Clinical Case Report

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Efficacy of eculizumab in an adult patient with HIV-associated hemolytic uremic syndrome

A case report

Marine Freist, MD[a], Cyril Garrouste, MD[a,b,*], Nora Szlavik, MD[c], Paul Coppo, MD, PhD[b,d,e], Alexandre Lautrette, MD, PhD[b,f], Anne Elisabeth Heng, MD, PhD[a]

Abstract

Introduction: Hemolytic uremic syndrome (HUS) in Human Immunodeficiency Virus (HIV)-positive patients has become a rare cause of kidney injury since the era of highly active antiretroviral therapy (HAART). Plasma exchange and antiretroviral therapy were previously recommended but often failed to achieve remission. We report a case of HUS in a HIV-positive patient treated successfully with eculizumab.

Case summary: A 52-year-old woman presented to hospital with acute renal failure, thrombocytopenia, anemia, and hypoxemia. She had been diagnosed with HIV infection in 1997. Kidney biopsy showed several fibrinous microthrombi in the glomerular capillaries, formation of thrombi in arterioles, moderate parietal and mesangial deposits of C3 and Immunoglobulin M, and intense glomerular and arterial deposits of Complement component 5b9 complement component. Serum HIV viral load was 227,848 copies/mL, and CD4 lymphocyte count was 120 cells/μL. A diagnosis of HIV-associated HUS was made. The patient had no confounding cause of HUS. Initiation of eculizumab and HAART resulted in complete hematological remission on day 32 and dialysis withdrawal on day 110. The patient has not relapsed during long-term follow-up (M17).

Conclusion: This observation suggests that eculizumab can achieve remission in HIV patients with HUS.

Abbreviations: CFH = factor H, HAART = highly active antiretroviral therapy HIV, HUS = hemolytic uremic syndrome, PE = plasma exchange, TMA = thrombotic microangiopathy, TTP = thrombotic thrombocytopenic purpura.

Keywords: case report, eculizumab, hemolytic uremic syndrome, HIV

1. Introduction

The incidence of thrombotic microangiopathy (TMA) in Human Immunodeficiency Virus (HIV)-positive patients has drastically decreased since the era of highly active antiretroviral therapy (HAART).[1,2] Two mechanisms of TMA associated with HIV have been documented: thrombotic thrombocytopenic purpura (TTP) with severe A disintegrin and metalloprotease with thrombospondin type 1 repeats (ADAMTS13) deficiency related to the presence of anti-ADAMTS13 antibodies, and hemolytic uremic syndrome (HUS), which begins at a later stage of the HIV disease. TTP usually occurs at the onset of infection, when there are few complications and high $CD4^+$ lymphocyte count,[3] and has a favorable prognosis after prompt treatment with plasma exchange and HAART.[4] The pathophysiology of HIV-associated HUS is poorly understood.[3,5] Plasma exchange and antiretroviral therapy were recommended but often failed to achieve remission.[5] End stage renal disease and high mortality rates are common.[3]

Eculizumab, a recombinant humanized monoclonal antibody against the complement protein C5, transformed the prognosis of complement-related/atypical HUS,[6,7] achieving resolution of TMA events in 88% of and an improvement of glomerular filtration rate of 15 mL/min in 53% with a cessation of dialysis in most cases.[7] Eculizumab has also been used successfully in cases of HUS associated with the catastrophic antiphospholipid syndrome,[8] Anti Neutrophil Cytoplasmic Antibody vasculitis,[9] antibody-mediated rejection,[10] and to some extent in shiga toxin-producing *Escherichia coli* (STEC)-HUS,[11] in which unregulated activation of the complement pathway has been documented.[6] So far, however, the efficacy of eculizumab in the specific context of HIV-associated HUS has not been assessed. Recent pediatric guidelines[12] recommend that eculizumab be started within the first 24 to 48 hours in complement-related HUS, except when there is a coexisting disease such as HIV. HIV infection was considered as an exclusion criterion in prospective studies of complement-related HUS treated with eculizumab.[7,13] As a consequence, data about the outcome of HIV-associated HUS treated with eculizumab are scarce.[14]

We report an exceptional case of HIV-associated HUS in an adult Caucasian woman treated successfully with eculizumab and HAART. This patient gave written informed consent.

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MF and CG contributed equally to the article.

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[a] Service de Néphrologie, Pôle REUNNIRH, CHU Clermont-Ferrand, Clermont-Ferrand, [b] Centre de Référence des Microangiopathies Thrombotiques, Paris, [c] Service d'anatomopathologie, CHU Clermont-Ferrand, Clermont-Ferrand, [d] Service d'Hématologie, Hôpital Saint-Antoine, CHU Paris Est, AP-HP, [e] Université Pierre et Marie Curie UPMC, Paris, [f] Service de Réanimation, Pôle REUNNIRH, CHU Clermont-Ferrand, Clermont-Ferrand, France.

[*] Correspondence: Cyril Garrouste, Nephrology, Dialysis and Transplantation Department, Clermont-Ferrand University Hospital, CHU Gabriel Montpied, 58 Rue Montalembert, 63003 Clermont-Ferrand, France (e-mail: cgarrouste@chu-clermontferrand.fr).

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2. Case report

2.1. Clinical history and initial laboratory data

In February 2016, a 52-year-old woman with acute renal failure, thrombocytopenia, anemia, and hypoxemia was admitted to the intensive care unit (ICU). She had been diagnosed with HIV infection in 1997 and started on zidovudine and lamivudine. The antiviral treatment was discontinued in 2010. At ICU admission, she had normothermia, high blood pressure (180/110 mm Hg), and jaundice. Laboratory findings showed: microangiopathic hemolytic anemia (hemoglobin 7.6 g/dL, reference range 13.0–18.0 g/dL), hemolysis (haptoglobin <0.08 g/dL, reference range 0.6–1.6 g/dL; lactate deshydrogenase (LDH) 1039 IU/L, reference range 87–241 IU/L), and numerous schistocytes on blood smear; thrombocytopenia (75,000 platelets/μL, reference range 150,000–450,000/μL); and acute renal failure requiring renal replacement therapy (serum creatinine 430 μmol/L, reference range 59–104 μmol/L) with microscopic hematuria (21×10^3/μL) and nephrotic range proteinuria (4.0 g/g) consistent with probable glomerular injury. Bone marrow aspiration was consistent with peripheral thrombocytopenia. Exploration of the complement system showed activation of the alternative pathway with C3 depletion (543 mg/L, reference range 660–1250 mg/L), normal C4 (332 mg/mL, reference range 93–280 mg/mL), low plasma levels of factor B (72 mg/L, reference range 90–320 mg/mL), and normal antigenic factor H (CFH; 77%, reference range 65–140%). Anti-CFH antibodies were negative. Complement component 5b (C5b)9 plasma level was mildly elevated: 428 ng/mL, reference range <420 ng/mL. ADAMTS13 activity was 58%. Serum HIV viral load was 227,848 copies/mL, and CD4-lymphocyte count was 120 cells/μL. Stool study was negative for Shiga toxins. Detection of serum cytomegalovirus (CMV) viremia by polymerase chain reaction was negative. Bronchoalveolar lavage confirmed the diagnosis of *Pneumocystis jirovecii*. Treatment by antiretroviral therapy was initiated on day 3: raltegravir 800 mg daily, abacavir 300 mg daily, and lamivudine 25 mg daily associated with atovaquone and steroids (1 mg/kg/d).

2.2. Kidney biopsy

Kidney biopsy was performed on day 2. The renal cortical tissue sample measured 0.7 cm and contained 12 glomeruli, none of which were sclerotic. Mesangial regions were expanded. The glomerular basement membranes were thickened with some "double contours." The endothelial cells were swollen with narrowing of capillary loops. In some glomeruli we observed intracapillary fibrinous thrombi, and capillary lumens were dilated with microaneurysm formation. In vascular section we observed a thrombus in an arteriole. Immunofluorescence studies performed on frozen sections showed mild parietal and mesangial deposits of C3 and Immunoglobulin M, and intense glomerular and arterial deposits of C5b9. No genetic analysis was available. These histopathological results, along with normal ADAMTS13 activity, were consistent with the diagnosis of HUS.

2.3. Clinical follow-up

Daily plasma exchange (PE) with fresh frozen plasma (60 mL/kg) was initiated on day 0 (Fig. 1). On day 10, the platelet count was 250,000/μL with no hemolysis and so PE was discontinued. Infusion of eculizumab at a weekly dose of 900 mg was performed from day 11. On day 18, hemolysis recurred (hemoglobin 7.3 g/dL, LDH 327 IU/L, haptoglobin 0.08 g/dL, platelets 133,000/μL), which was consistent with an exacerbation of the disease. After the third infusion of eculizumab, the platelet count increased to 234,000/μL and LDH decreased to 300 IU/L. Hemodialysis was discontinued at month 3 (Fig. 1).

At month 4, HIV viral load was undetectable, CD4 T-cell count was 238/μL cells/μL, hemoglobin 11.6 g/dL, platelet count 270,000/μL, serum creatinine 168 μmol/L, proteinuria 3.3 g/g, and haptoglobin 1.79 g/L. Complement hemolytic 50 was low (<10%), consistent with an efficient complement blockade by eculizumab. Eculizumab was discontinued at month 7 after a 16th infusion. There was no recurrence during the 12-month follow-up (Fig. 1). At month 17, the patient had complete remission of HUS. She had stable chronic kidney disease with a

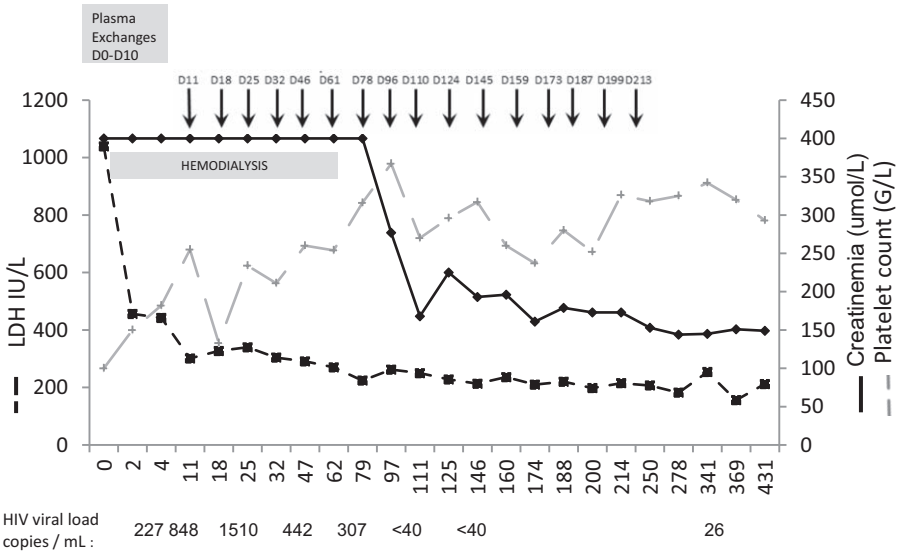

Figure 1. Biological course and treatment of an adult patient with HIV-associated HUS. HUS = hemolytic uremic syndrome. HIV = human immunodeficiency virus.

glomerular filtration rate estimated at 34 mL/min/1.73 m^2 (Modification of Diet in Renal Disease formula; Fig. 1).

3. Discussion

We report an original observation of HIV-associated HUS successfully treated with eculizumab. We ruled out other causes of HUS[6,12]: the patient had received no previous drugs and had no history of cancer, autoimmune disease, or infectious diseases such as STEC-related infection, John Cunningham virus, *Streptococcus pneumoniae*, influenza A, and CMV. There is only 1 documented case report[14] involving eculizumab treatment of HIV-associated TMA. This patient had a long history of HIV with HAART discontinuation. HUS was responsible for acute renal failure requiring renal replacement therapy.[14] Plasma exchange and reintroduction of HIV therapy were unsuccessful. Treatment with eculizumab achieved dramatic improvement in clinical and biological features and withdrawal of renal replacement therapy after 2 months.[14] The role of the complement system in HIV-associated HUS still remains unclear. In African patients with sepsis, complement activation was more pronounced in HIV-positive patients than in HIV-negative patients, mainly via the classical pathway.[15] In our patient, elevated serum membrane attack complex C5b-9 and anti-C5b-9 antibodies colocalized with arteriolar microangiopathic lesions on kidney biopsy, suggesting a role for the complement system in the occurrence of HUS. However, we could not search for gene mutations of the alternative complement pathway in our patient. Local complement activation on endothelial cells plays a pathogenic role in atypical HUS[16] and probably in HUS associated with an activation of the classical pathway.[17] C5b-9 deposits were prevented by the anti-C5 antibody eculizumab. The disappearance of these deposits and normalization of soluble C5b-9 levels are sensitive means of monitoring drug efficacy.[12,18]

The optimal duration for eculizumab therapy in atypical HUS[19] has yet to be established, and the relapse rate after eculizumab discontinuation can reach 25%.[20] We empirically decided to stop treatment in our patient at month 9 after a 17-month follow-up without relapse. In the observation cited above, the patient was still receiving eculizumab at last follow-up.[14]

The use of eculizumab in HIV patients is associated with good safety.[14] We observed only a *Staphylococcus aureus* catheter-related infection on day 80, successfully treated with vancomycin. Importantly, however, complement blockage can worsen the immune deficiency resulting from HIV infection and expose patients to serious adverse events. Complement blocking strategies should therefore be used cautiously in the setting of HIV infection, and careful long-term follow-up is needed to gain experience in the use of eculizumab in this clinical context.

In summary, treatment comprising eculizumab and HAART therapy can be beneficial in patients with HIV-associated HUS and evidence of complement pathway activation. Cessation of eculizumab can be considered when prolonged negative serum HIV viral load is observed and when there is evidence of sustained clearing of TMA. Further experience is needed in the use of complement blockers in HIV-associated atypical HUS.

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