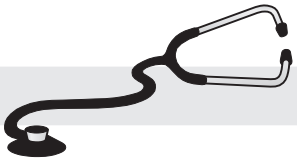

Severe Hemolytic Uremia Syndrome and Antiphospholipid Antibodies following Bowel Infection in the Absence of Major Vascular Occlusions: an Example of MAPS?

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Key words: MAPS, hemolytic uremic syndrome, antiphospholipid antibodies, plasma transfusions

IMAJ 2008;10:896–898

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Hemolytic uremic syndrome is characterized by acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. The majority of HUS cases occur after infectious diarrhea, and most of these cases are associated with E*scherichia coli* O157:H7 infection. However, atypical cases of HUS also occur in the absence of infectious diarrhea, although less commonly.

Antiphospholipid syndrome is a disorder characterized by recurrent venous or arterial thrombosis and/or fetal losses associated with characteristic laboratory abnormalities, such as persistently elevated levels of antibodies directed against membrane anionic phospholipids (i.e., anticardiolipin antibody, antiphosphatidylserine) or their associated plasma proteins, predominantly beta-2 glycoprotein I (apolipoprotein H), or evidence of a circulating anticoagulant. APS can occur in patients without evidence of any definable associated disease or in association with systemic lupus erythematosus or another rheumatic or autoimmune disorder. Traditionally, this has been referred to as primary or secondary APS, respectively, although, currently, the preferred terminology is APS with or without associated rheumatic disease. Although antiphospholipid antibodies are clinically linked to APS, whether they are involved in the pathogenesis or are an epiphenomenon is unclear. (Up to 5% of healthy individuals are known to have aPL antibodies.) We present a patient with the diagnosis of severe hemolytic uremic syndrome accompanied by antiphospholipid antibody elevations, which conformed to the subset of microangiopathic antiphospholipid-associated syndromes (MAPS) recently proposed by Asherson et al.

Patient Description

A 58 year old habitual drinker with no previous history of serious health problems and not taking any medication was admitted to our hospital because of abdominal pain, diarrhea, black stool for 3 days, vomitus with no blood, headache, fever and difficulty breathing. On admission it was noted that the patient's state of hygiene was very poor. His skin was dehydrated, warm and icteric. His body temperature was 38.9°C and blood pressure was 205/100 mmHg. When we examined his breathing we heard accented crackles and diminished breathing on the right side. The abdomen was palpable with no signs of perritoneal irritation. The liver was enlarged by about 5 cm, the spleen was normal and percussion of kidneys was negative, without pain. The lower extremities were without edema, and the peripheral pulses were palpable. The permanent catheter yielded dark reddish-brown urine, and the color of the stool, per rectum, was normal. The patient developed qualitative consciousness disorder over the first 24 hours, followed by somnolence that lasted 4–5 days.

We detected massive hemolysis in the blood – the serum was hemolytic – dark red, which prevented us from examining biochemical and hemocoagulation parameters. On the first hospitalization day it was possible to take a blood cell count only (hemoglobin 77–54 g/L, red blood cells 1.78×10^{12}/L, hematocrit 0.16, white blood cells $35.4–42 \times 10^{9}$/L, plateletes 205×10^{9}/L, reticulocytes 2.7–7.4%) and blood sugar 6.9 (normal 5.1).

Toxicological tests of the urine showed the presence of alcohol. Chemical examination of the urine revealed: red color, pH 7.0, urobilinogen and bilirubin ++++ (severe), ketones + (mild), Hb ++++ (severe),

* Died, 2008

HUS = hemolytic uremic syndrome
APS = antiphospholipid syndrome

aPL = antiphospholipid

Hb = hemoglobin

WBC ++ (moderate), nitrates positive, specific density 1015. Urine sediment showed 1–2 RBC per field (normal finding). On the 2nd day the blood results were as follows: urea 34.7 mmol/L (normal 7.0), aspartate aminotransferase 12.3 µkat/L (normal 0.6), and sodium 125 mmol/L (normal 135–145).

The WBC count of $35x10^9$/L on the first day increased to $42x10^9$/L, and hemoglobin decreased from 54 g/L to 48 g/L. Also noted were schistocytes, and reticulocytes in the peripheral blood count with a tendency to rise. We failed to raise the hemoglobin levels despite the daily administration of two units of RBC. The hemoglobin levels stayed very low at around 55 g/L without the expected increase. There were no signs of hemorrhage and the blood pressure was normal (no hemorrhagic shock). There was no indication of black stool, gastrointestinal bleeding (per rectum stool was normal color) or any other bleeeding. Anemia due to immune hemolysis was excluded; examination of red blood cell antibodies (Coombs' test) was negative.

On the 7th day we were able to determine other biochemical parameters such as alanine aminotransferase 1.0 µkat/L (normal 0.6), amylase 7.5 µkat/L (normal up to 3.5), creatinine in the serum 676 µmol/L, and total bilirubin 29 µmol/L (normal 20.5). On the 8th day the remaining biochemical and hemocoagulation parameters were: international normalized ratio 1.04 (normal 0.9–1.1), activated partial thromboplastin time/ratio 1.04 (normal 0.9–1.1), fibrinogen 6.09 g/L (normal 1.8–3.5), D-dimer 935 µg/L (normal 220). Because the clinical presentation indicated gastroenteritis and bronchopneumonia, the patient was given antibiotics (ciprofloxacin two doses of 200 mg i.v.) from the beginning of the hospitalization. WBC count peaked ($48x10^9$/L) on the 3rd day of his hospitalization. In the following days we observed a decrease in WBC count to normal levels and the patient became afebrile.

Laboratory results of autoantibodies showed highly positive anti-β2-glycoprotein I antibodies – more than 300 U/ml. Anticardiolipin immunoglobulin G antibodies were 29.3 U/ml, which indicated moderate activity. The levels of aminolevulinic acid in serum and uro- and coproporphyrin in the urine ruled out the diagnosis of porphyria; toxicological tests ruled out the use of drugs but proved the presence of alcohol. The ultrasound showed a typical picture of acute renal failure. Renal ducts were not dilated, there was one stone in the gall bladder, and other organs in the abdominal cavity did not show any pathology.

This case was interesting not only because of the final diagnosis, but because other parameters besides blood cell count and blood sugar levels were not measurable due to massive hemolysis. The urine and the serum were dark red. Due to the presence of schistocytes in the peripheral blood count and negative Coombs' tests, we reached the conclusion that the patient was suffering from severe microangiopathic hemolytic anemia and hemolytic uremic syndrome or antiphospholipid syndrome. We administered methylprednisolone 500 mg for 3 consecutive days, switching to prednisone 1 mg/kg/day on the 4th day. We also gave plasma transfusions 20 ml/kg/day. Exchange plasmapheresis could not be performed due to technical difficulties. Low molecular weight heparin was added and later switched to oral anticoagulants when we were able to measure the hemocoagulation parameters. We also gave the patient diuretics, because he was oliguric and antibiotics because of the fever and high inflammatory markers. Despite the diuretics (furosemid, manitol), uric levels rose. Since creatinine in the serum was not measurable, on the 4th day we instituted hemodialysis. The patient began to feel better, communication with him was becoming normal and his clinical appearance began to improve. The color of urine became lighter after the second pulse of methylprednisolone. On the 8th day of treatment we were able to measure all blood parameters for the first time. The patient refused a renal and skin biopsy. We discontinued hemodialysis due to sufficient diuresis. By the end of the hospital stay the hemolysis had resolved, hemoglobin was 105 g/L, platelets $192x10^9$/L and serum creatinine 206 µmol/L. After the patient's discharge from hospital we planned to conduct a follow-up but he never showed up again.

Comment

This case was particularly interesting not only because of the diagnosis of hemolytic uremic syndrome in an adult, but also because many of the serological parameters necessary for diagnosis (apart from blood cell count and blood sugar) could not be measured due to the massive hemolysis. There was no evidence of any large vessel occlusion accompanying the aPL.

Owing to the presence of schistocytes in the peripheral blood count, the intense hemolysis, renal dysfunction and thrombocytopenia (delayed for several days) suggested the diagnosis of severe hemolytic uremic syndrome accompanied by aPL. This conforms the hypothesis recently suggested by Asherson et al. [1,2] of a subset of patients with aPL in whom no large vessel occlusions are present. These authors suggested the eponym MAPS (**m**icroangiopathic **a**ntiphos**p**holipid-associated **s**yndromes) which includes thrombotic thrombocytonic purpura, hemolytic uremia syndrome, HELLP syndrome and thrombotic microangiopathic hemolytic syndromes (primary or secondary to diseases such as systemic lupus erythematosus). In this latter group, severe thrombocytopenia may also be present. Moreover, in addition to hemolysis, small vessel occlusions may occur, causing ischemia and even gangrene of the extremities. Large vessel occlusions are usually not evident (either venous or arterial) as in antiphospholipid syndrome. The presence of schistocytes are indicative of small vessel endothelial damage causing red cell fragmentation, and this endothelial damage is the cause of the apoptotic generation of non-pathogenic aPL. Their presence does not require the addition of anticoagulation therapy. In these syndromes (MAPS) there may be similar triggering factors (infections, drugs, pregnancy), clinical features and serological findings, and they may all respond to parenteral steroids and plasma exchange/plasmapheresis. It has also

WBC = white blood cells
RBC = red blood cells

MAPS = microangiopathic antiphospholipid-associated syndromes

been suggested that a continuum might exist between some of these conditions and the catastrophic antiphospholpid (Asherson's) syndrome [3]. Several reports recently identified such cases. In addition, "relapsing" catastrophic antiphospholipid syndrome might in fact also demonstrate deficiencies of ADAMTS 13 (a disintegrin and metalloproteinase with thrombospondine type 1 motif 13) and resemble thrombotic thrombocytonic purpura [4]. Although thrombocytopenia is usually present, in certain patients with thrombotic microangiopathic hemolytic anemia secondary to other conditions such as SLE/lupus-like disease may be mild or not present at all. This is unusual [5].

Hemolytic uremic syndrome was first described by Gasser in 1955, after which many reports followed, mainly in children. Diarrhea-associated hemolytic uremic syndrome is the most commonly encountered form in childhood. It has been shown to be related predominantly to enterohemorrhagic E*scherichia coli* (subgroup 0157:H7). Ninety-five percent of affected children survive without plasma exchange. In the 1980s with the advent of testing for anticardiolipin antibodies, patients with aCL positivity were documented, but this finding did not seem to alter the basic presentation of the disease. This combination has been described postpartum, and with paraneoplastic scleroderma.

The diagnosis of clinical units associated with thrombotic microangiopathic hemolytic anemia is often difficult because the clinical features overlap. Clinical signs and laboratory parameters will determine the final diagnosis of diseases associated with TMHA.

SLE = systemic lupus erythematosus

aCL = anticardiolipid anatibodies

TMHA = thrombotic microangiopathic hemolytic anemia

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