Preservation of Renal Function in Atypical Hemolytic Uremic Syndrome by Eculizumab: A Case Report

abstract

Genetic mutations in complement components are associated with the development of atypical hemolytic uremic syndrome (aHUS), a rare disease with high morbidity rate triggered by infections or unidentified factors. The uncontrolled activation of the alternative pathway of complement results in systemic endothelial damage leading to progressive development of renal failure. A previously healthy 8-month-old boy was referred to our hospital because of onset of fever, vomiting, and a single episode of nonbloody diarrhea. Acute kidney injury with preserved diuresis, hemolytic anemia, and thrombocytopenia were detected, and common protocols for management of HUS were followed without considerable improvement. The persistent low levels of complement component C3 led us to hypothesize the occurrence of aHUS. In fact, the child carried a specific mutation in complement factor H (Cfh; nonsense mutation in 3514G>T, serum levels of Cfh 138 mg/L, normal range 350–750). Given the lack of response to therapy and the occurrence of kidney failure requiring dialysis, we used eculizumab as rescue therapy, a monoclonal humanized antibody against the complement component C5. One week from the first administration, we observed significant improvement of all clinical and laboratory parameters with complete recovery from hemodialysis, even in the presence of systemic infections. Our case report shows that complement inhibiting treatment allows the preservation of renal function and avoids disease relapses during systemic infections. Pediatrics 2012;130:e1–e4
It is generally felt that atypical hemolytic uremic syndrome (aHUS) has heterogeneous causes. A genetic lack of complement inhibitors represents a major cause of aHUS, leading to uncontrolled complement activation with thrombotic microangiopathy. Plasma therapy (plasma infusion and/or plasma exchange) has empirically become the first-line treatment. The use of eculizumab (Soliris, Alexion Pharmaceuticals Cheshire, CT), a humanized monoclonal antibody against complement component C5, licensed for the treatment of paroxysmal nocturnal hemoglobinuria, has been recently approved for the therapy of aHUS in United States (September 2011) and in European Union (November 2011).

**PATIENT PRESENTATION**

CD, a child born in April 2009, was admitted to our hospital in December 2009 for fever, vomiting, and a single episode of nonbloody diarrhea. The child presented the classic symptomatic triad of HUS: acute kidney injury with preserved diuresis, anemia, and thrombocytopenia (Table 1). The patient showed resistance to plasma infusion (21 infusions from January 3 to March 17, dosage: 10 mL/kg) and plasma exchange (9 sessions from March 20 to April 6 on alternate days). Because of the persistence of hypocomplementemia, we hypothesized that the patient had complement-associated aHUS. Mutation screening of complement regulator genes revealed a heterozygous complement factor H (Cfh) nonsense mutation 3514G>T (patient’s serum levels of Cfh 138 mg/L, normal range 350–750; Mario Negri Institute, Ranica, Bergamo, Italy). The mutation was inherited from the mother, who was asymptomatic without renal abnormalities, despite the presence of low levels of C3 and Cfh.

In March 2010, the clinical status of the patient worsened dramatically, with persistent vomiting, sweating, anorexia, and drowsiness without neurologic impairments. Hemodialysis was started (serum creatinine 2.51 mg/dL; serum urea nitrogen 79.9 mg/dL) because of the occurrence of congestive heart failure, and 3 packed red blood cell transfusions were administered. After consulting published reports on the use of eculizumab in aHUS, we obtained the authorization of the local ethical committee and the child’s parents for off-label use of this drug. Eculizumab was provided by Alexion and used as rescue therapy. It was administered in April after meningococcal vaccination. Plasma infusion and exchange were stopped after eculizumab administration. During the first month, it was administered on a weekly basis (300 mg, intravenously; patient’s weight 10 kg), then every 14 days for 2 months, and subsequently every 3 weeks up to the present. One week after the first administration, a significant improvement in the platelet count and lactate dehydrogenase values was already registered. Dialysis was discontinued 5 days after drug administration (creatinine 1.33 mg/dL; serum urea nitrogen 49 mg/dL). No additional packed red blood cell transfusions were necessary. Despite the onset of catheter-related sepsis by *Staphylococcus aureus* (June 2010), the overall improvement was progressive and persistent over 12 months (Table 1). In September, the boy was admitted to nursery school, and no clinical relapses occurred, even in presence of 3 episodes of upper respiratory infections with fever.

**DISCUSSION**

The pathogenesis of aHUS with factor H deficiency is due to the uncontrolled activation of the alternative pathway of complement resulting in systemic endothelial damage. The onset and relapses of aHUS are triggered by infection or unidentified factors. As was the case for our patient, there is usually a poor response to plasma therapy and a progressive development of renal failure. Between the different complement regulators screened in our patient and his relatives, we identified a single mutation in *Cfh* that was originally described as a missense mutation of the last exon. Mutant protein has reduced binding to heparin, C3b/C3d, and endothelial cells. Heparin affinity chromatography revealed reduced binding of mutant protein to heparin, and surface plasmon resonance studies showed impaired binding to C3b and C3d. In addition, because the mutation was inherited by the healthy mother, our report confirms that this type of mutations have a penetrance of ~50%.

So far, the only therapeutic option available is early treatment with plasma infusion or plasma exchange at the onset of the disease, followed by a long-term...
Unlike the majority of cases described in the literature in which this drug was successfully used for the treatment of aHUS in children, each aged 3 years, our case report shows that the use of eculizumab to inhibit the detrimental effects of complement on renal tissue may lead to a regression of fibrosis and thrombotic microangiopathy at the renal level.

Eculizumab is a recombinant humanized monoclonal antibody that specifically binds to the complement protein C5, inhibiting its cleavage by the C5 convertase, which prevents the generation of the terminal complement complex C5b-9.4 Because of the absence of any systemic symptoms, we thus were able to continue the drug administration as planned, without any disruption of platelet count and proteinuria, and to resume the child’s daily activities.

Our case report shows that the use of eculizumab to inhibit the detrimental effects of complement on renal tissue may prevent the development of end-stage renal failure, whereas early use of prophylactic plasma therapy to prevent or in older patients, may lead to a progression of fibrosis and thrombotic microangiopathy.


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