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Atypical Hemolytic Uremic Syndrome, A Rare Entity: Case Report and Review of the Literature

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Abbreviations: HUS:Hemolytic Uremic Syndrome; TMAs: Thrombotic Microangiopathies; AKI: Acute Kidney Injury; FeNA: Fractionated Sodium; CNS: Central Nervous System, STEC: Shiga Toxin-Producing *Escherichia Coli*; ESKD: End-Stage Kidney Disease; MAC: Membrane Attack Complex

Introduction

Hemolytic uremic syndrome (HUS) is a rare condition which belong to a group of syndromes known as thrombotic microangiopathies (TMAs). Atypical HUS (aHUS) defines nonShiga-toxin-HUS which is defined by the triad of mechanical hemolytic anemia, thrombocytopenia and renal impairment. Atypical HUS (aHUS) is a rare disease that affects young adults and causes terminal chronic renal failure necessitating dialysis.aHUSdesignates a primary disease due to a disorder in complement alternative pathway regulation.Here in we present a case of aHUS in a previously healthy 37 year old female.

Case Presentation

A 37-year-old female with a history of recurrent *E-coli* urinary tract infections, pancreatic and kidney transplant was transferred to the hospital with complaints of fever, vomiting, abdominal pain, lethargy and altered mental status. The patient was then transferred to the ICU with suspicion of pyelonephritis and sepsis and bowel obstruction. She had a history of type 1 diabetes mellitus complicated with retinopathy, gastropathy and peripheral neuropathy. On day 1, she was febrile with a temperature of 101.5, Blood pressure was within normal limits and she was saturating at 99% in room air. She was lethargic and responded to name and painful stimulus. Examination of the systems were within normal limits. On the first day, lab results revealed a Hb count of 10.7gm/dl, a platelet count of 125000/µl, creatinine value of 0.5, and occasional schistocytes and reduced platelets on peripheral smear. CT scan of abdomen/pelvis showed diffuse wall thickening of the bladder with free fluid in the pelvis consistent with acute cystitis, edematous left transplanted kidney concerning for pyelonephritis.

Large stool burden reflecting possible fecal impaction was also noted in the imaging study. Urinalysis was positive for a yeast infection.She was treated symptomatically, and fleet enema was given, but the patient continued to vomit. Nasogastric tube was placed, and the patient was suspected for bowel obstruction was transferred to ICU for close monitoring. The patient was treated for suspected pyelonephritis and associated sepsis with ceftriaxone and fluconazole. The hemoglobin level dropped from 11.3 on Day 1 to 8.3 on Day 3; Platelet counts reduced to 32,0000/ul on day 2; she suffered Acute kidney injury (AKI) was confirmed with a fractionated sodium (FeNA) of 2.7 % and creatinine levels raised to 8.17 during this stay. Complement studies revealed a C3 level of 57 and a C4 level of 16.4. CMV and EBV was positive. Haptoglobin levels was 79.30, however LDH was elevated at 584. INR level was 1.74. Iron studies revealed; Iron -179, TIBC-213, Transferrin-152.

Kidney biopsy showed a rare glomerulus with marked capillary congestion and intraluminal thrombus, suggesting thrombotic angiopathy. Immunofluorescence studies showed linear and mesangial immunofluorescence for IgG and fibrinogen seen with thrombotic microangiopathy (TMA).The patient was

diagnosed with classical atypical HUS. Patient was transfused with platelets and eculizumab was started on fourth day. The patient's symptoms and signs steadily improved with therapy during the course of the hospital stay. The the labs stabilised. The patient was discharged with eculizumab.

Discussion

The incidence of aHUS is estimated in the USA to be 2 per million [1]. This case is a rare version of hemolytic uremic syndrome- Atypical HUS (aHUS). aHUS classically presents with thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure [2]. This patient presented with the classical characteristics described in literature where we observed dysregulation of the complement system witha low complement level.

aHUSis genetically or acquired disease which causes defective regulation of the alternative complement pathway [3]. Clinical features of aHUS are indistinguishable from other causes of TMA where TTP and HUSare distinct clinical entities, both manifesting as TMA. TMA with significant dysfunction of the central nervous system (CNS), severe thrombocytopenia, fever and non involvement of kidney is designated as TTP, while the term HUS was applied to cases with predominant renal involvement without neurological features [4,5]. Although aHUS often presents in childhood, but the initial presentation in 36% of genetically predisposed individuals was seen in adulthood [6]. aHUS is a non-post-diarrheal (D-) HUS, because the prodromal bloody diarrhea characteristic of Shiga toxin-producing Escherichia coli(STEC)i -HUS was rarely present in most of the cases that were reported . In many patients, an infection precedes the clinical triadand it is generally considered as trigger in aHUS.The prognosis of aHUS is poor compared with STEC-HUS, with a 3-year composite endpoint of death and end-stage kidney disease (ESKD) occurring in 53% (significantly worse in adults than in children) [6].

Atypical HUS (aHUS) is a multigenic complement mediated disorder. It is frequently associated with a genetic or an acquired defect which causes dysregulation of complement activation and subsequent destruction of host cells. Mutations in the following genes that encode complement proteins have been identified inmost of theaHUS cases [3,7]. The relative frequency of each affected gene for aHUS cases according to incidences include Complement factor H (CFH, 20 to 30 percent),CD46 (5 to 15 percent),Complement factor I (CFI, 4-10 percent),Complement factor 3 (C3, 2-10 percent),Complement factor B (CFB, 1-4 percent),Thrombomodulin gene (THBD, 3-5 percent). The complement proteins associated with aHUS are components of the alternative complement pathway andresults from a loss-of function mutation in a regulatory gene (CFH, CFI, or CD46) or a gain-of-function mutation in an effector gene (CFB or C3). The proposed mechanism for the development of HUS is a trigger event, such as infection or pregnancy, in a susceptible individual with a gene mutation(s) or antibodies to complement proteins, which leads to uninhibited continuous activation of the alternative pathway resulting in the formation of the membrane attack complex (MAC) and subsequentrenal endothelium damage and destruction of platelets leading to thrombotic microangiopathy[8].

Mutations of the complement factor H (CFH) gene, which encodes a regulatory protein in the alternative complement pathway, and CFH-related proteins (CFHR) are the most frequently identified genetic abnormalities seen in patients with aHUS[9,10]. Interestingly, renal survival is higher in patients with low CFH levels compared with those with normal levels of CFH. HUS associated with CD46 deficiency is characterized by onset in early childhood, a favorable renal outcome in most patients is seen. Mutations in CFI, the cofactor for CD46 and factor H, are also associated with HUS [11,12]. The prognosis of patients with HUS associated with CFI mutations is intermediate between those with HUS associated with CD46 and those with CFH mutations. Heterozygous C3 mutations resulting in persistently low C3 levels have been identified in patients with HUS [13,14]. Patients with C3 mutations typically develop severe disease, with one-half to two-thirds of patients progressing to ESRD within the first year following presentation.

Complement factor H (CFH) antibodies have been reported in approximately 8 to 10 percent of patients with atypical HUS. These antibodies interfere with the binding of CFH to the C3 convertase and are associated with a defective CFH-dependent cell protection. A study of 308 cases of atypical HUS (Newcastle cohort) reported the presence of CFH antibodies in 13 of 142 screened patients (9.2 percent) [15]. Most of these patients also had homozygous deletion of CFHR1 and/or CFHR3 genes, suggesting that this deletion has a pathogenetic role in the development of anti-CFH antibodies [16,17]. Mutations in other complement genes (CFH, complement factors I and B, CD46, and C3) also were identified in a minority of patients. These findings suggest that in some patients, multiple "hits" to the complement system may be necessary for the clinical presentation of complement-mediated HUS.

Although earlier studies suggested that HUS due to genetic mutations of the complement proteins was primarily a pediatric disorder, a French cohort of 214 patients reported that more than half of their cohort presented as adults (58 percent) [18]. In this study, genetic mutations were demonstrated in 60 percent of the patients. However, in children with complement-mediated HUS, presentation typically occurred in young patients less than two years of age. Several studies also suggest that patients younger than six months who present with HUS are more likely to have complement-mediated disease than Shiga toxin-producing E. coli (STEC)-HUS.It remains unclear what effect, if any, specific mutations have on the age of presentation. It does appear that patients with CD46 mutations (complement regulatory protein CD46) are more likely to present during childhood.In most patients (70 to 80 percent), there is an antecedent trigger event that is thought to play a role in complement activation. In most

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patients, the trigger is an upper respiratory infection, however, a diarrheal prodrome has been observed in approximately one-quarter of patients. Pregnancy has also been reported as a trigger event in adolescents and adult women.

The data on clinical presentation of aHUS are very limited. In the largest cohort of 273 patients, aHUS affected both children and adults, with onset during childhood being only slightly more frequent than in adulthood.Both children and young adults with aHUS have nonspecific symptoms likepallor, poor feeding, vomiting, fatigue, and drowsiness. Anuria or oligoanuria with or without peripheral edema may be present. Marked hypertension may also be present either from the acute kidney injury or from the ischemia caused by the TMA. Hypertension may be severe enough to provoke posterior reversible encephalopathy or cardiac failure. Half of children and the majority of adults need dialysis at admission. Extrarenal manifestations are observed in 20% of patients.

The most frequent extra renal manifestation is CNS involvement (10% of patients) with diverse presentations: irritability, drowsiness, seizures, diplopia, cortical blindness, hemiparesis or hemiplegia, stupor, and coma. Myocardial infarction due to cardiac microangiopathy has been reported in approximately 3% of patients and is presumed to be the cause of reported episodes of sudden death. Five percent of patients present with a life-threatening multiorgan failure due to diffuse TMA.Less commonly, aHUS patients have more of an insidious onset, with subclinical anemia and fluctuating thrombocytopenia for weeks or months and apparent normal renal function at diagnosis. Unusual presentations of aHUS are possible. Some patients have little or no anemia or thrombocytopenia and the only manifestation of an active TMA is hypertension and proteinuria with or without an overtly abnormal creatinine[19,20].

The variability of presenting symptoms and the inability to rule out other forms of TMA accounts for much offailure to classify patients as aHUS at presentation. The clinical context, predominant symptoms, and basic laboratory data at presentation may allow differentiation into TTP or typical HUS. The presence of a severe ADAMTS 13 deficiency allows a tentative diagnosis of TTP in some patients. The presence of a classic epidemic of bloody diarrhea or a confirmed positive Shiga toxin test will lead to the diagnosis of STEC-HUS. Not all of the remaining patients will be or should be classified as aHUS. aHUS should be considered when TTP or typical HUS seem less likely: when no other disease can be identified that would account for the signs and symptoms, and particularly when the systemic C3 complement level is low. This distinction is important, because many of the secondary TMAs will respond to treatment of the primary disease and an aHUS treatment algorithm would not need to be activated.

Making the diagnosis is challenging because screening for mutations and antibodies to complement proteins is not widely available. Screening should be considered in patients with a positive family history, previous episode of HUS, who present within the first six to twelve months of age, or who present during pregnancy or postpartum [21]. In addition, complement genotyping may be indicated in patients with HUS in whom evaluation does not identify an underlying cause and who have a poor clinical course.

As noted above, although many patients with complement-mediated HUS will have low C3 or C4 levels, normal plasma levels of C3, C4, CFB, CFH, and CFI do not exclude the diagnosis of complement-mediated HUS.

The initial management of aHUS is supportive and In addition to supportive care measures, the management of aHUS may include Plasma exchange, Eculizumab, a monoclonal antibody to C5 that blocks the terminal complement cascade. Supportive therapy include red blood cell transfusions for anemia when clinically indicated (eg, hemoglobin level in children is <6 g/dL or hematocrit <18 percent). Platelet transfusion for patients who have significant clinical bleeding or if an invasive procedure is required. Appropriate fluid and electrolyte management to maintain adequate intravascular volume and correct/avoid electrolyte abnormalities.Stopping nephrotoxic drugs or those that are implicated in the etiology of HUS.Initiation of dialysis therapy in patients with symptomatic uremia, azotemia (defined as a blood urea nitrogen >80 mg/dL [29 mmol/L]),severe fluid overload, or electrolyte abnormality that is refractory to medical therapy.

Plasma therapy is the first-line therapy for patients during the acute episode of atypical HUS. Although there are no supportive data from clinical trials, most experts in the field advocate plasma exchange (plasmapheresis) rather than plasma infusion as a means to both remove defective mutant proteins and antibodies to CFH and restore normal functioning complement proteins [22]. In addition, plasma exchange avoids the risk of volume overload and hypertension in patients with acute kidney injury.However, only approximately one-half of the patients with complement-mediated HUS will respond to plasma therapy with both renal (normal or improved renal function) and complete hematologic recovery (ie, no evidence of hemolysis and a normal platelet count).

In patients who fail to respond, but also in those who have responded to an initial treatment with plasma infusions or plasma exchange, it is recommended to switch to eculizumab. This strategy offers the best chance of complete renal recovery. However, patients who are in full remission and have normal renal function under plasma therapy without catheter complications nor plasma intolerance may remain on this therapy.

Several large case reports have demonstrated that eculizumab, a humanized monoclonal antibody to C5, is effective in the treatment of complement-mediated HUS due to genetic defects in complement proteins in native kidneys, or as rescue or preventive therapy in renal allografts. It also appears to be

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beneficial in patients with complement-mediated HUS due to autoantibodies to complement factor H (CFH).Eculizumab binds to complement protein C5, which blocks its cleavage, thereby preventing the production of the terminal complement components C5a and the membrane attack complex (MAC) C5b-9.This results in reduction of the terminal-complement activation that occurs in patients with complement-mediated HUS, thereby reducing endothelial damage and thrombosis, and subsequent renal injury.

There are now several case reports supporting its effectiveness in aHUS both before end-stage renal disease (ESRD) and after kidney transplantation. The major concern with eculizumab treatment is the risk for infection with encapsulated bacterial organisms, particularlyNeisseria meningitis, as a result of terminal complement blockade.Therefore, patients must receive meningococcal vaccination before being treated with eculizumab (and covered with appropriate antibiotics for 14 days if there is not enough time to wait for the immune response).

With the availability of eculizumab and its relative ease of administration, there is now a choice of plasma therapy or eculizumab for acute therapy. As has been proposed by Loirat et al, plasma exchange would be a reasonable first therapy, with eculizumab introduced for nonresponse to plasma or with transition to the outpatient setting, thus allowing time for successful meningococcal vaccination[23]. After the genetic studies are available, a longer-term plan for plasma therapy (ie, continuation with eculizumab or liver transplantation) can then be made based on safety, efficacy, and cost. Barriers to eculizumab use in the United States at this time include physician inexperience with aHUS and/or eculizumab, patient safety concerns, functional lack of immediate access to the drug, and cost. Since CFH, CFI, CFB, and C3 are synthesized in the liver, liver transplantation remains an appropriate option for some patients to provide a source of normal protein. There have been several liver transplantations performed in patients with aHUS.

Although the first 3 transplantation patients died, the subsequent liver transplantations (with and without simultaneous renal transplantation) after appropriate perioperative conditioning protocols have resulted in acceptable outcomes with no reported recurrences of aHUS to date. The recommendation of a liver transplantation requires consideration of the risks and benefits, including the experience of the transplantation center. If a kidney transplantation is required for the ESRD patient, a liver-kidney transplantation should be considered. Several patients with aHUS will progress to ESRD because of inadequate response to therapy or even delay in diagnosis. Other patients will present at ESRD. aHUS patients who need renal transplant require particular attention because of the high rate of recurrent disease without specific therapy in all patients except those with a mutation in MCP. There are no trials to support a required approach for renal transplantation; however, at the minimum, it has been recommended that a complete genetic investigation before transplantation be performed for known genes associated with aHUS, as well as a serologic assessment for relevant autoantibodies [24].

Patients with aHUS should undergo a renal transplant under the cover of eculizumab, and 1 or 2 sessions of preoperative plasma therapy should be considered.43 Even in patients in whom MCP is the only documented genetic mutation, another unidentified mutation in a second complement regulatory protein is possible and consideration should be given to using eculizumab, at least in the perioperative setting (especially if an abnormal C3 is present in the patient). In addition to other routine pretransplantation vaccination recommendations, meningococcal vaccine should be given to reduce the infectious risk when eculizumab therapy is used. Special attention must be given to the chronic dialysis patient, who is less likely to respond to immunization and in whom the risk for meningococcal infection may remain high after immunization.

Patients with mutations in genes for CFH, CFI, or C3 who fail to respond to plasma therapy, and/or have relapsing disease are likely to progress to ESRD. In these patients, the outcome of renal transplantation is poor because recurrence of disease occurs in 50 percent of the transplanted kidneys, and graft failure occurs in 90 percent of those with recurrent disease [25].

In contrast, limited data suggest a favorable outcome of renal transplantation in patients with mutations of CD46 or in those with disease due to antibodies to factor H, provided the autoantibodies to CFH are absent at the time of transplantation [26,27].

The variable prognosis emphasizes that all patients with HUS prior to transplantation should undergo complement genotyping to determine whether or not there is an underlying gene mutation. The above data suggest that renal transplantation alone without preventive therapy (eg, eculizumab therapy) is not an option for patients with HUS due to mutations of CFH, CFI, or C3 [28]. Patients with a low risk of recurrence do not need a preventive treatment. These include those with isolated membrane cofactor protein or DGKE mutations and patients with anti-complement factor H antibodies in whom the level of antibodies decreased to a negative level long-term.

The clinical course and outcome vary depending on the affected complement component. For example, patients with mutations of the gene for CFH have a poor prognosis as most patients with this gene defect progress to end-stage renal disease (ESRD) or death within the first year of presentation. In contrast, few patients harboring mutations that affect CD46 progress to ESRD, although relapse is common [29,30].

The data of two main cohorts of clinically documented patients: the French pediatric cohort [and the Italian cohort concerning children and adults, which included both retrospective and recent patients, but none treated by eculizumab. The overall

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mid-term prognosis of aHUS was poor, and more severe in adults than in children.

Recent progress in diagnosis (e.g. early detection of anti-CFH antibodies) and therapeutic options, including early aggressive and prolonged plasma therapy and the use of eculizumab, most probably will allow a much better outcome of the disease.

Conclusion

The progress since the last decade inunderstanding of the physiopathology and development of new therapies for aHUS has opened the way to new therapies which hopefully will prevent putting thepatients at risk for renal failureand allow a successful transplantation in the patients present on dialysis. Recent trials and clinical experience confirm the efficiency of the complement blocker eculizumab. There The challenge now is to define the best choice for each individual patient, according to the identified complement anomaly(ies) and the phase of the disease, between plasma therapy, eculizumab, liver or combined live-kidney transplantation and, in the near future, CFH concentrate or recombinant CFH.

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