Haemolytic uraemic syndrome, cardiomyopathy, cutaneous vasculopathy and anti-phospholipid activity

Sir,

Haemolytic uraemic syndrome (HUS) is a thrombotic microangiopathy that is characterized by non-immune haemolytic anaemia, thrombocytopenia and renal failure. It is one of the main causes of acute renal failure in children. The current concept divides HUS into two major types: the typical form, which corresponds to the great majority of cases of HUS and is associated with a prodromal diarrhoea ((D+) HUS), and another form not associated with diarrhoea ((D−) HUS) [1]. Atypical, (D−) HUS is a heterogeneous disorder, less common than (D+) HUS in children, and has a generally poor outcome. We describe a case of (D−) HUS in a child, with a relapsing course and a striking cardiac and cutaneous involvement associated with anticardiolipin antibodies and lupus anticoagulant.

Case. A 7-year-old male Caucasian patient was admitted with malaise, nausea, and vomiting for the previous 2 days. His personal history included an extensive burn involving more than 50% of the body surface, including the trunk and the upper limbs, which had occurred 1 year before and which left the patient with extensive scars, as well as a right-sided pneumonia 5 months prior to admission. There was no fever, neurologic abnormalities or diarrhoeal prodrome. The laboratory screening revealed urea 199 mg/dl, creatinine 1.5 mg/dl, haemoglobin 6.8 g/dl, platelets 28 × 10^9/l, increased reticulocyte count, and schistocytes in peripheral blood. Urinalysis revealed: protein, 300 mg/dl; white blood cells, 1–3/HPF; red blood cells, 10–20/HPF; and hyaline-granular casts. Other laboratory data were lactic dehydrogenase 1937 U/l, GOT 80 U/l, GPT 25 U/l, serum total bilirubin 37 mg/l, direct bilirubin 12.5 mg/l, serum haptoglobin 11 mg/dl and negative Coombs test. The PT, aPTT, AT-III, fibrinogen, plasminogen, and C and S proteins were within normal limits, but elevated D-dimer levels were found. Factor V Leiden mutation was not present. The value for proteinuria was 168 mg/m^2/h. The immunologic studies revealed normal serum level of C3, C4, immunoglobulins, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody, anticardiolipin antibody (ACA), HIV, HBV, HCV serologies were negative. Renal biopsy showed endocapillary proliferation with luminal stenosis and small vessel disease with arteriolar necrosis. Immunofluorescence study was positive for IgM and fibrinogen. Electron microscopy revealed swelling of the glomerular endothelial spaces, with granular material. The treatment included initially maintenance of fluid and electrolyte balance, blood transfusions, plasma infusions, and i.v. γ-globulin. Subsequently the patient developed oligoanuria, severe hypertension and uraemia (urea 99.4 mg/dl, creatinine 6.4 mg/dl), which led to the start of haemodialysis and plasmapheresis. An improvement in haematological parameters was noted after the start of plasmapheresis, but the patient never recovered renal function.

Because there was no resolution of renal failure, the patient received continuous ambulatory peritoneal dialysis as renal replacement therapy and was discharged. He was followed-up at our hospital. The general condition was stable except for persistence of hypertension. Seven months later, a relapse of the haemolytic activity was observed. The patient had hypotension and severe painful acrocyanosis and coldness involving the four limbs. Skin biopsy showed fibrin thrombi in the small blood vessels, without any inflammatory infiltrate. An echocardiogram (previously normal) showed a
Comment. This child presented with a HUS characterized by the simultaneous occurrence of microangiopathic haemolytic anaemia, thrombocytopaenia and acute renal failure. Extrarenal manifestations of HUS are being increasingly recognized and may lead to substantial morbidity and mortality. In this case the disease had a relapsing course with a progressive involvement of multiple organs. The severe cardiac and cutaneous involvement were probably due to the same pathological process that involved the kidneys, given the fact that several organs were affected in a relatively short period of time. Cardiac dysfunction is a relatively rare but recognized feature of HUS [2]. The presence of fibrin thrombi in the small blood vessels obtained from the cutaneous biopsy also points in the same direction.

Both the laboratory and clinical criteria for the diagnosis of the antiphospholipid-antibody syndrome were met in this case. The presence of an elevated value of IgG ACA (positive in two occasions more than 8 weeks apart) and lupus anticoagulant, associated with thrombotic phenomena and thrombocytopaenia, might allow the diagnosis to be made.

It is uncertain whether antiphospholipid syndrome was the cause of the HUS [3], or if the IgG ACA and lupus anticoagulants are immunological phenomena that may occur in some cases of HUS as one of the manifestations of the syndrome, with a possible pathogenic role.

Antiphospholipid syndrome has been described associated to several types of renal diseases, including IgA nephropathy [4]. In a study of D(+) HUS, antiphospholipid antibodies were found in 11 out of 17 patients, but no association could be demonstrated with the clinical variables [5].

In the present report, antiphospholipid antibodies were initially negative, later becoming positive. This fact strongly argues against antiphospholipid syndrome being the cause of the HUS. Further studies are necessary to elucidate this association, including the careful analysis of the time-course of the appearance of both the clinical phenomena defining HUS and the antiphospholipid activity.

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