28 Vascular Pathology of Antiphospholipid Antibody Syndrome

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Introduction

Antiphospholipid antibody syndrome (APS) is now recognized as a systemic vasculopathy involving complex interactions between endothelial cells, platelets, and inflammation and coagulation cascades [1–3]. *Vasculopathy* is a term often equated with thrombotic microangiopathy (TMA) but unfortunately continues to be used or confused with vasculitis (where inflammatory cells are present throughout the vessel wall) or perivasculitis (where the infiltrate is adventitial but the vessel wall is intact) [4–14].

The identification of TMA is dependent on many factors: (a) time course from symptomaticity to biopsy, (b) action of naturally occurring anticoagulants, or (c) time course of institution of antithrombotic treatments. TMA may involve changes on the intra-luminal side, through the vessel wall, and into the adventitia. At the light microscopic level, this spectrum involves endothelial cell swelling, thrombosis that is usually bland, but occasionally associated with a reactive cellular infiltrate as part of neoangiogenesis (reactive angioendotheliomatosis). Varying degrees of recanalization, fibrin, and/or platelet deposition in the vessel wall, proliferation of myointimal cells with attendent luminal decrease, medial thickening, and hyalinization usually with preservation of the internal elastic lamina occur, but in some instances discrete vasculitis or perivasculitis is present [1–14].

Limited electron microscopic studies have in some vessels identified indistinct electron dense deposits in sub-endothelial areas that have not yet been fully characterized as representative of antiphospholipid (aPL) antibodies but have been identified as immunoglobulin [2, 4, 6–12]. Some of the confusion in the APS literature is attributable to (a) poor differentiation of perivasculitis versus panvasculitis, (b) misinterpretation of positive fluorescent antibody (FA) studies for immunoglobulins and complement components as definitive of an immune complex vasculitis, when complement and markers of endothelial cell activation have new effector functions [1, 3, 9], (c) occurrence of co-existing vasculitis in secondary APS, most often in systemic lupus erythematosus (SLE), and (d) anatomic differences between arteries and veins versus capillaries, with their lack of limiting vascular smooth muscle cells and attendant inflammatory cell extravasation or spillage beyond capillary network without identifiable capillary necrosis (capillaritis) [4, 6–8, 12].

The major incremental knowledge over the last 4 years comes from the growing awareness of nephropathy in both primary and secondary APS, which in lupus patients do not relate to WHO Classification and its insidious association with hypertension, loss of renal function, cumulative vascular damage, and arterial thrombosis [6–8, 10].

Additionally, advances in the immunobiology of vascular inflammation and relationship of antibody-mediated vasculopathy to atherogenesis and vaso-occlusive disease are important [1, 3, 5]. Vascular pathology and clinicoserologic correlations in 18 patients with primary (1°) and secondary (2°) syndromes are presented in this chapter relative to the current spectra of APS involvement in the literature, which has expanded to include different combinations of vascular damage from reactive endotheliomatosis to calciphylaxis. Because there is no evidence-based approach or systematic reviews for these aspects of APS, small and large case series predominate. A prospectus is offered regarding processes of endothelial cell–platelet interactions in inflammation, injury, and repair that might help to explain the wide spectrum of vasculopathy in APS.

Methods

Biopsy, surgical, or autopsy specimens were obtained from patients seen in academic and consultative practice. The diagnoses of 1° or 2° APS were made by modified Harris and American College of Rheumatology (ACR) criteria, longitudinal aPL enzyme immunoassays (EIAs) done on at least 2 occasions 4–6 weeks apart for IgG/M anticardiolipin (aCL), IgG/M antiphosphatidylserine (aPS) performed in a laboratory certified by the aPL Standardization Laboratory of E. Nigel Harris, MD, simultaneous lupus anticoagulant (LA) profile by activated partial thromboplastin time (aPTT) or a dilute Russell viper venom time (dRVVT) performed according to the Standardization Committee's recommendations, and in 1 patient an anti-prothrombin antibody test [15, 16]. In other patients, a standardized IgG/M/A EIA for aCL, aPS, and antiphosphatidylethanolamine (aPE) were performed in addition to IgG/M aCL [17]. Epidemiologic, clinical criteria for the diagnosis of 1° or 2° APS, serologic- or coagulation-based tests, and major categories of vascular pathologic involvement with cross-reference to photomicrographs comprise Table 28.1. Eleven of the 18 patients had 1° APS, the remaining 7 had 2° APS due primarily to SLE. Eleven were white females (age range, 5 days–67 years); 3 were white males (age range, 23–45 years), and 4 were black females (age range, 26–50 years). Hematoxylin and eosin (H&E) stains were used except where specified: Vierhoeff van Gieson (VVG) for collagen and elastic tissue; Masson's trichrome for elastic tissue (fibrin red to blue-grey); Mallory's phosphotungstic acid hematoxylin (PTAH) for fibrin (purple); modified Giemsa (MG) for cells and bacteria (blue); and glial fibrillary acidic protein (GFAP) immunoperoxidase (brown); in selected skin or renal biopsies, and routine FA techniques for immunoglobulins G, M, A, and complement components C3 or C4 where specified [4–6].

As there are no systematic reviews or randomized control trials, most of the articles identified by re-performing the prior comprehensive Medline literature review (cross-referencing APS, aPL, lupus coagulation inhibitor, and vascular pathology categories) were reviewed for APS diagnostic criteria, EIA and coagulation-based