Antiphospholipid syndrome with proliferative vasculopathy and bowel infarction

Sir, Since antiphospholipid syndrome (APS) was first described in 1983 [1], many complications have been reported which result from vascular occlusion as a result of thrombosis [2]. More recently, a few cases have been described where a proliferative vasculopathy appears to have been the major mechanism of vascular occlusion rather than thrombosis or vasculitis [3–5]. Relatively few cases have been described with intestinal infarction as a result of vascular occlusion from this 'proliferative vasculopathy' of APS [6–9]. We describe one such patient who had massive intestinal infarction as a result of a proliferative vasculopathy involving the coeliac, superior mesenteric (SMA), and inferior mesenteric arteries (IMA).

A 43-yr-old female was first referred to us in January 1994 when she was diagnosed as having systemic lupus erythematosus with APS. The clinical features up to that point (developing over a 10 yr period) included polyarthralgia, immune thrombocytopenia necessitating a splenectomy, livedo reticularis, Raynaud's phenomenon, photosensitive skin disease, myocardial dysfunction with evidence of a left ventricular thrombus, and neurological events including initial transient facial weakness followed years later by a right sided middle cerebral artery stroke. She recovered from the neurological deficits except for a dysarthria for which she used an electronic communicator. Over the years the patient also developed hypertension with small smooth kidneys but normal renal function and no proteinuria. Interestingly, she had no history of fetal wastage (three sons and no miscarriages). Blood results included a positive antinuclear antibody (1/2560, homogeneous pattern) and DNA binding (237 IU/ml, normal <100 IU/ml). IgG anticardiolipin antibodies were mildly elevated at 10–12 GPL and IgM always negative (on repeated measurement). Antibodies to β2-GP1 were also negative. Protein C, protein S and complement levels were normal. Of interest, there was a mild prolongation of the PTT (partial thromboplastin time) at the time of the stroke, suggesting the presence of a lupus anti-coagulant. The platelet count always remained stable but depressed at around 120×10^9/l.

The patient remained well for a year on therapy with lisinopril, nifedipine, hydroxychloroquine, erythromycin and warfarin at optimal doses (INR always maintained at 3–4). However, in April 1996 she developed symptoms ascribed to an irritable bowel syndrome. Within 2 months she lost 6 kg in weight and was having symptoms of mesenteric angina. Endoscopy revealed multiple haemorrhagic areas in the small and large bowel, biopsies of which showed no vasculitis or thrombosis. However, histological features were in keeping with mucosal ischaemia. In the interim the patient developed an 'acute abdomen' and required urgent laparotomy. She was found to have extensive infarction involving the jejunum, ileum and large bowel extending to the sigmoid region, all of which required resection. Although inspection of the intestinal vessels appeared normal at surgery, intra-operative angiography revealed total occlusion of coeliac, SMA and IMA at their origins (with the right renal artery resembling radiological features of fibromuscular hyperplasia at its origin; Fig. 1). There was very extensive collateral vessel formation from the iliac and internal thoracic arteries indicating chronicity of the vascular disease. Despite intensive surgical and medical efforts including bowel resection, SMA revascularization by venous grafting, parenteral feeding, intravenous antibiotics, and total anticoagulation, the patient continued to deteriorate with ongoing features of ischaemia in the residual bowel. It was thus decided to embark on immunosuppression with pulse cyclophosphamide and steroids, but after a

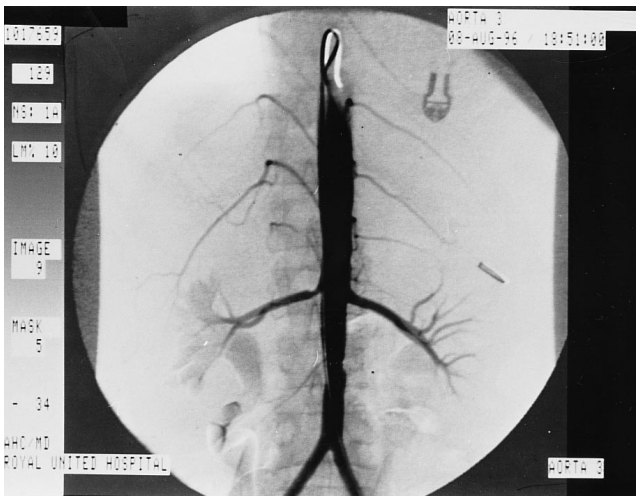

FIG. 1. The abdominal aortogram shows failure to fill the occluded superior mesenteric (SMA), inferior mesenteric (IMA), and coeliac vessels as well as a proximal stenotic lesion in the right renal artery. Extensive collateral vessels were seen on subsequent films arising from the iliac vessels (not shown).

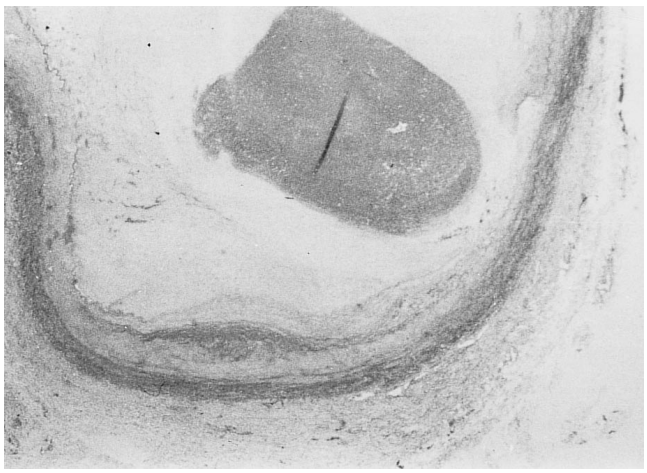

FIG. 2. A low-power view of the superior mesenteric artery revealed marked intimal hyperplasia with intact elastic lamina and intravascular thrombus. The higher power views (not shown) confirmed the absence of vasculitis and there was no evidence of a recanalization process (no haemosiderin-laden macrophages or neovascularization at the site of hyperplasia).

very brief and marginal improvement the patient developed pulmonary complications and died 6 weeks later.

The vascular pathology was the most striking feature with evidence of intimal hyperplasia involving the SMA, IMA, coeliac axis and the right renal artery only at their origins from the aorta (Fig. 2). The SMA had a small thrombus with ischaemia of the residual small bowel, but no haemosiderin-laden macrophages were seen and there was no sign of neovascularization at the site of hyperplasia, thus suggesting that the vasculopathy in this case was not due to recanalization of thrombus. There was no evidence of vasculitis and no significant atheroma in any vessel. The coronary vessels showed macroscopic features similar to the intestinal vessels and the previous myocardial infarction and fibrosis were evident. The brain, lungs, kidneys and myocardium all showed sites of septic emboli comprising *Aspergillus*-like organisms, suggesting that the cause of death was fungal septicaemia.

APS is now well recognized and its characteristic features have been reviewed elsewhere [2]. APS presenting with intestinal infarction is relatively rare in the reported literature [6–8], with a poor outcome in most cases. Presentation may vary from symptoms of mesenteric angina to acute bowel infarction and paradoxically also with bleeding from the gut [9]. It is therefore important to have a heightened sense of awareness of bowel complications in patients with primary and secondary APS. The true incidence of intestinal ischaemia and infarction associated with APS may be underestimated because of a lack of general awareness of the syndrome presenting as an acute abdomen. One must also guard against overdiagnosing 'irritable bowel syndrome' in these patients until ischaemia is ruled out. If histological analysis rules out vasculitis, further investigation should include angiographic study of the mesenteric circulation (in particular the superior and inferior mesenteric vessels) to look for evidence of narrowing, especially at the origin of the vessels from the aorta. Proximal narrowing appears to be the pattern of vascular involvement in a number of the cases described, including our patient.

There is some controversy as to whether the pattern of vascular involvement in APS with intimal/medial hyperplasia (histologically) and fibromuscular hyperplasia (radiologically) entails a distinct vasculopathy [3–5, 10]. It is possible that any vasculitis that may be present constitutes a feature of coexistent connective tissue disease and may not be responsible for the proliferative changes seen in the intima and media of the vessels. In addition, the current evidence is insufficient to exclude the possibility that the proliferative vasculopathy is part of a recanalization process secondary to thrombosis [11]. Interestingly, there is a striking similarity in the intimal and medial hyperplasia to the vascular remodelling that accompanies hypertension [12]. Further research is required in order to dissect out the relative contributions to the pathogenesis of the vasculopathy by the hypertension, thrombosis and recanalization, and endothelial dysfunction (due to current or remote vasculitis). Clearly, the implications for our management of these patients are immense. At present, therapy is largely restricted to anticoagulation and the use of immunosuppression and/or plasmapheresis where indicated. Immunosuppressive therapy is often associated with disastrous consequences as a result of infection. The role of fibrinolytic therapy is unknown, but it is unlikely that fibrinolytic drugs would have influenced the vascular proliferative changes seen in our patient.

This case demonstrates the importance of early recognition of mesenteric angina, a symptom that must be actively sought in any patient with APS. Appropriate

investigations at an early stage may help to define the frequency of vascular proliferative changes in the pathogenesis of the disease, and may also direct relevant intervention with modalities such as balloon angioplasty in an attempt to avert the disastrous consequences associated with late detection of bowel infarction. However, further systematic analysis of patients with APS and bowel ischaemia is indicated in order to understand fully the relative roles of the proliferative vasculopathy *vs* thrombosis.

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