Catastrophic anti-phospholipid syndrome associated with Escherichia coli O157 infection

Sin, Catastrophic APS (CAPS) is a term applied to aPL-mediated disorder in which multiple thrombi of small vessels affect the viscera over a relatively short period [1–3]. CAPS is rare in children and may be confused with haemolytic-uraemic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP) because of similar clinical manifestations. More importantly, it will be easily overlooked if associated with an acute episode of HUS/TTP itself.

We describe the case of a 9-year-old girl with haemorrhagic colitis caused by Escherichia coli O157 who developed CAPS during the course of her disease.

A 9-year-old girl with a 4-day history of fever, bloody diarrhoea and abdominal pain was transferred to our department because of suspected HUS after continued elevation of urea and creatinine levels despite adequate resuscitation. On examination, she had no purpura or oedema. Her consciousness was clear, and neurological examination was normal. Laboratory examinations showed increased CRP levels, 3.2 mg/dl; white blood cell count, 13.52 × 10⁹/l; haemoglobin, 12.3 g/dl; platelet count, 40 × 10⁹/l; signs of haemolysis with positive fragmented red cells in the blood smear; and elevated lactate dehydrogenase levels, 3474 U/l. Liver and kidney function tests showed elevated urea (47 mg/dl), creatinine (3.87 mg/dl), aspartate aminotransferase (281 U/l) and bilirubin (3.2 mg/dl) levels. Coagulation tests showed prolonged prothrombin time (15.1 s), increased fibrinogen degradation products (32.3 µg/ml) and increased D-dimer levels (10.5 µg/ml). Activated partial thromboplastin time and fibrinogen were normal. Stool culture and toxin assays for Shiga-like toxin were negative but O157 LPS antibody was positive, thus confirming infection with enterohaemorrhagic E. coli. The patient rapidly progressed to anuria and required placement of a dialysis catheter and initiation of haemodialysis. Haemodialysis improved her renal function; it was stopped on the ninth day after admission. Immunosorosological testing on the 10th day after admission showed a positive level of IgG aCL (14.2; <10 U/ml; ELISA), IgG phosphatidylserine-dependent prothrombin antibody (aPS/PT) (25; <10 U/ml; ELISA) and IgM aPS/PT (37; <10 U/ml; ELISA). IgG β2-glycoprotein I (β2GPI)-dependent aCLs and lupus anti-coagulant were negative. ANA was positive (30.7; index <20; ELISA). Other autoantibody tests, including RF, anti-ssDNA antibody, anti-dsDNA antibody and MPO-ANCA, were negative. The plasma level of ADAMTS-13 activity was slightly decreased to 15%, but the von Willebrand factor multimeric pattern was normal. A kidney biopsy performed on the 19th day after admission showed a typical histopathological picture of thrombotic microangiopathy (TMA) and no immune deposits (Fig. 1). Brain MRIs were normal. Radioisotope venography revealed left deep-vein thrombosis. The patient fulfilled the classification criteria for CAPS [3]. She received anti-coagulation therapy and was in clinical remission for 16 months.

Escherichia coli O157 is one of the most popular pathogens causing HUS. However, enteropathogenic E. coli has not been recognized as an infectious agent that triggers CAPS. To our knowledge, this is the first report of CAPS caused by E. coli O157 infection.

There are reports of a high frequency of aCL in children with diarrhea-associated HUS [4, 5]. Ardiles et al. [4] found a positive aCL in 59% (10/17) of the patients with classic HUS, without correlation with clinical variables. Furthermore, Te Loo et al. [5] reported a significant increase in aCL levels during the acute phase of diarrhea-associated HUS; IgM aCL was positive in 60% and IgG aCL in 41% of patients. A new subset of APS, termed microangiopathic APS (MAPS), was recently proposed. MAPS comprises those patients with TMA such as HUS/TTP, haemolytic, elevated liver enzymes, and low platelets syndrome and demonstrable aPL [6]. The aPL detected in this group of patients may be generated by endothelial damage or preceding infection [7]. Some of these non-pathogenic aPL may be rendered pathogenic by unknown factors in these conditions. However, we hypothesize that in some patients with HUS/TTP, the circulating aPL may contribute as a concomitant prothrombotic risk factor to the microvascular thrombotic process. The pathogenic role of aPL in clinical conditions of patients with TMA remains controversial; however, aPL should be examined in patients with TMA because anti-coagulant treatment is necessary in APS, particularly in CAPS.

aPS/PT was highly prevalent in patients with APS compared with patients with other diseases, and the detection of aPS/PT...
strongly correlated with clinical manifestations of APS [8, 9]. The specificity of aPS/PT for APS diagnosis is as high as that of aCL/β2GPI. Additional and prospective studies on aPS/PT are needed to establish the clinical relevance; aPS/PT is a useful tool for better recognition of APS. aPS/PT as well as aCL/β2GPI should be examined in TMA patients with positive aCL.

In conclusion, CAPS is rare in children but should be included in the differential diagnosis of HUS/TTP, and aPL, including aPS/PT, should be examined in patients with HUS/TTP.

Rheumatology key message
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Aortic aneurysm in MAGIC syndrome successfully managed with combined anti-TNF-α and stent grafting

Sin, A 48-year-old woman with MAGIC (Mouth And Genital Ulcers with Inflamed Cartilages) syndrome [Behçet’s disease (BD) and relapsing polychondritis [1]] consulted our medical department in 2000 following development of an acute left coeliaco-vestibular syndrome. She was discovered to have mixed type II cryoglobulinaemia and hepatitis C and responded fully to anti-viral therapy. Severe recurrent bipolar aphthosis, erythema nodosum and oligoarthritits first appeared in 2001, and were treated with an anti-malarial drug. In 2004, bilateral auricular and nasal chondritis was diagnosed, associated with lumbar inflammatory pain and bilateral aphagitis. MAGIC syndrome was diagnosed. Colchicine (1 mg/day) was prescribed, but replaced by SSZ (2g/day) because of digestive intolerance. In 2005, right coeliaco-vestibular syndrome developed, which responded to intravenous and then oral corticosteroids. Due to persistent biological inflammatory parameters, MTX (15 mg/week) was added to oral prednisone. Five months after discharge, she complained of persistent arthralgias and MTX was switched to AZA (15 mg/day), which obtained disease remission for almost 1 year, when she complained of heart palpitations, thoracic pain and repeated fainting episodes. A biological inflammatory syndrome was found: CRP 80 mg/l; fibrinogen 6 g/l. Echocardiography and pulmonary scintigraphy were normal. Thoracic CT angiograms revealed the presence of an aortic arch aneurysm, 4.4 cm in diameter, without signs of rupture. The positron emission tomography scan showed hyperfixation in the aortic arch and thoracic ascending aorta, suggestive of large-vessel vasculitis. Anti-TNF-α (infliximab, 3 mg/kg) was added to her regimen. Because biological inflammation persisted (CRP 55 mg/l; fibrinogen 5.5 g/l), infliximab was increased to 5 mg/kg at the fourth perfusion and monthly intravenous corticosteroids (15 mg/kg) were added. On this regimen, CRP and fibrinogen values normalized. After the seventh infliximab perfusion, endovascular stent-grafting (Valiant, TC3026C150X, Medtronic Europe, Tolucañaz, Switzerland) was performed. Infliximab infusions were spaced every 8 weeks and monthly intravenous corticosteroids were replaced by oral prednisone (10 mg/day). CT angiographic control of the stent showed a thrombosed aneurysm with no aortic wall thickening. The patient has remained asymptomatic on the same maintenance regimen for >2 years of follow-up.

To date, 19 cases of MAGIC syndrome have been reported [1–6]. Four of them, all women (mean age 32.5 years), three of whom (Table 1, Cases A–C) were taking immunosuppressant(s), developed a symptomatic aortic aneurysm involving the thoracic aorta [3–6]. Aneurysms seem to be a common complication of MAGIC syndrome (21.1%), even under immunosuppressants, and can require emergency surgery [3–6].

Vascular involvement occurs in 25–35% of BD patients [7, 8]. Aortic aneurysm is well described but uncommon and its optimal treatment, with immunosuppressant approaches [9] and surgical treatments [10], remains to be defined. Importantly, potential vein involvement means veins cannot be used as autograft replacement material. Endovascular graft-stenting successfully treated BD-associated vascular aneurysms in 20/21 reported patients [11, 12]. Ishikawa et al. [13] described abdominal aortic aneurysm progression 5 months after stent-graft placement that required prosthesi replacement.

In relapsing polychondritis patients, aneurysms develop in 5–7% of the patients and are multiple in 50% of them [14], usually involving the ascending aorta, and can cause aortic insufficiency. Moreover, they can occur during remission and under immunosuppressants. Aortic involvement is generally asymptomatic, and can be revealed by sudden rupture of the arterial wall.

Our patient, also a woman with MAGIC syndrome, developed a thoracic aortic aneurysm while taking AZA and oral corticosteroids. Unlike Case C, whose aneurysm occurred 2 years after starting anti-TNF-α [5], our patient achieved clinical and biological remission on monthly intravenous corticosteroids and infliximab, followed by infliximab and oral prednisone (10 mg/day) maintenance therapy. Once this remission was obtained, multidisciplinary consensus, in accordance with the patient’s...