The antiphospholipid syndrome: a syndrome in evolution

Since the original description and definition of the 'anti-phospholipid syndrome' (APS)
1 a number of distinct clinical manifestations related to it have been reported. Most of these may be ascribed to the hypercoagulable state, of which antiphospholipid antibodies seem either to be 'markers' or intimately connected in some way with the highly complex coagulation mechanisms resulting in thrombotic occlusions. Here, we bring these 'expanded' clinical manifestations together and examine specifically those situations which may now also be included under the broad umbrella of the APS.

Although less common than deep vein thrombosis, recurrent fetal loss, or stroke (the well recognised manifestations of the APS), these additional manifestations may occur not only in association with a defined systemic lupus erythematosus (SLE) or 'lupus-like' disease but also in the 'primary' APS. We may further subdivide patients with these lesser known associations into (a) those in whom coagulopathy and thrombosis have been adequately demonstrated as the underlying mechanisms (table 1); and (b) those in whom the association remains unproved or indefinite because no radiological or histopathological evidence of vascular occlusions is available (table 2).

Table 1  Proved associations with thrombosis

<table>
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<tr>
<th>1 Hepatic</th>
<th>Budd-Chiari syndrome</th>
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<tr>
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<td>Hepatic infarction</td>
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<td>Hepatomegaly and increased enzyme activity (possible)</td>
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<td></td>
<td>Nodular regenerative hyperplasia (possible)</td>
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<td>2 Adrenal</td>
<td>Addison's disease</td>
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<td>3 Pulmonary</td>
<td>Thromboembolic pulmonary hypertension</td>
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<td>4 Cerebral</td>
<td>Sneddon's syndrome</td>
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<td>5 Cardiac</td>
<td>Multi-infarct dementia</td>
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<td>Lupus encephalopathy</td>
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<td>Acute cardiomyopathy</td>
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<td>Chronic cardiomyopathy</td>
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<td>Segmental ventricular dysfunction</td>
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<td>Heart valve lesions</td>
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<td>Cerebral thromboembolism</td>
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<td></td>
<td>Pseudoinfective endocarditis</td>
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<td>6 Renal</td>
<td>Valve obstruction</td>
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<td>Intra-cardiac mass</td>
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<td>Thrombotic microangiopathy</td>
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<td>Renal artery occlusion or stenosis</td>
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Table 2  Indefinite associations with thrombosis

<table>
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<th>Non-thromboembolic pulmonary hypertension</th>
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<td>Transverse myelitis</td>
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<tr>
<td>Guillain-Barré syndrome</td>
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<tr>
<td>Chorea</td>
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<td>Avascular necrosis of bone</td>
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</table>

Proved associations with thrombosis

HEPATIC

Several hepatic complications associated with the presence of antiphospholipid antibodies are consequent on vascular occlusions of intrahepatic or extrahepatic vessels. The particular clinical manifestation depends on the site of the vessel affected, size, whether there is occlusion of veins or arteries, on the acuteness or chronicity of the process and on the accompanying reaction of liver cells—for example, hyperplasia, necrosis, fibrosis, etc.

Hepatic vein occlusion with the production of a Budd-Chiari syndrome is the most commonly recognised complication. Nine of 11 patients recently reviewed2 were classifiable as examples of a 'primary' APS.

Hepatic artery thrombosis and infarction, though less common, has now been reported by several investigators.3-6 Histopathological evidence of small vessel occlusion has been presented in two recent papers7 8 and may explain the hepatomegaly and increased enzyme activity, not dependent on infection, congestion, or degenerative and metabolic causes, seen in patients with the APS.9-11

The possibility that nodular regenerative hyperplasia is related to an underlying coagulopathy is not too far fetched, and this relation has recently been postulated by Pérez-Ruiz et al.12

ADRENAL

The occurrence of either hypoadrenalism or Addison's disease in patients with antiphospholipid antibodies has recently been extensively reviewed13 and, simultaneously, several additional patients with this unusual complication were reported.14-16 It is clear that this manifestation may occur spontaneously, postoperatively, or during periods of stress, such as extensive physical exercise.15 It should also be considered as one of the differential diagnosis in any patient presenting with the recently described 'catastrophic antiphospholipid syndrome'17 or 'acute occlusive vasculopathy syndrome'18 associated with antiphospholipid antibodies. In only a few patients is primary adrenal haemorrhage consequent on anticoagulation treatment. In most, the adrenal infarction and haemorrhage seem to be secondary to increases in adrenal venous pressure consequent on the creation of a 'vascular dam' which occurs after adrenal venous occlusion, as suggested by Rao et al.18 Glandular hypervascularity mediated by stress may be seen with severe illness, in the postpartum state, and during pregnancy. Necropsy evidence has proved the presence of this vascular occlusion in three cases to date.19 20 No fewer than 17 of the
22 cases reported thus far conform to the diagnosis of a 'primary' APS, four had SLE, and one had discoid lupus. Confusion, lethargy, abdominal pain, vomiting, and hypertension may lead one to suspect the condition. This has to be differentiated from other abdominal emergencies associated with the antiphospholipid antibodies, such as mesenteric, splenic, or hepatic infarction.

PULMONARY
Thromboembolic pulmonary hypertension is reported as occurring in several series of patients with the 'primary' APS,\textsuperscript{21} \textsuperscript{22} and there have been several single case reports.\textsuperscript{23} \textsuperscript{24} Thromboembolic pulmonary hypertension is unusual, however, in SLE despite the high prevalence of deep vein thrombosis.

CEREBRAL
\textit{Sneddon's syndrome}
Sneddon, an English dermatologist, first drew attention to the association of livedo reticularis with cerebrovascular disease and hypertension in 1965.\textsuperscript{25} Clearly, no immunological testing of his original patients was carried out at that time, and it was not until the 1980s that a link between this condition and the APS was noted. It has been suggested that at least some of the patients with Sneddon's syndrome may in fact be examples of the 'primary' APS.\textsuperscript{26} \textsuperscript{28}

\textit{Multi-infarct dementia}
The association of multi-infarct dementia with antiphospholipid antibodies has now been well reported.\textsuperscript{29} \textsuperscript{30} It may be preceded or accompanied by overt transient ischaemic attacks or strokes, but may also present without identifiable focal neurological deficit and may closely resemble other dementias of the Alzheimer type. As patients with the 'primary' APS are often negative for antinuclear antibodies this diagnosis may either be completely missed or the patient may be misdiagnosed as having a degenerative untreatable condition or even multiple sclerosis. It is now well recognised that computed tomographic scans or magnetic resonance imaging lesions occurring in cerebral lupus, for example, may closely resemble those seen in multiple sclerosis. The importance of recognising this condition cannot be over emphasised as treatment directed towards the clotting process may retard the downward progression of the condition.

\textit{Acute lupus encephalopathy}
Diffuse lupus encephalopathy is a common form of central nervous system lupus and is characterised by an acute organic syndrome, psychosis, and/or seizures. It has usually been ascribed to diffuse cerebritis in patients in whom the symptomatology is not readily explained by the presence of infection, overt stroke, haemorrhage, steroid psychosis, or aseptic meningitis. Several reports have suggested that antibodies directed against lymphocytes, neurones, or ribosomal P protein may play a part in the pathogenesis of cerebral lupus. Briley \textit{et al}\textsuperscript{31} and Fields \textit{et al}\textsuperscript{32} described several patients who were acutely ill, confused, and obtunded with asymmetrical signs. One patient in the series of Briley \textit{et al} had seizures.\textsuperscript{31} With one exception, the acute encephalopathy seemed to be part of an SLE illness. This group of patients, however, had the highest antiphospholipid antibody levels compared with the other patients with less severe neurological dysfunction. Treatment of these severely ill patients included plasmapheresis and immunosuppression, which was effective in only two. Computed tomography, however, showed either generalised cortical atrophy or small focal cortical hypodensities not unlike those seen in patients with multiple sclerosis. Fields \textit{et al}, using magnetic resonance imaging, showed infarct-like lesions in their four patients.\textsuperscript{32} It is likely that vascular occlusions of small cerebral vessels may be responsible for some of the clinical manifestations of this condition, again opening the way for anticoagulation treatment.

\textit{Cardiac}
\textit{Acute cardiomyopathy}
Apart from large vessel occlusion, which results in overt myocardial infarcts,\textsuperscript{33} there have been several reports of multiple small vessel thromboses affecting the myocardial circulation. Brown \textit{et al} first reported a young woman with SLE who suddenly died from circulatory failure.\textsuperscript{34} This was followed by the report from Murphy and Leach of a similar patient.\textsuperscript{35} In both, extensive histopathology was available. It seems that the rapidity of development of these multiple microthrombi determines the clinical course. When large numbers of vessels are acutely affected, as in the 'catastrophic antiphospholipid syndrome', sudden death from cardiopulmonary arrest can be expected.

\textit{Chronic cardiomyopathy}
If the process is recurrent and affects small groups of vessels it is not unreasonable to expect a clinical picture and course similar to that of a chronic cardiomyopathy resulting from the gradual attrition and obliteration of the myocardial blood supply. If this is localised, segmental ventricular dysfunction might supervene. Several patients with this type of disorder have been reported by Nihoyannopoulos \textit{et al}.\textsuperscript{36} Coronary angiographic studies showed occlusion of the left anterior descending coronary artery in three of the five patients. Another patient, however, with extensive inferior akinesis had a normal coronary angiogram. Leung \textit{et al} also encountered segmental motion abnormalities among their 75 patients.\textsuperscript{37} In two, congestive cardiac failure had supervened and resulted from global left ventricular dysfunction. Two other patients had asymmetrical left ventricular dysfunction. We have also seen such patients in our clinics. Obvious difficulties of echocardiographic interpretation exist in the presence of valve lesions or hypertension. Segmental ventricular dysfunction implies a localised process, however, perhaps different from the global dysfunction consequent on overload. Pathological studies on this second group are awaited.

\textit{Valve lesions}
We shall not dwell on these valve lesions themselves or situations encountered when thrombus is deposited on valves, resulting in thromboembolism, valve obstruction, or intracardiac thrombus formation. These have been adequately dealt with in recent papers.\textsuperscript{38} \textsuperscript{39} A diagnostic and therapeutic problem may, however, arise, albeit uncommonly, with left sided clinically obvious valve lesions and echocardiographic evidence of vegetations in the presence of fever, high levels of antiphospholipid antibodies, splinter haemorrhages, and persistently negative blood cultures.\textsuperscript{40} Splinter haemorrhages are now well documented as occurring in the APS.\textsuperscript{41} and clearly the differential diagnosis between infective endocarditis and active SLE with antiphospholipid antibody associated thrombus on valves may be difficult. Measurement of C reactive protein, which should be low in SLE and high in infective endocarditis, and antiphospholipid antibody levels, which may be high in SLE with thrombosis but are usually low or,
less commonly, moderately raised in patients with infective endocarditis, might assist in the differential diagnosis. Treatment of the two patients reported included antibiotics, but anticoagulation as prophylaxis against thromboembolism was also given to these patients.

RENAL
Thrombotic microangiopathy syndrome
Fibrin deposits can be found in a wide variety of diseases, causing lesions of the glomeruli, arteries, and arterioles of the kidney. This may result from both generalised and localised intravascular coagulation. The lesions may be reversible, such as occurs in acute tubular necrosis, or irreversible, leading to chronic renal failure. This latter situation may be seen in scleroderma as well as in the thrombotic microangiopathy. Kant et al first drew attention to, and stressed the importance of, coagulation factors and platelets as mediators of glomerular damage in SLE.42 These authors studied 71 patients with SLE and, additionally, attempted to correlate the histopathological findings with the presence of lupus anticoagulant activity. They found a striking association between the presence of lupus anticoagulant and the occurrence of glomerular thrombosis without necrosis in renal biopsy specimens. Negative tests for antibodies to double stranded DNA and normal concentrations of complement were found in these patients. Kincaid-Smith et al, in a subsequent paper, stated that the thrombotic lesions previously described in the renal circulation in lupus nephritis were not, as had been assumed, a manifestation of the so called 'lupus vasculitis', but represented a new form of thrombotic microvascular complication associated with the presence of a circulating lupus anticoagulant.43 The recent study by Leaker et al provided striking evidence that renal disease is not uncommon in patients with antiphospholipid antibodies.44 Renal biopsy specimens in all their patients showed evidence of ischaemic changes with no evidence of active lupus nephritis and there was insidious loss of renal function. By inference, therefore, more detailed studies on the renal function status of patients with a 'primary' APS should be made as this obviously has therapeutic implications.

Pulmonary hypertension may also be explained on the basis of renal thrombotic microangiopathy.17

Renal artery stenosis
Two patients with renal artery stenosis, hypertension, and antiphospholipid antibodies have now been reported. The first,45 a 13 year old girl, also had occlusion of the superior mesenteric artery and a cerebrovascular accident. She had defined SLE but the antinuclear antibody titre was low and very high levels of antiphospholipid antibodies were recorded. This patient probably falls into the category of patients with the 'catastrophic antiphospholipid syndrome'. As she had three separate vascular occlusions within a short period of time. She was treated with plasma exchanges and improved. The second patient,46 an adult man, who presented with hypertension and renal artery thrombosis, was an example of the 'primary' APS.

Indefinite associations with thrombosis
The indefinite associations listed include non-thromboembolic pulmonary hypertension, transverse myelitis, Guillain-Barré syndrome, chorea, and avascular necrosis of the bone.

Although antiphospholipid antibodies have been demonstrated in a minority of patients with primary idiopathic pulmonary hypertension, their levels were low and unassociated with thromboembolic events.47 It is likely that they represent a background of immunological disturbance in this condition similar to a positive antinuclear antibody test or anti-smooth muscle antibodies.48 Although some patients with SLE and pulmonary hypertension have very high antiphospholipid antibody levels, the significance of this fact is unknown.47

The association of transverse myelitis,49 Guillain-Barré syndrome,50 chorea,51 and avascular necrosis52 53 all lack radiographic or histopathological evidence of vascular occlusion because of the obvious difficulty in obtaining biopsy material. Computed tomography and magnetic resonance imaging scans in patients with chorea have been singularly lacking in radiological evidence of infarction of the basal ganglia.

Although isolated case reports of patients with the 'primary' APS and avascular necrosis, in the absence of previous steroid treatment are appearing, the significance of the association remains as yet unproved. Vascular factors, including Raynaud's phenomenon or vasculitis, have been proposed by previous investigators.54

In summary, we have given a brief description of the many diverse conditions which now seem to be part of the APS. It is no longer essential for patients to present with deep vein thrombosis, recurrent fetal loss, or thrombosis to qualify for inclusion in this syndrome. In our opinion, any of the manifestations discussed as 'proved associations with thrombosis' may now be considered as part of the condition.
Asherson R. The catastrophic antiphospholipid syndrome. *J Rheumatol.* In press.


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