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Case Report

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Influenza A H1N1 Triggering Complement-Mediated Hemolytic Uremic Syndrome

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Abstract

Complement-mediated hemolytic uremic syndrome (CM-HUS) is a condition characterized by hemolytic anemia, thrombocytopenia, and renal impairment, typically associated with a chronic dysregulation of the complement system. Few adult cases of CM-HUS triggered by influenza infection have been described. Here we present a case of a 56-year-old female with multiple myeloma receiving cancer treatment who presented with Influenza A H1N1-associated CM-HUS. She was treated with anti-complement therapy and at her 1-month follow-up had complete resolution of renal dysfunction and hemolytic anemia. This case highlights influenza infection as a trigger for CM-HUS in an immunocompromised adult and the role of anti-complement therapies.

Keywords: CM-HUS; Atypical HUS; Influenza

Introduction

Complement-mediated hemolytic uremic syndrome (CM-HUS) also known as "atypical HUS" - a term initially coined to distinguish any HUS not preceded by a diarrheal infection - is associated with a genetic, acquired, or both, dysregulation of the complement system leading to endothelial damage, platelet and leukocyte activation and systemic thrombotic microangiopathy (TMA) [1]. CM-HUS is a subtype of TMA, and a diagnosis of exclusion, established after ruling out other causes of TMA such as Shiga toxin-producing *Escherichia coli* (*E. coli*) infection and severe ADAMTS13 deficiency. Unlike other TMAs, the underlying mechanism in CM-HUS is dysregulation of the complement system [2]. Complications of this complement dysregulation include extrarenal (e.g., neurologic, cardiovascular, and pulmonary) organ damage and acute kidney injury with progression to end-stage renal disease (ESRD) [3]. Though traditionally thought to be a disease of children, the incidence of CM-HUS during adulthood appears to be similar to that in children [3]. Historically, plasma exchange has been the main modality of treatment, with a CM-HUS related mortality up to 25% and ESRD incidence of 50% [4]. With the advent of complement inhibitors, such as eculizumab, significant improvements in renal function rates have been observed with complete renal recovery in up to 52.3% of patients [4].

CM-HUS can be triggered by a heterogeneous group of etiologies: infections, drugs, autoimmune conditions, transplant, pregnancy, and metabolic conditions [5]. Influenza A, particularly the H1N1 subtype, as well as influenza B have been documented as potential triggers for CM-HUS [6-8]. While most cases of influenza-related HUS (iHUS) are reported in children, this case outlines an immunocompromised adult who developed iHUS [6-8]. The mechanisms by which influenza virus triggers CM-HUS are not fully understood; however, some putative mechanisms have been proposed, ranging from endothelial damage leading to platelet adhesion, to direct effect on platelet aggregation and thrombin generation [6]. Additionally, there is evidence suggesting that iHUS may be directly mediated through neuraminidase (NA), expressed on the viral membrane, sialidase activity, allowing for exit of the virus from the cell, and causing direct viral-mediated complement system activation and dysregulation [7]. In addition, aberrations of genes involved in the coagulation and fibrinolytic systems have been linked with CM-HUS. These include *THBD* (thrombomodulin), *DGKE* (diacylglycerol kinase-epsilon), *VWF* (von Willebrand factor), factor XII, and *PLG* (plasminogen) [6, 8]. The presence of both complement dysfunction and influenza viral particle mediated activation of the coagulation cascade are thought to be the triggers for iHUS. Herein, we present the case of a 56-year-old female with multiple myeloma (MM) receiving cancer treatment, who presented with influenza A H1N1-associated CM-HUS.

Case Report

History

A 56-year-old female presented to the emergency department after 4 days of progressive malaise, body aches, cough, back pain, fever, epistaxis and dark cola colored urine. Three weeks prior to the presentation, she completed treatment for a mild coronavi-

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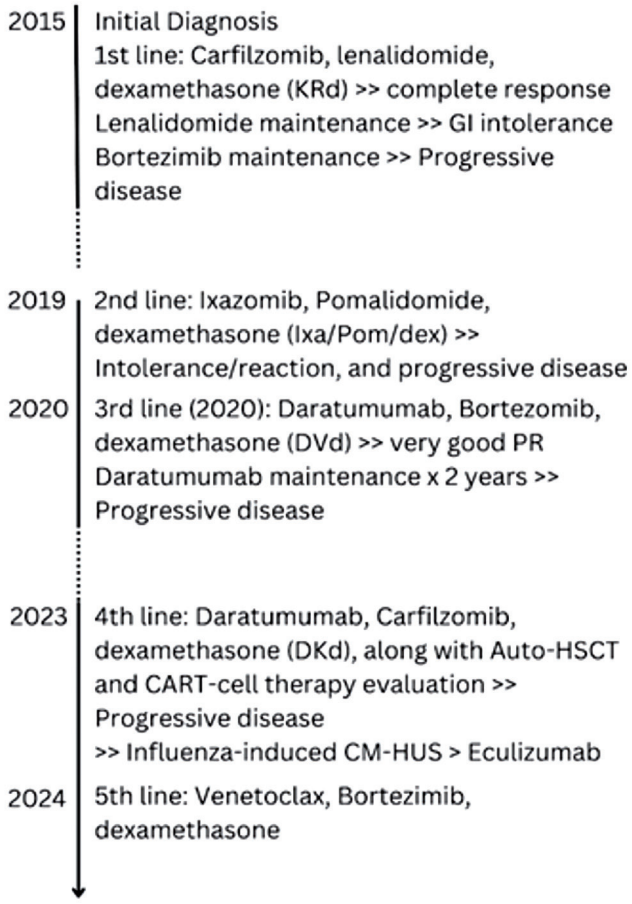

Figure 1. Patient's oncologic treatment timeline. CM-HUS: complement-mediated hemolytic uremic syndrome; PR: partial response; GI: gastrointestinal; auto-HSCT: autologous hematopoietic stem cell transplantation; CAR-T: chimeric antigen receptor T-cell therapy.

rus disease 2019 (COVID-19) infection with molnupiravir with resolution of her symptoms. In the week prior to the presentation she had attended a local family event, after which multiple people were feeling sick. Six days prior to presentation, she received her 11th cycle of carfilzomib and daratumumab for maintenance therapy for MM. The timeline of her oncologic treatment for MM is detailed in Figure 1. She did not smoke, drink alcohol, or use recreational drugs. She had not recently traveled, started any new medications or supplements, or received insect bites, surgery, or trauma. She was up to date with recommended cancer screenings. She worked at a meat-packing facility and was not aware of anyone else being sick at the facility.

Physical exam

On presentation, her vital signs were as follows: oral temperature 38.1 °C, blood pressure 184/109 mm Hg, heart rate 100/min, and respiratory rate 19/min. On examination she was alert and oriented, had nasal congestion, rhonchi were heard on auscultation of both lungs. There was no scleral icterus, petechiae, purpura, or abdominal tenderness.

Investigations

Laboratory tests showed a hemoglobin of 9.9 g/dL (reference range 11.2 - 14.9 g/dL), platelets 7 × 10^9/L, (reference range 168 - 382 ×10^9/L), creatinine 1.63 mg/dL (reference range 0.44 - 1.03 mg/dL), aspartate aminotransferase (AST) 396 IU/L (reference range 10 - 42 IU/L), alanine aminotransferase (ALT) 165 IU/L (reference range 6 - 45 IU/L), total bilirubin 1.3 mg/dL (reference range 0.2 - 1.3 mg/dL), direct bilirubin 0.1 mg/dL (reference range 0.0 - 0.03 mg/dL), D-dimer 507 ng/mL (reference range 0 - 80 ng/mL), haptoglobin 53 mg/dL (reference range 35 - 250 mg/dL), lactate dehydrogenase (LDH) 1,898 IU/L (reference range 100 - 220 IU/L), reticulocyte percentage 1% (reference range 0.9-2.7%), fibrinogen 247 mg/dL (reference range 150 - 480 mg/dL), prothrombin time (PT) of 11.6 s (reference range 10 - 13 s), activated partial thromboplastin time (aPTT) of 29.0 s (reference range 24 - 32 s), serum complement C3 level 98 mg/dL (reference range 83 - 193 mg/dL), serum complement C4 level 22 mg/dL (reference range 15 - 57 mg/dL), and a negative direct Coombs test. Urinalysis was notable for dark red urine with 20 red blood cells (RBCs) (reference range 0 - 5 per high power field). Human immunodeficiency virus (HIV), antiphospholipid, and antinuclear antibody tests were negative. The chest X-ray was largely unremarkable, and an abdominal ultrasound showed increased kidney echogenicity suggestive of medical renal disease. The peripheral smear was consistent with the laboratory values, multiple fragmented RBCs and schistocytes were identified, suggestive of intravascular hemolysis. Testing for viral respiratory pathogens via polymerase chain reaction (PCR) was positive for influenza A H1N1 virus. Given the concern for thrombotic microangiopathy (TMA) such as thrombotic thrombocytopenic purpura (TTP), an ADAMTS13 level was immediately dispatched. While in the emergency department, the ADAMTS13 activity resulted normal at 104%, therefore ruling out TTP (reference range 80-132%; a level ≤ 10% is considered diagnostic of TTP).

Treatment

She was admitted to the medical intensive care unit for supportive care and monitoring, intravenous hydration, with the impression of severe influenza A infection. Broad-spectrum antibiotics for a possible superimposed community acquired pneumonia were initiated. By the second day of admission, her hemoglobin trended down to 5.6 g/dL, platelet count dropped to 5 × 10^9/L, and creatinine level rose to 3.47 mg/dL. Two units of packed RBCs were administered. Despite worsening kidney function, the patient did not develop metabolic abnormalities or oliguria requiring renal replacement therapy (RRT). Given the progressive laboratory deterioration on day 2, oseltamivir was started for the impression of progressive complications from severe influenza infection considering her immunocompromised status. On day 3 of admission, due to lack of clinical or laboratory improvement, a decision was made to start eculizumab at a dose of 900 mg weekly for a strong clinical suspicion for CM-HUS, which was further supported by

Table 1. Etiologies of Complement-Mediated Thrombotic Microangiopathies

Etiology	Mechanism
Genetic mutations in complement regulators: (e.g., *CFH*, *CFI*, *MCP*/*CD46*, *C3*, *CFB*)	Lead to loss of control over the alternative complement pathway, resulting in excessive complement activation, endothelial injury, and microvascular thrombosis
Acquired autoantibodies (e.g., anti-factor H)	Autoantibodies inhibit function of complement regulatory proteins, causing unrestrained complement activation and endothelial damage
Pregnancy	Increased complement activation triggering disease
Infections (e.g., influenza, HIV)	Trigger for complement overactivation
Surgery or trauma	Systemic inflammation and complement activation
Certain medications (e.g., calcineurin inhibitors)	Drug-induced endothelial injury
Transplantation	Immunological stress and complement activation

HIV: human immunodeficiency virus.

the exclusion of alternative etiologies for her TMA, including TTP and other infectious etiologies. Prior to eculizumab, she was given meningococcal vaccines and started on penicillin V 500 mg once daily (for a 5-day course). Renal biopsy was deferred given the high risk of bleeding in view of her severe thrombocytopenia.

Follow-up and outcomes

Gradually over the course of days 4 and 5 of admission, her platelet counts increased to 17 × 10^9/L. Upon discharge on day 7 of admission, her hemoglobin had stabilized at around 8 g/dL, platelet count had increased to 126 × 10^9/L, creatinine level had started to trend down, and fragmented red cells were no longer identified on the peripheral blood smear. She received three additional 900 mg weekly doses of eculizumab in the outpatient hematology clinic and was subsequently placed on maintenance eculizumab therapy at a dose of 1.2 g every other week. At the 1-month follow-up, her blood pressure and renal function had completely normalized, and the hemolysis markers were within normal range. After hospital discharge the MM treatment was held until resolution of cytopenias and renal dysfunction, her therapy was then switched to the combination of venetoclax, bortezomib, and dexamethasone given documented disease progression on therapy with carfilzomib and daratumumab. She returned to work 2 months after hospital admission once her energy returned to baseline. She continues to be followed in the hematology clinic, has completed 6 months of biweekly eculizumab therapy, and has not had CM-HUS recurrence after 8 months of follow-up since her iHUS diagnosis.

Discussion

HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Case reports during the H1N1 pandemic described influenza infection being associated with CM-HUS; however, this was largely observed in pediatric cases. Our case describes influenza A as a trigger for HUS in an immunocompromised adult patient. The diagnosis of CM-HUS was supported by the classical triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute kidney injury, along with evidence of complement dysregulation indicated by low-normal levels of complement proteins. The recognition of this etiology in immunocompromised adult patients and the early identification of iHUS is of utmost importance, as the use of complement inhibitor therapies can lead to faster recovery and prevent long-term kidney damage and other complications, as demonstrated in this case [9].

Diagnosing CM-HUS is challenging because its presentation overlaps with other thrombotic microangiopathies, requiring careful exclusion of conditions like TTP. Current diagnostic criteria emphasize ruling out these other causes (Table 1), then supporting the diagnosis with evidence of complement dysregulation through laboratory and genetic testing, though such findings are not always present or definitive [1, 8, 10]. Typical cases of iHUS present with acute kidney injury with proteinuria; MAHA with elevated LDH, presence of schistocytes, thrombocytopenia, negative Coombs testing; evidence of fibrinolysis with elevated D-dimer and low fibrinogen levels; normal to low C3 and C4 complement levels; and often a genetic complement mutation or acquired deficiency due to autoantibodies [6]. Acute kidney injury is seen in all case reports of iHUS, with up to 40% of them requiring RRT [6]. In the presence of classic clinical and laboratory features, a kidney biopsy is not necessary to make a diagnosis of CM-HUS; however, it may be necessary in cases of renal-limited TMA or to rule out other etiologies of kidney failure. Our patient did not undergo kidney biopsy given her clinical picture and the risk of bleeding from severe thrombocytopenia. Anti-complement therapies have revolutionized the management of CM-HUS and reduced its associated morbidity and mortality [4]. The expected course of thrombocytopenia includes a *nadir* platelet level between 5 and 80 × 10^9 /L with an expected recovery after a median of 9.5 days, which was concordant with our patient [6]. Her platelet *nadir* of 7 × 10^9/L and her renal function started recovering within days of eculizumab initiation.

Patients with CM-HUS have an underlying complement dysfunction due to autoantibodies or underlying genetic predisposition - either a loss of function or gain of function mutation, even while having complement levels within normal

limits [7, 8]. While genetic studies were not conducted in this patient, recent consensus guidelines recommend their use in selected patients with CM-HUS [10]. Case reports have also highlighted the utility in testing for plasma terminal complement complex sC5b-9 to measure complement activation and determine the frequency of treatment with anti-complement therapy and aid in treatment discontinuation decisions [11]. Additionally, serial serum complement antigenic levels, and factor H autoantibodies can aid in management decisions [8]. Despite the lack of further complement testing, our patient was started on eculizumab, and her blood counts and kidney function showed improvement after one dose of eculizumab, reaffirming the clinical diagnosis.

Immunization history is vaguely reported in existing literature of iHUS. Our patient had been vaccinated for influenza during the prior fall, 5 months before her presentation. At the time her immunoglobulin G levels were within normal limits; however, during the subsequent months, she continued to receive treatment for MM. It is possible that in our patient, the treatment for MM, may have inhibited an efficacious immune response to the seasonal influenza vaccine. Additionally, carfilzomib has been previously recognized as a trigger for developing CM-HUS [9]. Based on a large case series of 37 patients, carfilzomib-associated HUS typically presents at a median of 3.5 months after treatment initiation and the majority presented with an infectious trigger like influenza [12]. Our patient's aHUS onset at 12 months makes this etiology unlikely but it remains unclear whether carfilzomib in combination with the influenza infection may have played a role in our patient's complement dysregulation.

In iHUS, viral NA cleaves sialic acid residues from host cell surfaces, exposing underlying glycan structures that can trigger the alternative complement pathway [6]. This direct activation leads to uncontrolled complement system activity and endothelial injury, resulting in the microangiopathic features of HUS. Individuals with genetic mutations in complement regulatory proteins are particularly vulnerable, as the viral infection unmasks their predisposition to complement dysregulation. NA inhibitors, such as oseltamivir, are the mainstay of therapy for influenza infections. However, there is not much data regarding NA inhibitor effects on iHUS. In some reported iHUS cases, patients were given NA inhibitor therapy, and early initiation was suggested to offer possible benefit [13]. However, patients were often co-treated with complement inhibitor therapy or plasma exchange. In our case, oseltamivir initiation was delayed, and the patient's clinical picture and laboratory values continued to deteriorate with NA treatment alone, pointing towards likely no benefit of delayed NA initiation once iHUS has developed, furthermore highlighting the importance of anti-complement therapy for iHUS. The role of combining these medications or not while managing iHUS in patients who present within 48 h of influenza symptom onset may be an area of further study.

With the advent of terminal complement blockade using agents such as eculizumab - a recombinant humanized monoclonal antibody that binds complement component C5 and prevents its cleavage by the C5 convertase - and, most recently, ravulizumab, a long-acting monoclonal antibody against C5, the morbidity and mortality from CM-HUS have significantly decreased [4, 14]. Anti-complement therapies have shown to improve renal outcomes in this population, while showing a similar hematologic response to that of plasma exchange (PLEX), plasma infusions, or steroids [4]. Historically, patients treated without anti-complement therapies ultimately progressed to ESRD and required RRT or renal transplant [3]. Our patient had a rapid and sustained renal recovery shortly after treatment with eculizumab, similar to previous reports, and had no reported side effects [4, 15, 16]. Our patient's case reaffirms the role of early anti-complement therapy initiation, when available, in the management of iHUS. However, access to anti-complement therapies remains a major challenge in many developing countries and resource-limited settings, given their high cost and limited availability. Plasma exchange and immunosuppressive treatments remain the primary options in these settings despite being less effective and riskier [5, 17, 18]. Addressing these barriers through investment in diagnostic and treatment infrastructure is crucial for enabling equitable, evidence-based care for CM-HUS globally.

Conclusions

This case illustrates a rare but critical manifestation of influenza A H1N1 infection triggering CM-HUS in an immunocompromised adult. The diagnosis was supported by classic clinical and laboratory findings consistent with TMA and confirmed through exclusion of other TMAs such as TTP. Prompt initiation of eculizumab led to a rapid hematologic and renal recovery, reaffirming the pivotal role of early anti-complement therapy in managing CM-HUS. While access to terminal complement inhibitors like eculizumab has revolutionized outcomes, disparities in global access remain a major barrier, with many regions still relying on plasma exchange or immunosuppressive treatments. This case emphasizes the importance of maintaining a high index of suspicion for CM-HUS in adults with influenza infection, especially those who are immunocompromised.

Learning points

This case underscores the significance of considering CM-HUS as a potential complication of influenza A infection (iHUS), particularly in immunocompromised adults. While historically rare, this association warrants attention given its potential life-threatening consequences. The prompt recognition and initiation of anti-complement therapy played a pivotal role in the successful management and recovery of this patient. This case also highlights the importance of vigilance in the setting of viral infections, and the need for assessing immunological response to seasonal vaccines in immunocompromised patients.

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Conflict of Interest

The authors report no competing interests related to this work.

Informed Consent

Patient consent for publication was obtained.

Author Contributions

Caring for the patient: all authors. Planning: all authors. Conception and design: SM, MA and BMR. Acquisition of data: SM and MA. Interpretation: all authors. Drafting of manuscript: SM. Approve of the final manuscript: all authors.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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