Atypical hemolytic uremic syndrome associated with *Clostridium difficile* infection and partial membrane cofactor protein (CD46) deficiency

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Hemolytic uremic syndrome is mostly a disease of childhood typically presenting with the classic triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. The vast majority of typical HUS cases are sporadic and known to be triggered by infection, most notably certain strains of *Escherichia coli* and other bacteria that produce toxic substances called Shiga-like toxins. The typical form most often affects children younger than 10 years old and is not known to be associated with genetic mutations. Adult HUS, also referred to as "non-diarrheal HUS" or atypical HUS, accounts for 5–10% of all documented cases of HUS, and unlike childhood disease is associated with a poor prognosis. It is a rare disease, occurring at an estimated incidence of 1 in 500,000 people per year in the United States. Triggers for development of aHUS are more diverse, and include drugs, systemic illnesses, cancer, pregnancy, infections, and idiopathic. Cases of aHUS caused by diarrhea infectious agents have seldom been reported [1,2].

Recently, aHUS was demonstrated to be a disorder of the complement alternative pathway system which is detectable in approximately 60% of patients. Three major regulatory proteins of the complement system are linked to the development of aHUS: complement factor H, complement factor I and membrane cofactor protein. A single or combined mutation in any of the genes encoding these regulatory proteins can lead to dysregulation of the entire complement system and increase the risk for developing aHUS. Over 75% of the reported mutations cause a reduction in MCP expression [1,2]. Mutations in the membrane cofactor proteins, which predispose to the development of aHUS, were first identified in 2003 [3]. MCP is a single-chain, trans-membrane glycoprotein expressed on many human cells. MCP functions to protect host cells from complement attack. It is an intrinsic complement regulator that inhibits the actions of the cleaved C3b and C4b from destroying the cell. MCP mutations are present in approximately 15% of all patients with aHUS and more than 20 different mutations in MCP have now been identified. Many of these mutations have been functionally characterized and have helped to define the pathogenic mechanisms leading to aHUS development.

We present here a rare case of an adult patient with aHUS associated with partial MCP deficiency and triggered by infection with *Clostridium difficile*.

PATIENT DESCRIPTION

A 73 year old woman of Ethiopian ancestry was admitted with severe watery diarrhea of 2 weeks duration, respiratory distress, chills and anuria. Her past medical history was notable only for chronic obstructive pulmonary disease that was treated with bronchodilators. Physical examination and vital signs were normal but the patient's condition deteriorated. Initial laboratory studies demonstrated mild anemia (hemoglobin 11.6 g/dl), thrombocytopenia 71,000/mm^3 and acute renal failure with a creatinine level of 11.63 mg/dl and urea 335 mg/dl. Also noted was severe metabolic acidosis with a pH of 7.16 and hyponatremia 110 mEq/L, hyperphosphatemia 9.8 mEq/L, elevated uric acid 13.3 mEq/L and lactate dehydrogenase 2524 U/L. Hepatocellular liver enzymes and coagulation profile were normal. Ultrasound of the kidneys showed normal-sized kidneys, with no signs of renal stones or hydronephrosis, and an empty urinary bladder. Chest X-rays and abdominal and chest computed tomography scans were interpreted as normal. Treatment with intravenous fluids, bicarbonate, bronchodilators, along with intravenous steroids, was instituted and hemodialysis was performed, with immediate amelioration of her symptoms.

Additional lab tests the following day demonstrated worsening anemia of 8.0 g/dl, extremely low haptoglobin levels of 6.9 mg/dl (normal value 28–284 mg/dl)

* The first two authors contributed equally to this study

HUS = hemolytic uremic syndrome

MCP = membrane cofactor protein

and reduced complement levels: C3 62 mg/dl (normal range 88–206 mg/dl) and C4 9 mg/dl (normal range 13–75 mg/dl). Lactate dehydrogenase remained persistently elevated and the platelet count was consistently low (around 70,000/mm^3 on repeated tests). A test for antinuclear antibody returned negative. Peripheral blood smears demonstrated abundant schistocytes and burr cells, and a diagnosis of HUS was made. *C. difficile* toxin was detected in the stools and treatment with metronidazole was begun, resulting in a resolution of the diarrhea a few days later. The patient's mononuclear cells were analyzed by flow cytometry after labeling with anti-MCP/CD46 antibodies. About 4% of the cells were found to be MCP-negative and a small reduction in the level of expression of MCP was noted in the rest of the cells (mean fluorescence intensity 117 as compared with 134 in a healthy control) [Figure]. The patient's clinical condition improved, with a gradual normalization of renal function and blood count and she was discharged in overall good condition.

COMMENT

This is the first reported case of *C. difficile*-associated aHUS in Israel. Several features of our patient deserve consideration. She was found to have abnormal mononuclear cells; about 4% of the cells were completely deficient in MCP and the rest had a slightly lower MCP level relative to normal control mononuclear cells. The significance of this finding is not entirely clear. Most of the published data report a reduction of over 50% in MCP levels in patients who develop aHUS. Furthermore, some MCP mutations do not result in reduced expression; rather they cause a functional disorder. Our patient's MCP functional activity has not been tested so at this point a functional abnormality cannot be ruled out. It should also be noted that no other genetic mutations (CFH, CFI) have been tested, so it is unclear whether she has additional mutations and whether or not she has a genetic predisposition for the disease. While gene mutations increase the risk of aHUS, they are often not sufficient to cause the disease. In people with one (or more) of the genetic abnormalities mentioned above, the development of aHUS may be triggered by the presence of external factors such as infections [3]. Thus, it is conceivable that the *C. difficile* infection in our patient triggered her aHUS. Rare cases of *C. difficile* infection triggering aHUS have been previously reported [4].

The treatment of choice for aHUS is plasma exchange therapy [2]. Interestingly, our patient had made a full recovery when treated with corticosteroids only, without the need of plasmapheresis. This clinical course is in agreement with previous reports of patients with aHUS who had been treated with steroids alone and had made a full recovery [2,5]. In addition, MCP gene mutations have been described as having the best prognosis of all genotyped cohorts and renal function is generally preserved for years after the disease, despite a relapsing course of the illness, while patients with other mutations will eventually reach end-stage renal disease. It is possible, therefore, that our patient's recovery was not related to her steroid therapy but followed the natural history of her disease.

In summary, we believe that a partial MCP deficiency together with *C. difficile* infection triggered the aHUS in our patient. The full recovery of this patient suggests that corticosteroids and supportive therapy may obviate the need for plasmapheresis in similar patients.

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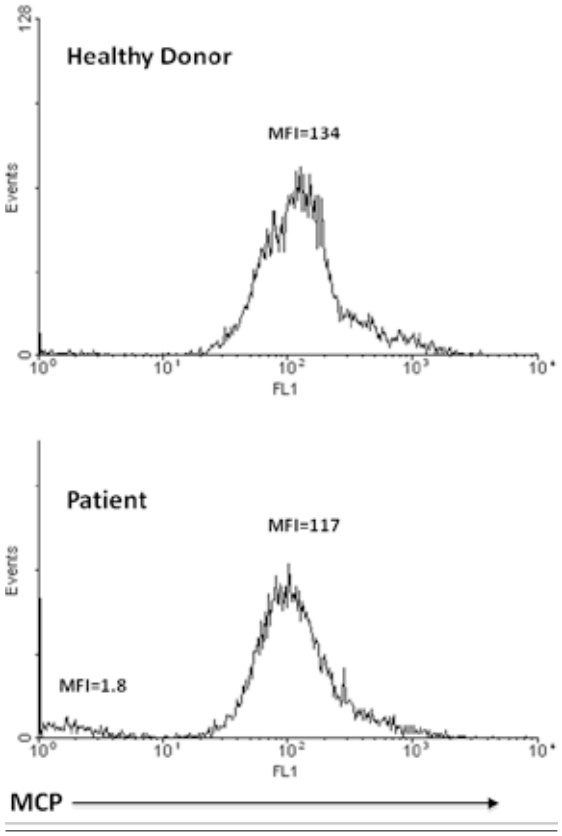
aHUS = adult HUS

CFH = complement factor H
CFI = complement factor I

FACS analysis of peripheral blood mononuclear cells from the patient and control, showing a small reduction of MCP expression in the patient's cells with 4% of cells expressing no MCP. Anti-MCP/CD46 mAb was used to detect the presence of MCP



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