Thrombotic microangiopathy and human immunodeficiency virus in the era of eculizumab

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Abstract

Thrombotic microangiopathies (TMAs) include thrombotic thrombocytopenic 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.
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 had been treated with antiretroviral therapy (HAART) since 1997, although recent compliance was in question. There had been treated with antiretroviral therapy (HAART) since 1997, although recent compliance was in question. There had been treated with antiretroviral therapy (HAART) since 1997, although recent compliance was in question. The patient had no family history of kidney disease.

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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 was no history of diarrhea, over the counter drugs, herbal medications or illicit drug use.

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 (10³/µL)       | 3.5–11.44       | 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 (×10³/µL)              | 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.
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 ADAMTS13 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.

**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].

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                   |
| CFIh1 gene NGS   | Mutation detected             |
| CFIh3 gene NGS   | Mutation detected             |
| CFIh4 gene NGS   | No mutation                   |
| CFIh5 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                      |
| CFIh1 gene mutation | Heterozygous deletion    |
| CFIh3 gene mutation | Heterozygous deletion    |
| CFIh4 gene mutation | Negative                    |
| CFIh5 gene mutation | Negative                    |
| THBD gene mutation | Negative                    |
| PLG gene mutation | Negative                      |
| DGKE gene mutation | Negative                    |

NGS, next generation sequencing.
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