and thrombosis within. × 150

Discussion

The main clinical manifestation associated with APS is thrombosis. It occurs in venous and in arterial blood vessels. Leg vein thrombosis and pulmonary emboli are the most frequent events of venous APS related thromboses. Transient ischemic attacks and cerebral infarction are the most frequent arterial damage in arterial APS related thromboses. However, thrombosis has been recorded in almost every vessel of the human body. It was initially thought that only large and medium vessels were affected. It has recently become evident that small vessels might also be involved. Therefore, many diverse clinical manifestations resulting from vascular occlusions in the liver, adrenal glands, lungs, heart, kidney, eyes may be present in APS.

Cutaneous manifestations of APS are extremely diverse and heterogeneous, ranging from minor symptoms to life threatening conditions [5]. We could summarize that the process thrombosis is a constant and characteristic feature in all these skin lesions which were minimal and non traumatic like livedo reticularis, and serious and dangerous, like cutaneous gangrene and necrosis. Discrete lesion on the skin as erythema, edema and purpura could be very important sign and the first clinical sign of a thrombotic disease, leading to extensive skin manifestations. Hyalinizing vasculitis, which is typical for livedo vasculitis must be included in the spectrum of vasoocclusive vasculopathy and could be a marker for underlying thrombooclusive process, such as APS.

In conclusion, we have demonstrated that in very different skin lesions, vascular thrombosis could be found and this should alert the physicians to think for this rare and in some cases catastrophic disease—APS.

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