

Anti-Phospholipid Antibodies: Case Report and Review of the Literature

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ABSTRACT

There is currently considerable interest in antibodies directed against phospholipids. Several clinical associations with these antibodies have been defined, the strongest ones being with thrombosis and recurrent foetal loss. These antibodies were originally studied in patients with systemic lupus erythematosus, but they have also been found to occur in patients who do not have this disease. This paper describes two such patients and discusses current views on antiphospholipid antibodies

CASE REPORTS

Case No. 1

The patient, a 22 year old Saudi Arabian male, presented with a day's history of painful swelling in his left lower limb, which was warm and tender. Venography confirmed left sided ilio-femoral thrombosis. The patient had been well previously, except for right sided femoral thrombosis six months previously for which he had received warfarin for three months. Investigations included: prolonged activated partial thromboplastin time (before heparin was started), which was not corrected by adding normal plasma; normal prothrombin time; platelet count $60 \times 60 \times 10^9/l$; VDRL positive; *Treponema pallidum* haemagglutination test (TPHA) negative; fluorescent anti-nuclear antibodies negative. IgG anticardiolipin antibodies were elevated. The patient was anticoagulated, initially with heparin, and later with warfarin; aspirin was also given in a dose of 300 mg daily. Three years after the episode he remains well.

Case No.2

A 33 year old of Maltese woman who was in the tenth week of her first pregnancy, presented with painful swelling of her left calf.

A clinical diagnosis of deep venous thrombosis was made, and the patient was anticoagulated with heparin for 10 days. About 2 months later she developed abdominal pain and noted petechiae on her lower limbs. Platelet count was $11 \times 10^9/l$. Abdominal ultrasound showed a dead 20 week old foetus. Following induction, she

passed a dead foetus with an infarcted placenta. Investigations showed prolonged activated partial thromboplastin time, normal fibrinogen level, absent fibrin degradation products, negative VDRL, as well as negative fluorescent nuclear and anti-double stranded DNA antibodies. Bone marrow aspiration showed increase number of megakaryocytes. IgG anti-cardiolipin antibodies were considerably elevated. The patient was treated with corticosteroids, the initial dose being 60 mg prednisolone daily, and one year later she remains well, with normal platelet counts and no recurrence of deep venous thrombosis. She is on a maintenance dose of prednisolone of 10 mg daily, and aspirin 300 mg daily.

COMMENT

Phospholipids are widely distributed in nature. They are found in endothelial cell membranes, platelets as well as brain tissue. The first antibody to phospholipid that was described was reagin, present in the sera of syphilitic patients, and detected by the Wassermann reaction. In 1941, it was discovered that the antigen bound by reagin was a phospholipid that could be extracted by alcohol from ox heart muscle: it was therefore called cardiolipin. Following widespread screening with the Wassermann test, it soon became clear that some patients had a positive test without showing any clinical evidence of syphilis. Among this group there was a high prevalence of autoimmune diseases such as rheumatoid arthritis and acquired haemolytic anaemia. In 1952 Conley and Hartmann¹ described two patients with systemic lupus erythematosus, both of whom had false positive tests for syphilis, as well as prolonged whole blood clotting and prothrombin times. The clotting defect has since been referred to as lupus anticoagulant. There is a close correlation between the antibody responsible for lupus anticoagulant activity and anticardiolipin, both of which are antiphospholipid antibodies. Anti-cardiolipin antibody is also responsible for the false positive tests for syphilis.

Anti-phospholipid antibodies prolong phospholipid-dependent coagulation tests, especially the partial thromboplastin time, Russel viper venom time, and — less commonly — prothrombin time. It has no effect on thrombin time. This prolongation

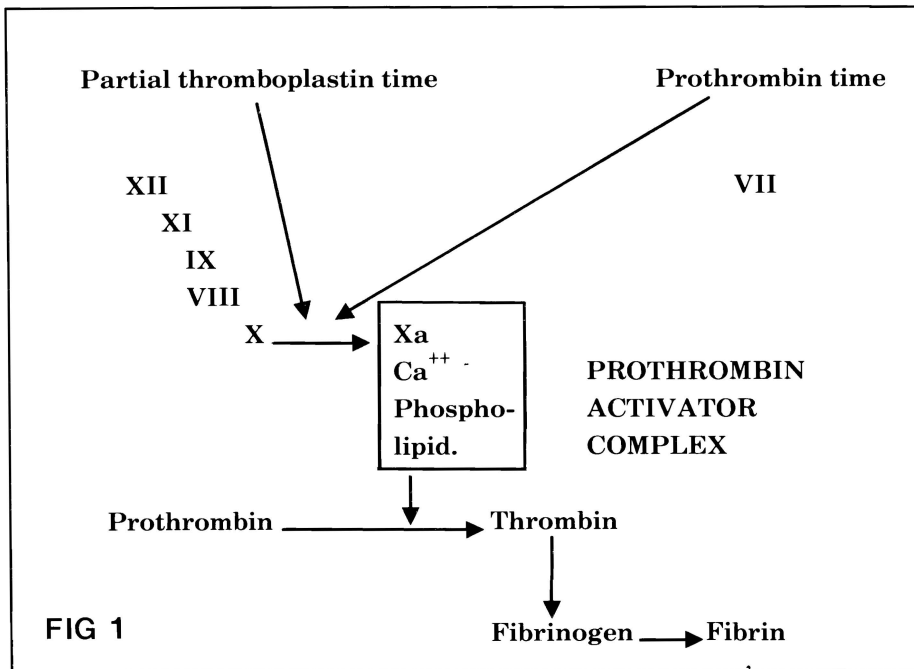
is not due to a clotting factor deficiency, because the test is not normalised by the addition of normal plasma. It is believed that the abnormality results from an interaction between antiphospholipid antibodies and the phospholipid moiety of the prothrombin activator complex, thereby interfering with the conversion of prothrombin to thrombin (Fig 1). Neither the activated partial thromboplastin time nor VDRL are sensitive enough to be used as screening tests for antiphospholipid antibodies. More sensitive immunoassays are now available for their detection².

Anti-phospholipid antibodies were initially studied in patients with connective tissue diseases, particularly systemic lupus erythematosus. Various studies quote frequencies of these antibodies in 25 to 40% of patients with systemic lupus erythematosus.^{3,4} The relationship between anti-phospholipid antibodies and antinuclear antibodies is not clear. While some studies have shown a cross-reaction between anti-DNA antibodies and cardiolipin, other have found no such correlation⁵. Some observers believe that patients with anti-phospholipid antibodies form a separate subgroup of connective tissue diseases, the anti-phospholipid antibody syndrome, while other feel that such patients belong to the same spectrum of disease typified by systemic lupus erythematosus. A better understanding of the pathogenesis of these diseases is required to settle the issue.

Anti-phospholipid antibodies have also been identified in patients who have no clinical or serological evidence of systemic lupus erythematosus or other connective tissue disorder⁶. Several clinical associations have been described with these antibodies: paradoxically, the strongest one is with thrombosis^{7,8}. Despite the in vitro property of these antibodies to prolong coagulation tests, 25 — 50% of patients possessing antiphospholipid antibodies, whether or not suffering from lupus erythematosus, have

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had thrombotic episodes. No part of the vascular bed seems immune from thrombotic episodes. While thrombosis in the deep veins of lower limbs has been most commonly described — as in both our patients — it also been reported in the renal and hepatic veins⁹, as well as in cerebral, coronary, brachial, mesenteric and other arteries. Pulmonary hypertension due to pulmonary thrombosis in situ or recurrent pulmonary embolism has been described¹⁰.

How these antibodies cause thrombosis is uncertain. It has been suggested⁵ that they may interfere with the release of arachidonic acid from the endothelial cell membrane, thereby reducing prostacyclin production. Reduced levels of prostacyclin increase platelet aggregation and thereby may facilitate thrombosis. Other alternative explanations have included:

- i) direct platelet activation by binding to phospholipid in the platelet membrane;
- ii) reduced plasminogen activator release due to immune complex mediated endothelial cell damage;
- iii) inhibitory interaction with a protein C—phospholipid complex.¹¹

There have been several reports of an association between anti-cardiolipin antibodies and thrombocytopenia^{7 12}, as was noted in both our patients. It is possible that the antibodies may bind phospholipids in platelet membranes resulting in increased uptake and destruction by the reticuloendothelial system. Some studies, however, have failed to notice such an association^{13 14}.

Another condition associated with these antibodies is recurrent abortion. This has been noted in patients with systemic lupus

erythematosus, but it has also been described in women who do not have this disease, and whose only serological abnormality has been the presence of anti-cardiolipin antibodies. In recent clinical studies, anti-cardiolipin antibodies were present in a significant proportion of women with otherwise unexplained recurrent abortions^{15 16 17 18}.

It has been suggested that reduced prostacyclin production by the placental blood vessels may cause platelet aggregation and lead to diminished placental blood flow, placental infarction and foetal loss.

Several other associations have been described, but less commonly.^{6 11} These include livedo reticularis, various central nervous syndromes (cerebral thrombosis, transient ischaemic attack, migraine-like headaches, epilepsy, chorea, myelopathy) as well as positive Coombs test (with and without haemolytic anaemia) and labile hypertension.

The management of patients with antiphospholipid antibodies is largely empirical, as the natural history of the condition has not yet been well documented. Although there are very few published controlled trials, there is evidence that corticosteroids and aspirin may produce a successful pregnancy outcome in patients with recurrent abortion^{18 19}. They are also useful in managing thrombocytopenia. Anti-coagulants with an antiplatelet agent have been recommended for patients in whom vascular thrombosis develops; these patients not uncommonly relapse once anticoagulant therapy is stopped²⁰ — as happened in Case No. 1 — and long-term therapy is therefore recommended. There is however no current evidence to justify prophylactic therapy in the hope of lowering antiphospholipid antibody levels²¹.

The clinical associations of antiphospholipid antibodies have expanded considerably over the past few years, and they are still a topic of widespread interest. Indeed, because of their association, they promise implications far beyond the connective tissue diseases. However, a cause and effect relationship has yet to be proved, and it may eventually be shown that these antibodies are of little pathogenic importance. This seems unlikely to happen, mainly because of the strong clinical associations, particularly with thrombosis. *As the presence of these antibodies may have a bearing on treatment and its duration, it is suggested that antiphospholipid antibodies should be looked for in appropriate clinical settings, such as in young patients with thrombosis without an obvious cause and in unexplained repeated abortions.*

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