Letters to the Editor

Catastrophic antiphospholipid syndrome associated with anti-beta-2-glycoprotein I IgA

Sir, Catastrophic antiphospholipid syndrome (CAPS) is an uncommon complication of the APS. It presents as acute multi-organ failure and more frequently involves the kidneys, lungs, gastrointestinal tract, adrenal glands and the skin. CAPS is caused by widespread thrombosis of small and large vessels [1]. APS presenting as limited cutaneous involvement affecting small vessels has been noted to proceed to multi-organ involvement and can be a warning sign of impending CAPS [2].

A 29-yr-old white female with a 15 yr history of systemic lupus erythematosus (SLE) was admitted with a 2 month history of painful palpable purpurlc macules on her trunk and extremities. There was a past history of malar rash, arthritis and renal involvement with no history of vascular thrombosis. Bilateral nephrectomy 10 yr prior, for resistant hypertension, was followed by a living donor kidney transplant after 2 yr of haemodialysis.

Physical examination revealed numerous indurated cold cyanotic plaques of variable size associated with livedo reticularis and palpable purpura. These involved the upper extremities, buttocks and thighs. Laboratory data included a slight leucocytosis, normal platelet count and an unremarkable peripheral blood smear. PT and APTT were normal. Antinuclear antibody was positive at a titre of 1:40 with a speckled pattern. Complement levels were normal. Rapid plasma reagin (RPR) was non-reactive. Anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) were negative. Extensive infectious aetiology work-up was negative and malignancy studies were unrevealing.

Pre-admission cyclosporin and methylprednisolone 10 mg twice daily were continued. Intralesional corticosteroids resulted in limited improvement. Empirical treatment for vasculitis was initiated with azathioprine and oral colchicine. Nevertheless, active lesions continued to appear. Subsequent immunosuppressive interventions attempted through the hospital course included mycophenolate mofetil, i.v. gamma globulins, i.v. pulse corticosteroids, i.v. and oral cyclophosphamide, tacrolimus and OKT3. In each instance, disease progression continued unabated.

Skin biopsy revealed multifocal fibrin-platelet thrombosis, minimal inflammation, confluent epidermal necrosis and incipient subepidermal blister formation (Fig. 1). Repeat biopsy demonstrated classic changes of a thrombo-occlusive disease with multifocal vascular thrombosis and minimal inflammation. Direct immunofluorescence of the skin was negative for IgG, IgM, IgA and C3.

Although a diagnosis of a hypercoagulable state was favoured, laboratory analysis revealed negative LA and aCL studies. Protein S, protein C and anti-thrombin III levels were normal, and a monoclonal gammopathy was excluded.

The indurated plaques progressed to multifocal, sharply demarcated, painful necrotic ulcers covered by black eschars. Annular purpuric plaques with dusky cyanotic peripheries, focal erosions, haemorrhagic bullae and necrotic epidermis were also noted. Hands and the feet were spared, and peripheral pulses remained palpable.

Treatment was initiated for widespread cutaneous necrosis due to the APS (albeit with negative laboratory tests). Given that the patient had already been on immunosuppressive and anti-inflammatory treatment at the time of tissue sampling, the possibility of vasculitis contributing to the clinical syndrome was not discounted. Treatment added included i.v. heparin. Heparin resistance was noted and low-molecular-weight heparin tried. On week 3, warfarin was started. Despite anticoagulation, skin lesions progressed.

Repeat LA [hospital day (HD) 32] was positive by tissue thromboplastin inhibition test. High levels of beta-2-glycoprotein I (β2GPI) IgA antibodies (120 EIA units) were then detected and confirmed on repeat testing. Tissue plasminogen activator (tPA) was introduced at 20 mg i.v. over 4 h after plasmapheresis, followed by 30 mg doses for a total of eight treatments (HD 35–45). Epoprostenol, a prostacyclin analogue, was continuously infused i.v. on weeks 10–13 (HD 64–95) in yet another attempt to interrupt the hypercoagulable state.

There was no evidence of SLE flare or renal transplant rejection throughout the hospital course with normal serum creatinine and normal urinary sediments. By week 13, skin lesions were covering 30% of the total body surface. Skin integrity was poor and daily wound care provided by the burn unit team was only tolerable under general anaesthesia. There was also evidence of sepsis with progressive multi-organ failure involving the kidneys, pancreas and lungs. On HD 93, in the presence of
Widespread cutaneous necrosis is an uncommon presentation of the APS [2]. The diagnosis of APS in this patient, with serologically and clinically controlled SLE, was based on findings of multifocal cutaneous small-vessel thrombosis, and positive serology for β2GPI IgA antibodies. We believe that this is the first description of a catastrophic presentation of the APS (CAPS) in a patient with β2GPI IgA antibodies [3].

Approximately 30% of lupus patients with aPL may develop thrombotic complications. These have been found to correlate with the level of the antibody, the IgG isotype, and the presence of the protein cofactor β2GPI [4, 5]. β2GPI is a normal plasma protein [6]. In vitro, it acts as a natural anticoagulant by inhibiting the intrinsic pathway and adenosine diphosphate-induced platelet aggregation, but its physiological function is not known [3]. β2GPI is required for the binding of auto-immune IgG and IgM aPL, as well as for IgA aPL [7]. In one study of 47 patients with SLE, 17 (36%) were found to have IgG anti-β2GPI. There was a correlation to the presence of LA and aCL, and a strong association with thrombosis [8]. The presence of IgG anti-β2GPI has been found to pose a greater risk of thrombosis than LA and aCL in patients with primary or SLE-associated antiphospholipid antibodies [9].

CAPS is associated with high mortality [1]. Currently applied therapy in APS and CAPS [10] tries to target an autoimmune-driven hypercoagulable state, but the mechanism of aPL-mediated thrombosis is still unknown [3]. The hypercoagulable state was not controlled in this patient, as illustrated by the progression of skin lesions, and the development of new ones, despite aggressive anticoagulation and immunosuppression.

This case illustrates how anti-β2GPI IgA APS presenting with skin manifestations can result in a fatal form of CAPS.

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