15 Primary Antiphospholipid Syndrome

Tonia L. Vincent and Charles G. Mackworth-Young

Introduction

The emergence of the antiphospholipid syndrome (APS) over the last 30-odd years has been one of the most striking developments in clinical autoimmunity. The identification of a pure or primary variant of the syndrome has been central to this story, not least in enabling us to establish the place of this remarkable condition in the wide spectrum of autoimmune disease.

Circulating antiphospholipid antibodies (aPL), as detected by the false-positive biological test for syphilis, have been known for more than 40 years [1], and their ability to cause prolongation of the partial thromboplastin or kaolin clotting time generated the term *lupus anticoagulant* (LA) [2]. Although the phenomenon was initially described in an systemic lupus erythematosus (SLE) patient associated with a hemorrhagic disorder, by the 1960s it was apparent that the presence of the LA was paradoxically linked to the risk of thrombosis [3]. Following this, associations with thrombocytopenia [4] and recurrent miscarriage [5–7] were established. Not all of these patients had SLE – so the term lupus anticoagulant was thus misleading, not only because of its procoagulant associations in vivo, but also because some patients had no evidence of lupus.

In vitro studies showed that the LA activity was mediated by antibodies [8]. The association of false-positive tests for syphilis led to the suggestion that these antibodies may bind to phospholipids. This was supported by an earlier study, which demonstrated that LA activity could be partially abolished by pre-absorption of test serum with cardiolipin [9].

Direct confirmation came in 1983 with the development of a sensitive immunoassay for anticardiolipin activity in serum [10]. Antibodies detected by this method were subsequently shown to exhibit LA activity [11]. Derivatives of this assay still perform a pivotal role in the diagnosis of the APS.

Defining APS

The direct detection of anticardiolipin antibodies (aCL) enabled Hughes and coworkers to make the first formal description of the APS [12, 13]. They recognized a group of patients with SLE who had raised levels of these antibodies and clinical features including recurrent venous thrombosis, central nervous system disease,

and recurrent miscarriage. Serologically, the majority of these patients demonstrated aPL. By 1985 it had become apparent that some of such patients exhibited few or no features of underlying connective tissue disease, and the concept emerged that this syndrome could exist as a separate entity [14–17].

In 1989 three units published clinical series establishing the primary antiphospholipid syndrome (PAPS) [18–20]. They described a group of patients in whom recurrent thrombosis, miscarriage, and thrombocytopenia were associated with aCL; although several patients were positive for anti-nuclear antibodies, none fulfilled classification criteria for the diagnosis of SLE.

APS as a Clinical Spectrum

From these early reports four categories of APS or Hughes syndrome could be defined:

(i) APS associated with underlying connective tissue disease, most usually SLE; (ii) patients with APS with no underlying features of connective tissue disease, the primary APS; (iii) patients with APS and lupus-like disease who have features of connective tissue disease but who do not fulfill classification criteria for the diagnosis of SLE; (iv) APS due to other causes, such as drugs, malignancy, and infection. Many of these patients exhibit increased aCL in the absence of an overt clinical syndrome. When clinical disease is apparent it is usually mild and transient.

These are a heterogeneous group of patients and as such are likely to represent a spectrum of disease rather than discrete disease entities. This is supported by documented development of overt SLE in patients with an original diagnosis of PAPS. In a 5-year follow up by Asherson et al [21], 19 patients with APS (9 with associated SLE; 7 with lupus-like disease; and 3 with PAPS) were studied. During this interval, 3 patients with lupus-like disease progressed to a diagnosis of SLE, and 1 patient with PAPS developed lupus-like disease.

In some instances this transition may take many years. The same unit [22] performed a retrospective study of 80 patients seen over a 10-year period with PAPS. Two cases developed SLE more than 10 years following the initial presentation of PAPS and 1 developed lupus-like disease. Andrews et al [23] described 2 patients with PAPS developing SLE after 8 and 10 years. These findings and similar anecdotal experience mean that clinicians should be mindful of the long transition times from PAPS to SLE-associated APS, even though the studies would suggest that this is a relatively uncommon event.

Differentiation Between SLE-associated APS and PAPS

There are both clinical and serological features that help differentiate between these groups of patients. Vianna et al [24] conducted a multicenter study of primary and secondary APS. Of 114 patients, 56 had SLE-associated APS and 58 had PAPS. They found that both groups of patients had similar clinical presentations with the exception of endocardial valve disease, which occurred in 63% of lupus patients versus 37% of patients with PAPS ($P < 0.005$). Other more predictable differences included autoimmune hemolytic anemia (21% vs. 7%; $P < 0.05$), neutropenia (11% vs. 0%;