

## Atypical Hemolytic Uremic Syndrome with Membranoproliferative Glomerulonephritis

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Received: May 05, 2012;

Initial review: May 31, 2012;

Accepted: April 27, 2013

Atypical hemolytic uremic syndrome (aHUS) associated with membranoproliferative glomerulonephritis (MPGN) is an uncommon clinical presentation, especially in children. We report a 8-year-old-boy who presented like aHUS but the kidney biopsy showed MPGN type 1.

**Keywords:** Atypical hemolytic uremic syndrome, Hypocomplementemia, Membranoproliferative glomerulonephritis.

**A**typical hemolytic uremic syndrome (aHUS) and membranoproliferative glomerulonephritis (MPGN) are uncommon diseases. Both these conditions are widely studied and reported to be associated [1,2]. Previously they were considered to be chance association but now there are reports of the role of factor H in the etiopathogenesis of MPGN and aHUS.

### CASE REPORT

An 8-year-old boy was brought with the complaints of decreased urine output, generalized edema and fever since one week. He had no history of similar episodes in the past or history suggestive of chronic kidney disease in the family. There was no history of diarrhea, sore throat, rash or hematuria preceding this illness. Examination revealed anasarca, periorbital puffiness and pallor. Patient did not have rash, joint involvement or purpura. Blood pressure was normal. He had abdominal distension due to ascites. Liver was tender and palpable 4 cm below the subcostal margin with a span of 10 cm. Spleen was not palpable.

Investigations on admission, revealed hemoglobin level of 4.6 g/dL, reticulocyte count of 2%, leukocyte count of 12,200/cu mm with 67% neutrophils, 25% lymphocytes and platelets 1,72,000/cu mm. Peripheral smear showed microcytosis, anisocytosis, schistocytes, few tear drop and target cells. Blood level of albumin was 3.1 g/dL, total proteins 5.6 g/dL, pH 7.4, pCO<sub>2</sub> 26 mm Hg and bicarbonate 16.1 mEq/L, creatinine 1.2 mg/dL, urea nitrogen 65 mg/dL, sodium 136 mEq/L and potassium 5.7 mEq/L. Antistreptolysin O (ASO) was negative, C3 was 28 mg/dL and hepatitis B and C serology were negative. Urinalysis showed 3+ proteinuria, 10-15 red cells/hpf and 5-10 leukocytes/hpf. Prothrombin time was 17 seconds (control 19 seconds) and aPTT was 27 seconds. Lactate dehydrogenase and D-dimer were 772 IU/L and

2000 ng/dL, respectively. Serum C4 was normal and antinuclear antibodies anti-ds, DNA were negative. A diagnosis of acute renal failure with microangiopathic hemolytic anemia due to HUS was made. There was a steady increase in blood urea, creatinine and potassium with a fall in urine output over the next two days. Peritoneal dialysis was done for 72 hours following which these levels normalized and the urine output improved.

Renal histology showed ten enlarged glomeruli with diffusely thick basement membrane, proliferation of mesangial cells, fewer endothelial cells and neutrophil infiltration. The loops were obliterated. The tubules showed focal necrosis, hydrophobic changes and atrophy. The vessels showed mild luminal narrowing due to myointimal thickening. The interstitium revealed few lymphocytes. Immunofluorescence revealed deposition of IgM, C<sub>3</sub> and C1q in the mesangium and capillary loops. IgG and IgA were negative. Electron microscopy revealed proliferation of endothelial and mesangial cells. The lamina densa showed excess of basement membrane material with zones of interpositioning and subendothelial electron dense deposits. The foot processes were flat. The findings were suggestive of membranoproliferative glomerulonephritis (MPGN) type 1.

The patient was treated with oral prednisolone at a dose of 2 mg/kg/day and fresh frozen plasma for the first few days followed by alternate day transfusions to which patient responded well. These were then tapered and stopped when the activity of HUS decreased. During the course of prednisolone therapy, blood pressure increased requiring multiple agents. Urine albumin reduced, but 5 months later showed significant albuminuria. Therapy with mycophenolate mofetil resulted in decrease in proteinuria.

Two months later, he was admitted with fever, vomiting, diarrhea and abdominal pain and 4+ proteinuria. He rapidly developed septicemia with hypotension and multiorgan failure, and died after four days of intensive care and ventilator support.

### DISCUSSION

HUS with MPGN has been widely studied and reported in the past [1,3]. The earliest reports just mention it as a chance association or as HUS secondary to MPGN whereas, recent reports implicate the role of factor H which is an important component of the alternate complement pathway in both HUS as well as MPGN [1,2]. Ten percent of HUS patients are due to atypical form which is distinct and different from the typical HUS. The atypical form of HUS has a poor prognosis and terminal renal insufficiency occurs in over 50% with death rates close to 25% [3].

Our patient had a clinical presentation of aHUS on admission and his renal biopsy was suggestive of MPGN type I. There was no evidence of HUS on the biopsy findings, yet the patient responded well to plasma infusions. The co-existence of HUS with MPGN can be explained on the basis of factor H deficiency.

Mutations in the factor H gene are associated with severe and diverse diseases including the rare renal disorders of HUS and MPGN, and the more frequent age related macular degeneration [4-6]. In a study on 19 patients of glomerulonephritis with C3 deposits, assays were performed for factor H, factor I and membrane cofactor protein to determine whether they share a common genetic susceptibility. The study suggested that dysregulation of the complement alternative pathway is probably associated with a wide spectrum of diseases ranging from HUS to MPGN with C3 deposits [6]. The clinical clue to the diagnosis of MPGN in this case was persistent low C3 complement, which is found only in factor H deficient or complement associated HUS. In a study of 16 factor H-deficient patients, six had a

homozygous deficiency of which four presented with MPGN and two had aHUS. Patients with heterozygous mutations in factor H gene are also reported to develop aHUS [7].

Treatment options include control of hypertension, plasma infusions or plasmapheresis and use of steroids, which will help in control of MPGN as well as a HUS. Eculizimab has also been used in the treatment of refractory MPGN [8] and has been found useful in patients where mycophenolate mofetil does not result in a satisfactory response.

*Competing interests:* None stated; *Funding:* None.

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