Clinical Kidney Journal

ckj

OXFORD

Leading European Nephrology

Clinical Kidney Journal, 2016, vol. 9, no. 4, 576–579

doi: 10.1093/ckj/sfw035
Advance Access Publication Date: 17 May 2016
Exceptional Case

EXCEPTIONAL CASE

Thrombotic microangiopathy and human immunodeficiency virus in the era of eculizumab

Anna Jin[1,2], Laleh Boroujerdi-Rad[1,2], Gaurang Shah[1,2] and Joline L.T. Chen[1,2]

[1]Division of Nephrology and Hypertension, Department of Medicine, University of California Irvine, Orange, CA, USA and [2]Nephrology Section, Department of Medicine, Long Beach Veteran Affairs Health System, Long Beach, CA, USA

Correspondence and offprint requests to: Joline L.T. Chen; E-mail: joline.chen@va.gov

Abstract

Thrombotic microangiopathies (TMAs) include thrombotic thromobocytopenic purpura and hemolytic uremic syndrome (HUS). Among these conditions, atypical HUS is now recognized to be a disease of alternative complement pathway dysregulation. Eculizumab is a recombinant humanized monoclonal antibody that binds to the complement protein C5 and prevents the cleavage of C5 to C5a and C5b. Eculizumab has been used as a novel treatment for complement-mediated TMA. We present a case of a patient with human immunodeficiency virus infection who developed TMA and was successfully treated with eculizumab. The effect of long-term treatment with this new medication is unknown, and further studies are needed to establish guidelines in the management of this condition.

Key words: complement, HIV, intensive care, plasma exchange, thrombotic microangiopathy

Introduction

Thrombotic microangiopathy (TMA) is a clinical syndrome that can present as thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS) [1]. In TMA, platelet microthrombi or the presence of fibrin results in the consumption and disruption of platelets and red blood cells (RBCs) in the microvasculature [1]. TTP is historically characterized by the pentad of fever, microangiopathic hemolytic anemia, thrombocytopenia, acute kidney injury (AKI) and neurologic deficits [1], whereas HUS is a clinical triad composed of hemolytic anemia, thrombocytopenia and AKI. The renal manifestations are predominant in HUS, while the neurologic derangements are predominant in TTP [2]. The most commonly accepted nomenclature in the contemporary literature defines TMAs to include both TTP and HUS (typical and atypical forms) [3]. TTP is now known to be associated with an acquired or congenital deficiency in the von Willebrand factor (vWF)-cleaving protease, known as ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), leading to microvascular thrombosis [3]. Atypical HUS (aHUS) is a term reserved for patients with dysregulation of the alternative complement pathway.

Most recently, an international consensus was published to further clarify the nomenclature of HUS [4]. HUS is classified based on etiology—autoimmune, hereditary, post-infectious, coexisting conditions or unexplained HUS. An example of autoimmune HUS is anti-complement factor H antibodies. Hereditary HUS includes cobalamin C defect, diacylglycerol kinase ε mutation and alternative complement pathway dysregulation. Common mutations found in the alternative complement pathway dysregulation include thrombomodulin, membrane cofactor protein, C3 and complement factors B, H or I. Therefore, the term complement-mediated TMA has also recently emerged and is often used interchangeably with aHUS [5]. Post-infectious HUS includes H1N1 influenza, *Streptococcus pneumoniae* as well as Shiga toxin and *Shigella*, which are referred to as ST-HUS.

Received: October 28, 2015. **Accepted:** March 31, 2016

Medical diseases that are known to be associated with HUS include bone marrow or solid organ transplantation, malignancy, systemic lupus erythromatosus and human immune virus (HIV) infection.

With the advent of the complement inhibitor, eculizumab, the only agent approved for treatment of aHUS, the spectrum of treatment has expanded and there is a notable improvement in mortality and outcome [6]. We present a case of a patient with TMA associated with HIV infection that is successfully treated with eculizumab. To our knowledge, this is the first report of its kind.

Case report

A 59-year-old African-American man with long-standing history of HIV and normal kidney function was transferred to our hospital from an outside emergency room with abdominal pain and confusion. The patient had no family history of kidney disease. Risk factors for HIV included multiple heterosexual partners and a distant history of blood transfusion. The patient had been treated with highly active antiretroviral therapy (HAART) since 1997, although recent compliance was in question. There was no history of diarrhea, over the counter drugs, herbal medications or illicit drug use.

En route to our hospital, the patient had his first episode of generalized seizure. Vital signs upon arrival were as follows: temperature 37.1°C, heart rate 80 beats per minute, respiratory rate 20 per minute and blood pressure 164/92 mmHg. The patient was initially awake and coherent, but lethargic. Cardiopulmonary exam was normal. Abdomen was soft but mildly tender on palpation. No lower extremity edema or skin rash was observed. There were no focal neurological deficits except for slurred speech. The remainder of the exam was unremarkable.

Initial laboratory data, summarized in Table 1, was notable for a serum creatinine level of 141.4 μmol/L (1.6 mg/dL), profound thrombocytopenia and unknown values for serum potassium level, serum lactate dehydrogenase level and liver function panel due to hemolysis. The peripheral smear was noted for many schistocytes. The patient's CD4 count was 73 cells/μL, and serum HIV viral load was 448 copies/mL. Urinalysis showed 2+ protein, a large amount of blood, 11 RBCs/high power field (HPF) and 4 white blood cells/HPF. The urine sediment was notable for dysmorphic RBCs, but no casts were seen. A stool study was negative for *Salmonella*, *Shigella* and Shiga toxins 1 and 2.

The patient's clinical condition rapidly deteriorated with altered mental status and respiratory failure requiring intubation on hospital day 3. TTP was the initial diagnosis given the findings of thrombocytopenia, AKI, neurologic changes with seizures and hemolytic anemia. The patient received daily plasmapheresis for presumed TTP. The kidney function continued to worsen, and the patient was anuric by hospital day 9, requiring initiation of hemodialysis treatment. Over the following 2 weeks, the patient continued to have seizures despite anticonvulsant therapy and required daily platelet and/or packed RBC transfusions.

The result of the ADAMTS13 assay obtained prior to plasmapheresis initiation was reported to be normal at 72%; thus, the working diagnosis shifted to HUS. Plasmapheresis was discontinued, and eculizumab 900 mg every week was initiated. By the third eculizumab infusion, platelets improved to 60–90 × 10^9/L. At the time of the fourth treatment, the platelets had normalized to 200 × 10^9/L. By the sixth treatment, the hemoglobin stabilized around 6.2 mmol/L (10 g/dL). The kidney function gradually improved, and the patient no longer required hemodialysis after 2 months. His mental status improved gradually, and he remained seizure-free. The patient was weaned off ventilator support after 2 months.

Subsequently, our patient underwent genetic testing (performed by Machaon Diagnostics, Oakland, CA, USA) using a database of over 230 aHUS-associated mutations, disease-associated polymorphisms and benign polymorphisms, which did not reveal any relevant mutation for aHUS (Table 2). The patient was heterozygous for CFHR1–CFHR3 deletion; however, only the homozygous deletion has been shown to be associated with a HUS [7]. A test for anti-factor H autoantibody was negative.

Table 1. Laboratory data

Variable	Reference range	2–3 Months prior to admission	Admission to our hospital	Day 1	Day 8	Approximately 6 months after admission
Sodium (mmol/L)	135–145	138	142	142	146	138
Potassium (mmol/L)	3.5–5	3.1	Hemolyzed	Hemolyzed	4.2	3.6
Chloride (mmol/L)	95–105	103	109	112	100	108
Carbon dioxide (mmol/L)	24–32	24	23	22	32	21
Glucose (mmol/L)	3.9–6.1	5.6	7.1	7.5	13.7	4.8
Urea nitrogen, serum (mmol/L)	2.9–8.9	4.6	4.3	3.9	21.4	3.6
Creatinine (μmol/L)	70–120	97.2	141.4	132.6	724.9	123.8
Estimated glomerular filtration rate* (mL/min)	>60	86.5	55.8	59.3	Not applicable	62.5
Direct bilirubin (μmol/L)	0–7		Hemolyzed	Hemolyzed		1.7
Total bilirubin (μmol/L)	0–17		Hemolyzed	Hemolyzed		10.3
White cell count (10^9/L)	3.53–11.44	6.3	3.2	3.3	7.1	5.22
Hemoglobin (mmol/L)	8.1–11.2	9.5	7.9	7.7	4.6	7.3
Hematocrit	0.36–0.54	0.45	0.37	0.38	0.22	0.35
Platelet (×10^9/L)	126–383	206	64	46	43	184
Lactate dehydrogenase (U/L)	100–225			Hemolyzed	435	
Fibrinogen (g/L)	2.69–5.89			4.53		
Haptoglobin (g/L)	0.43–2.12			Hemolyzed	<0.26	
CD4 (cells/μL)	401–1153	781	73			561
HIV viral load (copies/mL)	0	<20	448			0

*eGFR calculated based on the Modification of Diet in Renal Disease (MDRD) formula.

Table 2. Genetic test results

Genetic test	Result
CFH gene NGS	Variant likely benign
MCP (*CD46*) gene NGS	Variant likely benign
CF1 gene NGS	No mutation
C3 gene NGS	No mutation
CFB gene NGS	No mutation
CFHR1 gene NGS	Mutation detected
CFHR3 gene NGS	Mutation detected
CFHR4 gene NGS	No mutation
CFHR5 gene NGS	No mutation
THBD gene NGS	No mutation
PLG gene NGS	No mutation
DGKE gene NGS	No mutation
CFH gene mutation	Homozygous-p.Val62Ile; heterozygous-p.His402Tyr
MCP (*CD46*) gene mutation	Heterozygous polymorphism-78 G.A
CF1 gene mutation	Negative
C3 gene mutation	Negative
CFB gene mutation	Negative
CFHR1 gene mutation	Heterozygous deletion
CFHR3 gene mutation	Heterozygous deletion
CFHR4 gene mutation	Negative
CFHR5 gene mutation	Negative
THBD gene mutation	Negative
PLG gene mutation	Negative
DGKE gene mutation	Negative

NGS, next generation sequencing.

Discussion and literature review

Based on the clinical history and relevant tests, we concluded that our patient had TMA associated with HIV disease. Re-initiation of HIV therapy and plasma exchange did not improve this patient's clinical condition. However, he had a dramatic response in clinical and hematologic parameters only after initiation of a complement blockade therapy. The complement system comprises a large network of proteins responsible for the body's defense against pathogens and maintenance of homeostasis. Altered regulation in this intricate pathway can result in disease. There are three pathways in the cascade: the classical, lectin and alternative pathways, and all ultimately lead to the production of C3. The C3 protein is spontaneously activated, and through the cleavage and binding of various proteins, results in the formation of the membrane attack complex (MAC) responsible for lysing microbes [8]. Mutations in the alternative pathway regulatory proteins, complement factor H, membrane cofactor protein, factor I, and thrombomodulin, C3 convertase proteins, C3 and factor B, have been found to play a significant role in the pathogenesis of complement-mediated TMA [9]. Alterations in these regulatory proteins can result in cell damage and chronic inflammation, while overactivation would subsequently lead to endothelial damage [10]. Exposure of the MAC to the endothelium is thought to trigger vWF secretion, resulting in platelet activation and aggregation, leading to a prothrombotic state, causing thrombus formation, endothelial cell detachment, inflammation and arteriolar occlusion [11].

With the discovery of the ADAMTS13 cleaving protease, the understanding of TMA has advanced significantly [12]. In the past, it was difficult to distinguish TTP from HUS based on clinical presentations only. Now, TTP and HUS are considered distinct entities based on their disease mechanism. TTP, now known as ADAMTS13 deficiency, is defined as <10% of the normal level and can occur as a result of circulating anti-ADAMTS13 autoantibodies or due to genetic mutations [4, 13].

The association between HIV and TMAs has been documented as far back as 1984 [14]. A systematic review by Benjamin *et al.* reported results from the Oklahoma TTP-HUS Registry where 351 out of 362 patients had a co-diagnosis of HIV and TTP [15]. Prior to the days of the HAART therapy, TTP was reported in 0.6–7.1% of HIV patients [16]. After the introduction of HAART, none of 347 HIV-positive patients had TTP or HUS, according to Gervasoni *et al.* [17]. Whether the HIV virus or the HAART therapy may affect ADAMTS13 activity or complement pathway regulation in HIV patients with TMA remains unclear. In a study by Gunther *et al.*, 70% (14/20) of HIV patients had severely reduced levels of ADAMT13 activity suggestive of TTP, while the remaining 30% (6/20) likely had HUS with normal ADAMTS13 activity [18]. Similar to our patient, low CD4 counts were often correlated with normal ADAMTS13 levels in their series. The variability seen in this study suggests that high viral activity and low CD4 counts may be contributing to the clinical manifestations of the TMA syndrome [18]. The exact cause for TMA in our patient is unclear, although it is possible that HIV viremia could contribute to complement pathway dysregulation, given the subsequent treatment success with a complement inhibitor.

In the past decade, with a better understanding of the mechanism underlying complement-mediated TMA, treatment options have expanded. Most recently, eculizumab has been added to the clinician's armamentarium [10]. Eculizumab is a recombinant humanized monoclonal antibody that binds to the complement protein C5, preventing the cleavage of C5 to C5a and C5b, which blocks complement-mediated endothelial injury due to formation of the MAC [19]. Nester has recently favorably reviewed the safety and efficacy of eculizumab in complement-mediated TMA [20]; however, the optimal duration for eculizumab therapy or its effectiveness in treating other TMAs remains unknown. Based on available case reports, the relapse rate of aHUS after discontinuation was 25–28% [20]. Given the high risk of relapse and severity of the initial presentation in our patient, we have continued therapy for 16 months without any adverse effects. While we suspect active HIV viremia may have a pathogenic role, it is unclear whether adequate HIV treatment alone would be preventive of future recurrences of aHUS.

Eculizumab is now considered an important treatment of complement-mediated TMA, and patients now have improved morbidity and mortality outcomes. To the best of our knowledge, this is the first report of an HIV-positive patient who has been successfully treated with eculizumab with remarkable recovery. More studies are needed to understand HIV infection and its relationship to complement-mediated TMA.

Conflict of interest statement

None declared. All authors declare that the results presented in this paper have not been published previously in whole or part, except in abstract format.

Disclaimer

A.J., G.S. and J.L.T.C are employees of the US Department of Veterans Affairs. Opinions expressed in this paper are those of the authors and do not necessarily represent the opinion or official policy of the Department of Veterans Affairs or the US Government.

References

1. Moake JL. Thrombotic microangiopathies. *N Engl J Med* 2002; 347: 589–600
2. Ruggenenti P, Noris M, Remuzzi G. Thrombotic microangiopathy, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura. *Kidney Int* 2001; 60: 831–846
3. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Eng J Med* 2014; 371: 654–666
4. Loirat C, Fakhouri F, Ariceta G *et al.* for HUS International. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol* 2016; 31: 15–39
5. Nester CM, Barbour T, de Cordoba SR *et al.* Atypical aHUS: state of the art. *Mol Immunol* 2015; 67: 31–42
6. Verhave JC, Wetzels JFM, van de Kar NCAJ. Novel aspects of atypical haemolytic uraemic syndrome and the role of eculizumab. *Nephrol Dial Transplant* 2014; 29: iv131–iv141
7. Zipfel PF, Edey M, Heinen S *et al.* Deletion of complement factor H-related genes CFHR1 and CFHR3 is associated with atypical hemolytic uremic syndrome. *PLoS Genet* 2007; 3: e41
8. Noris M, Mescia F, Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. *Nat Rev Nephrol* 2012; 8: 622–633
9. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. *Orphanet J Rare Dis* 2011; 6: 60
10. Kaplan BS, Ruebner RL, Spinale JM *et al.* Current treatment of atypical hemolytic uremic syndrome. *Intractable Rare Dis Res* 2014; 3: 34–45
11. Ståhl A, Vaziri-Sani F, Heinen S *et al.* Factor H dysfunction in patients with atypical hemolytic uremic syndrome contributes to complement deposition on platelets and their activation. *Blood* 2008; 111: 5307–5315
12. Levy GG, Nichols WC, Lian EC *et al.* Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. *Nature* 2001; 413: 488–494
13. Froehlich-Zahnd R, George JN, Vesely SK *et al.* Evidence for a role of anti-ADAMTS13 autoantibodies despite normal ADAMTS13 activity in recurrent thrombotic thrombocytopenic purpura. *Haematologica* 2012; 97: 297–303
14. Boccia RV, Gelmann EP, Baker CC *et al.* A hemolytic-uremic syndrome with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; 101: 716–717
15. Benjamin M, Terrell DR, Vesely SK *et al.* Frequency and Significance of HIV infection among patients diagnosed with thrombotic thrombocytopenic purpura. *Clin Infect Dis* 2009; 48: 1129–1137
16. Brecher ME, Hay SN, Park YA. Is it HIV TTP or HIV associated thrombotic microangiopathy? *J Clin Apher* 2008; 23: 186–190
17. Gervasoni C, Ridolofo AL, Vaccarezza M *et al.* Thromobotic microangiopathy in patients with acquired immunodeficiency syndrome before and during the era of introduction of highly active antiretroviral therapy. *Clin Infect Dis* 2002; 35: 1534–1540
18. Gunther K, Garizio D, Nesara P. ADAMTS13 activity and the presence of acquired inhibitors in human immunodeficiency virus-related thrombotic thrombocytopenic purpura. *Transfusion* 2007; 47: 1710–1716
19. Keating G. Eculizumab: a review of its use in atypical haemolytic uraemic syndrome. *Drugs* 2013; 73: 2053–2066
20. Nester C. Managing atypical hemolytic syndrome: chapter 2. *Kidney Int* 2015; 87: 882–884