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Case Report

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Treating Patients with Atypical Familial Hemolytic Uremic Syndrome (aHUS) In the Critical Care Setting: A Case and Discussion

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Introduction

Hemolytic Uremic Syndrome (HUS) is usually recognized as the diarrheal associated (D+) and less as atypical/non diarrheal (aHUS). AHUSis caused by over activation of the alternative pathway of the complement system. It is a rare genetic disorder that is not often seen. Here we present a case of a patient with aHUS, who came to our ICU, discuss the pathophysiology, and how to treat and monitor a patient with aHUS with plasmapheresis and eculizumab in the critical care setting

Case

Our patient is a twenty-nine-year-old female with a past medical history of generalized anxiety disorder and attention deficit disorder who presented to the emergency department after a syncopal episode at work. When emergency medical services arrived at her workplace the patient had regained consciousness. On arrival vital signs were within normal limits. The patient denied any immediate preceding symptoms to her syncopal episode and did not display any post-ictal symptoms. On further history she admitted to feeling nauseous for 3 days prior and reported 4 episodes of non-bloody non-bilious vomiting over the same time period. Review of systems was otherwise negative. Her family history was significant for atypical hemolytic uremic syndrome on her paternal side with her paternal grandmother, aunt, and father all effected to differing degrees. The patient said she had never been tested for the gene mutation because she had never exhibited any of the same symptoms her family had displayed. Physical exam showed a well appearing pale female who was alert and oriented. Exam was otherwise benign. Initial lab work was significant for hemoglobin (Hb) of 7.3 g/dl, platelet count of 35 K/UL (manual of 45 K/UL), sodium (Na) of 131 mmol/L, total bilirubin of 1.5, and blood urea nitrogen (BUN)/ Creatinine (Cr) of 51/3.5 mg/dl. ICU was consulted for acute renal failure and anemia and hematology was consulted for possible aHUS given laboratory values and family history. Further lab work was significant for lactate dehydrogenase (LDH) of5, 004 IU/L. ADAMTS-13 and complement levels were ordered. She was initially treated in the ICU aggressively with numerous units of packed red blood cells (PRBCs) and IV hydration. Hematology recommended plasmapheresis and eculizumab. Plasmapheresis was started followed by a single induction dose of 900mg of eculizumab (patient had received meningococcal vaccine 1.5 years prior). The patient's clinical condition and lab results began to improve and the patient was monitored for a few more days before being discharged home on a standard eculizumab regimen. On follow up patient seemed to being tolerating the medication well with a baseline Cr of 1.5. She was tested and found to have a mutation of the CD46 gene as did her father, who died recently from complications of aHUS. She is currently following up closely with nephrology and hematology.

Discussion

Disease and Prevalence and Pathophysiology

Hemolytic uremic syndrome is recognized by the triad of renal failure, hemolytic anemia (microangiopathic) and thrombocytopenia. Most cases seen are caused by infectious etiology most noted being Ecoli 0157:H7. The incidence of aHUS is estimated to be 1 in 500,000 [1]. However our case is rare because aHUS accounts only for 10% of all HUS. 50% of those cases require dialysis and the disease carries a poor prognosis [2]. Of the 10% with aHUS only 20% reported cases run in families, as in our case, and are generally sporadic. If the disorder is familial the inheritance can be either autosomal recessive or autosomal dominant [1]. In our case the inheritance pattern pointed towards autosomal dominant.

aHUS is caused by environmental and genetic factors. Mutations in a gene called CFH are the most common and are linked to 30% of all cases. 30% are not linked to any genetic cause. The rest are associated with other gene mutations, in our case CD46. However, those associated with certain genes are thought to express disease after exposure to environmental triggers such as pregnancy, malignancy, sepsis, connective tissue disorders, bone marrow transplantation, and infections [3]. It is thought that when someone with a genetic predisposition encounters an environmental trigger this leads to over-activation of the alternative pathway of complement. Cells that line blood vessels in the kidney are attached leading to inflammation and formation of clots that cause narrowing of small blood vessels. This platelet count decreases as platelets clump together to make abnormal clots which ultimately leads to renal failure. Hemolytic anemia occurs when the red blood cells undergo hemolytic as they attempt to travel through small blood vessels leading to anemia [1].

Diagnosis and Treatment in Critical Care Setting

Due to conditions that have similar presentations such as thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation (DIC), a proper history focusing particularly on

family history is imperative especially in the critical care setting where there is no time to obtain genetic testing before starting the appropriate treatment. Therefore, in the acute setting, it must be treated as a diagnosis of exclusion from TTP and related thrombotic microangiopathic anemias. Testing for ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs 13) which is a deficient in TTP and is ultimately what results in clumping of platelets in TTP. Levels are also reduced in aHUS however, not to the degree that they are in TTP [4].

It is thought that until TTP is excluded plasma exchange should be started [5]. In larger laboratories the ADAMST13 takes a few hours to run; however in smaller hospitals such as ours the study takes a couple of days. In this case algorithms have been developed to aid in diagnosis such as one by Coppo et al, where TTP is suggested by low platelet count, mildly elevated serum creatinine and detectable antinuclear antibodies [4]. However complement 3 (C3 levels are low) in 40% of patients with aHUS [3]. A recent review article summarizing considerations of differential diagnosis of aHUS in the ICU points to the importance of key steps once features of a thrombotic microangiopathy (TMA) are seen. First is to exclude other causes such as malignancy, drugs, and pregnancy, followed by ruling out DIC and sepsis, followed by ruling out TTP as summarized above. If testing of ADAMTS13 is not available, algorithms such as the Coppo algorithm should be considered [4].

Unfortunately, cases are scant at best and there are no official formal recommendations made for the critical care setting. However, a review of the literature over the past decade does show certain trends. Therapeutics remains a challenge in aHUS. aHUS is generally treated with plasmapheresis and eculizumab [6].

Previously aHUS and TTP were treated similarly with plasma exchange being the only recommended option [3]. Plasma exchange shows great efficacy in TTP lowering mortality rate from 90 to 10%. However, in aHUS 50% ultimately need hemodialysis. When beginning plasma exchange while waiting for testing it is important to make sure not to begin if the patient has a relative contraindication such as metastatic cancer. Platelet concentrates should also be avoided or used cautiously as they can cause further platelet [3]. When ADAMTS13 is proven deficient it is fair to begin eculizumab.

In 2011 eculizumab was approved and has proven improved outcomes in prospective trials [1, 6, 7]. The monoclonal antibody works by stopping the overactive complement system by blocking the cleavage of c5 which stops the formation of C5a and C5b [3]. However none of the studies examined the use of eculizumab in the critical care setting. In our case its use ultimately stopped further TMA progression leading to increased platelet count and improvement of renal function. Similar results are seen in the literature and it is imperative in the treatment of HUS that shows no or minimal improvement with plasma exchange alone. That being said, there are some contraindications such as unresolved Neisserial infection and unvaccinated individuals as impairing terminal complement would be detrimental in certain diseases. Generally, vaccination 2 weeks prior to onset of use is preferred. If in the critical care setting empiric antibiotics should be started if the patient has an unknown vaccination history. 80% of cases seen in the literature on dialysis at baseline were able to discontinue dialysis after treatment with eculizumab [7].

Conclusion

Familial aHUS is an extremely rare cause of HUS. Due to the paucity of cases there are no firm guidelines on treatment and diagnosis in the critical care setting. This case report aims to help shed some more light on this rare disorder documenting a patient admitted to our ICU with familial aHUS that responded well to plasmapheresis and eculizumab. Diagnosis is best aided with proper history and genetic analysis. This is not always possible and the use of the literature and algorithms used by other intensivists can aid by using a diagnosis of exclusion approach followed by rapid treatment and close monitoring.

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