ANTIPHOSPHOLIPID ANTIBODIES AND SYNDROMES: RELEVANCE FOR THE GP

RONALD A ASHERSON, *MB ChB, MD (Hon), FRCP, FCP (SA)*
Consultant Rheumatologist,
Rosebank Clinic, Johannesburg

With the discovery of the anticardiolipin antibodies in 1983 and subsequent research on the antiphospholipid antibodies over the ensuing 20 years, many of the clinical events and paradoxes in this field before this time have been explained. Although a positive lupus anticoagulant test (a functional clotting test performed by most laboratories) was at first thought to be due to the presence of interfering antibodies against phospholipids, an integral part of the clotting process, it has since been shown that these antibodies are directed against proteins. The binding of phospholipid to certain domains on one protein in particular (beta 2 glycoprotein 1 (β2GP1), one of the body's natural anticoagulants) alters the conformation of peptides at certain positions on the molecule, forming what is known as a cryptic epitope or neoantigen against which the antiphospholipid antibodies are directed (Fig. 1).

Between 5% and 8% of normal individuals produce antibodies to phospho-

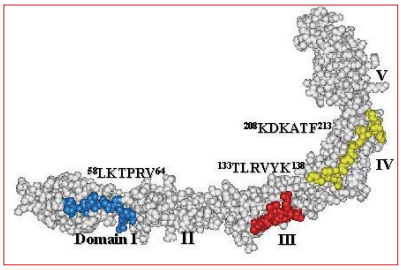

Fig. 1. Location of the 2GPI-related peptides identified by the peptide phage display library.

lipids. The function of these antibodies, it seems, has to do with clearance of dying or apoptotic cells. Because of this and because these antibodies may also appear in many other conditions (e.g. infections, malignancies, vasculitic conditions, certain drugs), criteria for an antiphospholipid syndrome were formulated and modified from time to time. The mechanism by which antiphospholipid antibodies are formed during the course of certain infections (mainly bacterial, but some viral) is known as molecular mimicry (Figs 2 and 3).

The antiphospholipid syndrome (Hughes' syndrome)[1,2] consists of thromboses, usually of large veins and or arteries, and/or recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia in the presence of one or other of the antibodies directed against serum proteins, phospholipids or a positive lupus anticoagulant. The test should be positive on at least 3 occasions initially and at 6 and 12 weeks. With regard to the family of autoantibodies only one test may be positive – therefore a phospholipid screen of all common autoantibodies is now advised. Although the deep veins of the lower limbs (causing DVTs) and cerebral arteries (causing strokes) are usually affected, other vessels may also be affected, causing many differing clinical manifestations. From the general practitioner's perspective, this should be requested in any patient suffering from a DVT or pulmonary embolus, and in any patient under the age of 45 years who has had a stroke. They constitute an additional risk factor for older patients with other conditions, e.g. hyperlipidaemias, hyperhomocysteinaemia, diabetes mellitus, hereditary mutations such as factor V or prothrombin gene polymorphisms and deficiencies of natural anticoagulant proteins such as protein C. This might result in thrombosis.

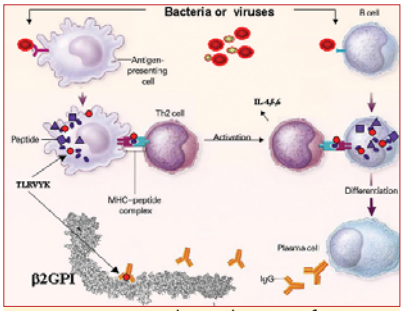

Fig. 2. Proposed mechanism for generation of anti-b2GPI Abs based on molecular mimicry between the pathogen and the b2GPI molecule.

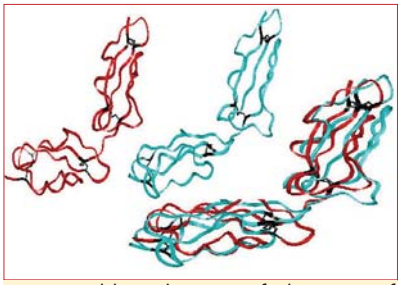

Fig. 3. Ribbon diagram of alignment of b2GPI (domain 3-4 A21-A243) (blue) and vaccinia virus homologue (red).

The antiphospholipid syndrome may either be primary or secondary. The primary syndrome, more frequent in men, is a purely thrombotic disorder, but these patients may demonstrate a low antinuclear antibody/antinuclear factor (ANA/ANF). A small percentage may, after many years, go on to develop systemic lupus erythematosus (SLE). The secondary syndrome is usually seen in patients with SLE or the closely related lupus-like disease, although infrequently it is seen in patients with other connective tissue diseases (e.g. rheumatoid arthritis, Sjögren's syndrome) or vasculitic conditions, such as polyarteritis nodosa, with malignancies.

Besides DVTs, strokes and recurrent fetal losses, other thrombotic manifestations may include CNS manifestations such as cognitive impairment, a multiple sclerosis-like syndrome, cardiac features, e.g. heart valve lesions or myocardial infarctions, and intraventricular thrombus, renal glomerular lesions (thrombotic microangiopathy), adrenal failure, retinal vascular occlusions, a variety of pulmonary syndromes and peripheral vascular occlusions resulting in ischaemia of extremities and gangrene.

Skin manifestations, e.g. leg ulcers, livedo reticularis, as well as non-thrombotic associations such as chorea, transverse myelitis, migraines, non-infective endocarditis, where other mechanisms such as interaction of antiphospholipid with brain phospholipids or antiphospholipid antibody deposition with phospholipid and complement, may also occur.

A devastating syndrome termed the catastrophic antiphospholipid syndrome (Asherson's syndrome)[3] has now been documented in almost 300 patients. This consists of rapid occlusion of small vessels, patients usually being admitted to intensive care units in multiorgan failure, with death ensuing in 50% of cases.

If an antiphospholipid syndrome is suspected, a phospholipid screen should be ordered from the appropriate laboratory. The results will be expressed as positive or negative and some laboratories will report the antibody isotype. The IgG isotype is the most important pathogically, but cases have been described where the IgM isotype is elevated and, rarely, IgA might be the only one demonstrable. The level of the isotype (high, moderate or low) is also significant, with moderate to high levels most commonly being associated with clotting.

Three types of antibody are now being tested in South Africa, i.e. anticardiolipin antibodies, antibodies to β2GP1 and antibodies to prothrombin. In addition, the lupus anticoagulant is also still being measured.

Currently, the antiphospholipid syndrome is the most important immunological cause of thrombosis and should be considered in any patient with any of the above presentations.

References available on request.