Cryptic Activity of Atypical Hemolytic Uremic Syndrome and Eculizumab Treatment

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KEY WORDS
hemolitic uremic syndrome, end-stage renal disease, proteinuria

ABBREVIATIONS
aHUS—atypical hemolitic uremic syndrome
CFH—complement factor H
ECU—eculizumab
FFP—fresh-frozen plasma
LDH—lactate dehydrogenase
TMA—thrombotic microangiopathy

Drs Belingheri and Ardissino conceptualized the study, and drafted and reviewed manuscript; Drs Possenti, Tel, Paglialonga, and Testa coordinated and supervised data collection, and critically reviewed the manuscript; Dr Salardi coordinated the genetic analysis, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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abstract

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening disease often related to uncontrolled complement activation. The use of eculizumab has changed the management and the outcome of aHUS, becoming the frontline treatment of the acute disease and for the prevention of relapses. We report the case of a male patient with aHUS due to complement factor H gene mutation who was shifted from plasmatherapy to eculizumab for preventing disease relapses. The shift to eculizumab was associated with a significant decrease in proteinuria, revealing disease activity otherwise unsuspected, being the classic criteria of disease activity (platelet, haptoglobin, LDH, schistocytes), all in the normal range.

The condition of proteinuria as the only sign of thrombotic microangiopathy activity is here designated as "cryptic activity of aHUS." *Pediatrics* 2014;133:e1769–e1771

Atypical hemolytic uremic syndrome (aHUS) is a rare, genetic, life-threatening disease mainly (although not necessarily) related to uncontrolled complement activation. A number of gene abnormalities, complement factor H (CFH), factor I, membrane cofactor protein, complement component 3, factor B, thrombomodulin, and an autoimmune condition (anti-CFH antibodies) have been identified as pathogenetic factors responsible for the thrombotic microangiopathy (TMA), which is often triggered by infections, pregnancy, delivery, or surgery.[1] aHUS is burdened with a severe prognosis; in children, the case-fatality rate is estimated at 6.7%,[2] with 16% of patients reaching end-stage renal disease 1 year after the disease onset and 80% relapsing after kidney transplantation.[3]

Since 2009, the use of eculizumab (ECU), an anti–complement component 5 humanized antibody, has dramatically changed both the management and the outcome of aHUS, becoming the frontline treatment of the acute disease[4] and for the prevention of recurrences in patients who have received transplantation.[5,6] The role of ECU in the prevention of relapses on native kidney is less obvious, particularly in those patients with a disease sensitive to fresh-frozen plasma (FFP).

PATIENT PRESENTATION

Herein we present the case of a young male patient with CFH mutation (SCR20 - p.Val1197Ala) who had developed aHUS at age 6 months. He recovered from the acute phase with a residual severe chronic renal insufficiency (serum creatinine 1.8 mg/dL), and after several relapses, from age 7 years, he was addressed to prophylactic weekly infusion of FFP.

During the subsequent 4 years, the child had no more recurrences of aHUS, but a mild proteinuria, considered as the consequence of the severe chronic glomerular damage (creatine clearance 28 mL/min/1.73 m^2), persisted together with severe hypertension requiring 4 medications (amlodipine, atenolol, ramipril, and minoxidil) to obtain acceptable blood pressure control.

At the age of 11 years (with a body weight of 35 kg), without any evidence of TMA activity (Fig 1 C, D, and E), the child presented a progressive deterioration of renal function (Fig 1B) together with increasingly severe urticarial reactions to FFP for which the patient was switched to ECU treatment: 900 mg every 14 days.

During the subsequent year, no relapse was detected, and ECU proved to be effective to maintain the disease into remission (Fig 1 C, D, and E). Complement component 3 significantly decreased after ECU (from a mean of 58.0 ± 5.7 mg/dL during FFP to 41.4 ± 6.1 mg/dL, $P < .0001$), while C4 remained

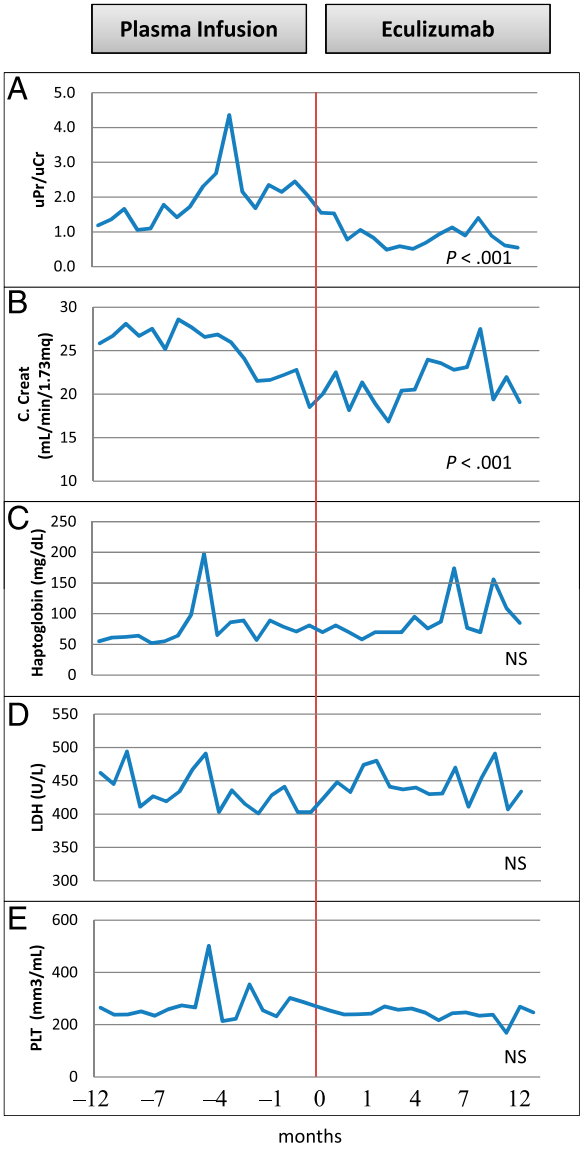

FIGURE 1

Time course of proteinuria (expressed as proteinuria/creatinuria ratio [uPr/uCr]), creatinine clearance (C. Creat), haptoglobin, LDH, and platelet count (PLT) during the year before and after the first ECU infusion. The differences between periods (plasmatherapy versus ECU) were analyzed with a nonparametric test (Mann-Whitney).

unchanged (28.0 ± 4.1 mg/dL to 27.0 ± 4.4 mg/dL).

Global complement functions, as measured by the AP50 and CH50 (Unit of alternative and classic pathways activity, respectively), were completely suppressed by ECU (from a mean value of 82.0% ± 6.0% and 110.0% ± 4.4% during FFP to 0.2% ± 0.6% and 0.2% ± 0.4%).

Renal function did not improve (Fig 1B), but a striking decrease in urinary protein excretion (Fig 1A) was observed immediately after the first administration of ECU. The reduction in proteinuria persisted during the subsequent 12 months (without changes in antihypertensive therapy, particularly in angiotensin-converting enzyme inhibitors). Also, hemoglobin level increased significantly (from a mean of 11.1 ± 0.3 during FFP to 12.3 ± 0.8 during ECU; $P < .001$), although hemolytic biomarkers (haptoglobin, lactate dehydrogenase [LDH], schistocytes, and platelet count) did not change.

DISCUSSION

The significant reduction in urinary protein excretion after the switch from FFP to ECU was completely unexpected. The persistent mild proteinuria had been, perhaps erroneously, attributed to the chronic kidney damage, but the impact of ECU on proteinuria raises (and supports) the hypothesis that the proteinuria was a subtle expression of TMA activity, although the classic criteria for the diagnosis of HUS relapse were absent.

In our opinion, this observation should drive our attention to the low sensitivity of biomarkers commonly used to monitor disease activity in aHUS. The concept of "partial aHUS" has been already been postulated by Sallée et al to indicate an aHUS occurring without thrombocytopenia.[7,8] The entity emerging from our case description would better fit the label of "cryptic aHUS": a relapse of aHUS, although none of the 3 criteria for the diagnosis are present (perhaps hidden by a patient's sensitivity to plasmatherapy).

In the described case, not only was the classic triad missing, but also a diagnosis of partial aHUS does not fit: the child's haptoglobin and LDH were normal. The increase in hemoglobin after ECU, despite the worsening of renal function, without changes in recombinant human erythropoietin (rhEPO) dosage, further support the possibility that subclinical hemolysis was present during plasmatherapy. A renal biopsy might have been diagnostic of active TMA; however, it was not performed because the relapse was not suspected.

Alternative explanations for the reduction of urinary protein after ECU, other than the attainment of complete remission of a subtle TMA, have been explored. The discontinuation of FFP and of the related protein overload, might have changed the renal hemodynamic (protein-induced hyperfiltration). However, proteinuria secondary to plasma infusion per se, has never been reported in both normal and reduced renal function. Moreover, although the dose and the modality of FFP administration remained unchanged during the period considered, proteinuria had increased quite significantly, making the increase itself unlikely related to the regular infusion of FFP. Even in our own experience with plasma supplementation in patients with congenital thrombotic thrombocytopenic purpura or aHUS (unpublished data by G.A.), we never observed proteinuria associated with plasmatherapy. Finally, a direct antiproteinuric effect of ECU seems unlikely although cannot be ruled out, but it has never been observed or reported.

CONCLUSION

Based on the present case report, we recommend to carefully screen patients with aHUS in remission by means of proteinuria together with the classic indicators of disease activity and to address those with high urinary protein excretion to renal biopsy, which remains the gold standard diagnostic procedure for TMA. If a diagnosis of active TMA is ruled in, ECU may be helpful.

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