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Case Report

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Complement Amplifying Conditions and Atypical Hemolytic Syndrome should Eculizumab is the First Line Therapy?

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Abstract

Atypical Hemolytic Uremic Syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury (in form of end organ damage). Atypical HUS carries a significantly high morbidity and mortality if not treated in a timely manner. Recent data have emphasized the critical role of complement amplifying conditions (CACs) as atypical HUS is increasingly being reported to be associated with CACs. Complement amplifying conditions may be considered as precipitating events that can lead to the development of atypical HUS. Infection in a susceptible individual (with gene mutation or autoantibodies to complement factors) can act as a CAC and initiate a cascade of uncontrolled activation of complement system leading to endothelial damage, thrombotic microangiopathy and end organ damage. Herein, we present two cases with infection (endocarditis and leptospirosis) that presented with atypical HUS. Instead of eculizumab, treatment strategies focused on treating the CAC. In both cases, thrombotic microangiopathy resolved completely without the need for eculizumab. CACs are emerging as important events resulting in atypical HUS. Management strategies must first focus on treating the CAC instead of initiating therapy with eculizumab.

Keywords:

Microangiopathy; Eculizumab; Atypical HUS; Complement amplifying conditions

Introduction

Atypical hemolytic uremic syndrome (HUS) is a syndrome of thrombotic microangiopathy (TMA) characterized by clinical features of microangiopathic hemolytic anemia (MAHA), thrombocytopenia and target organ injury particularly the kidney [1-3]. With presentation of TMA like syndrome the primary differential diagnoses are thrombotic thrombocytopenic purpura (TTP), typical HUS and atypical HUS (aHUS). Differentiation between aHUS and TTP can be challenging as symptoms overlap and rapid availability of the ADAMTS 13 level is limited in many medical centers across the United States. Thus, due to high morbidity and mortality associated with atypical HUS and lack of a definitive test warrants maintaining a high clinical suspicion and institution of prompt treatment strategies.

Dysregulation of alternative pathway of the complement system leading to its uncontrolled activation is considered to be the underlying pathophysiology of aHUS [4]. Recent data have focused on the double-hit hypothesis indicating that both genetic predisposition and the occurrence of an event known as complement amplifying condition (CAC) can precipitate aHUS [4]. Current standard of care for the treatment of aHUS is eculizumab. Herein, we present two cases of atypical HUS precipitated by CACs (in the form of infective endocarditis and leptospirosis infection), which successfully resolved once the complement amplifying condition was treated without the use of eculizumab.

Case Report

Case 1

A 36-year-old white female was brought to the emergency room for progressively worsening encephalopathy. Past medical history was significant for active intravenous drug abuse, and untreated chronic hepatitis C. Patient had reported associated fatigue, fever, chills and headaches for past 2-3 days. Rest of the review of systems was limited due to patient's worsening mental status. Prior to arrival to the emergency department (ED) her blood sugar was 36 mg/dl. She was given intravenous dextrose (D50) with normalization of serum blood glucose level. However, she remained lethargic.

Physical examination in the ED revealed a blood pressure of 92/56 mm Hg, a pulse of 58 beats/min, respiratory rate of 18/min, pulse oximetry of 98% on 2 l of oxygen by nasal cannula and a temperature of 99°F. On neurological examination patient was lethargic. Pertinent negatives included normal motor and sensory examination. Cardiovascular examination revealed diastolic murmur over the aortic and tricuspid region. Rest of the physical examination was unremarkable. Initial laboratory work revealed acute renal failure with serum creatinine of 6.5 mg/dL (0.44-1.00 mg/dL), and blood urea nitrogen (BUN) of 69 mg/dl (5-25 mg/dl). Complete blood count showed leukocytosis of 15.5 K/uL (4.5-11.0 K/ul), anemia with hemoglobin of 9.3 gm/dL (12.0-16.0 gm/dL) and thrombocytopenia with a platelet count of 36 K/uL(140-450 K/uL). Peripheral smear revealed prominent schistocytes. Urine drug screen was positive for opiates and amphetamines. A computed tomography scan of head/brain did not show any acute infarcts or intracranial hemorrhage. HIV test was negative.

Given the constellation of acute renal injury, thrombocytopenia and anemia; a preliminary diagnosis of TMA was made (Table I). Two sessions of plasmapheresis were delivered at the discretion of the treating physician and broad-spectrum antibiotics were started for suspected endocarditis. ADAMTS 13 returned at 53% (>60% activity) and blood culture grew serratia marcescens sensitive to cefepime. Transthoracic echocardiogram showed aortic valve and tricuspid valve vegetation. Eventually, mental status and renal function returned to normal. She was discharged to rehab to complete antibiotic course with normal platelet count and renal function. A repeat transthoracic echo

showed significant resolution of the vegetation and laboratory analysis revealed normalization of hemoglobin.

	Reference range	Day 1	Day 2	Day 5	Day 7	Day of discharge
Complete Blood Count						
White Blood Cell	4.5-11.0 K/ul	15.5	15.9	17.9	17.6	7.7
Hemoglobin	12.0-16.0 gm/dl	9.3	8.6	6.8	7.7	8
Hematocrit	35.0-48.0%	27.7	25.5	20	22.8	24.4
MCV	80-100 fl	78.2	77.3	78.1	81.1	86.8
MCH	25.0-35.0 PG	26.3	26.1	26.6	27.4	28.5
Platelet count	140-450 K/ul	36	16	14	68	274
MCHC	31-36%	33.6	33.7	34	33.8	32.8
Reticulocyte count	0.40-2.50%	0.15				
Peripheral Blood Smear		+ve Schistocytes				
ADAMTS 13	>60% activity			53%		
Complete Metabolic Panel						
Sodium	136-145 mmol/l	130	133	140	133	136
Potassium	3.5-5.2 mmol/l	3.6	3.2	3.1	4	4.3
Chloride	96-110 mmol/l	93	103	107	106	104
Bicarbonate	24-31 mmol/l	16	21	24	23	25
BUN	5-25 mg/dl	61	49	32	19	16
Creatinine	0.44-1.00 mg/dl	6.88	3.94	1.2	0.8	0.65
GFR	>60 mL/min	7	13	45	>60	>60
Glucose	70-99 mg/dl	126	142	151	150	83
Total Bilirubin	0.2- 1.3 mg/dl	3		1.6		0.5
Direct Bilirubin		1.8				
Indirect Bilirubin		1.2				
LDH	91-200 iU/l	199				
Haptoglobin		Low				
Urine drug screen		+ve for opiods				

Table 1: Laboratory results on admission for Case 1.

Case 2

A 32 year old sewer worker with no significant past medical history presented with fever, nausea and vomiting. He did not report any diarrhea, bloody stools or urinary symptoms. He had worked in a sewer a week prior to the symptoms. Although he wore protective equipment while in the sewer, he reported of being stuck with needles and had contact with water contaminated by animal feces. Patient initially presented to the ED, whereupon he was noted to have mildly elevated total bilirubin of 1.7 mg/dl (0.2- 1.3 mg/dl) and thrombocytopenia of 110 K/ul (140-450 K/ul), with no other laboratory abnormalities. Patient was presumed to have gastroenteritis and was discharged. However, two days later he returned to the ED with persistent nausea and vomiting that had become bloody.

On physical examination his blood pressure was 118/67 mmHg, a pulse of 113 beats/min, respiratory rate of 18/min, pulse oximetry of 97% on room air, and a temperature of 98.4°F. He had icteric sclera and jaundiced skin. On abdominal examination the patient was noted to have diffusely tender abdomen without hepatomegaly or splenomegaly. Rest of the physical examination was unremarkable. Laboratory data revealed a significant elevation of his total bilirubin from 1.7 mg/dl to 10.4 mg/dl. Patient also had developed mild transaminitis with alkaline phosphate of 127 iU/l (38-126 iU/l), AST of 60 iU/l (10-42 iU/l) and

ALT of 68 iU/l (10-60 iU/l). Kidney function had also significantly worsened with serum creatinine of 5.87 mg/dl (from 1.03 mg/dl two days earlier). Patient also developed significant thrombocytopenia from 110 K/ul to 58 K/ul. He was anemic at 12.7 gm/dl (12.0-16.0 gm/dl) with elevated LDH of 305 iU/l (91-200 iU/l). Patient was presumed to have to leptospirosis and was treated with doxycycline and ceftriaxone. Given constellation of thrombocytopenia, anemia, and renal impairment, TTP vs aHUS was suspected and ADAMTS 13 was ordered. Plasmapheresis was not initiated.

Patient's hospital course was complicated by oliguria, which required hemodialysis. Patient eventually recovered renal function after receiving one session of hemodialysis (Table 2). ADAMTS 13 returned at 80% activity. Eventually patient creatinine normalized to 1.12 mg/dl and thrombocytopenia resolved prior to discharge (Table 2). Patient was discharged on doxycycline. Patient's microscopic agglutination test (MAT) later confirmed leptospirosis.

	Reference Range	Day 1	Day 2	Day 5	Day 7	Day of discharge
Complete Blood Count						
White Blood Cell	4.5-11.0 K/uL	15.8	13.5	16.7	17.5	9
Hemoglobin	12.0-16.0 gm/dL	13.7	12.3	11.8	12.9	10.2
Hematocrit	35.0-48.0%	37.7	33.4	32.5	34.8	30.8
MCV	80-100 fL	82.5	81.7	81.7	82.3	89.5
MCH	25.0-35.0 PG	30	30.1	29.6	30.5	29.7
Platelet Count	140-450 K/uL	58	66	192	404	842
MCHC	31-36%	36.3	36.8	36.3	37.1	33.1
Reticulocyte count	0.40-2.50%			0.84		
Peripheral Blood Smear						
ADAMTS 13	> 60% activity	84%				
Complete Metabolic Panel						
Sodium	136-145 mmol/l	134	133	134	131	137
Potassium	3.5-5.2 mmol/l	3.3	3.4	3.3	4.4	4.9
Chloride	96-110 mmol/l	95	99	100	98	101
Bicarbonate	24-31 mmol/l	22	21	22	21	27
BUN	5-25 mg/dl	54	87	36	25	13
Creatinine	0.44-1.00 mg/dl	5.87	7.25	1.74	1.12	0.81
GFR	>60 mL/min	11	9	45	>60	>60
Glucose	70-99 mg/dl	153	120	186	103	86
Total Bilirubin	0.2- 1.3 mg/dl	10.4	12	19.6	17.5	6
Direct Bilirubin		7				
Indirect Bilirubin		3.4				
LDH	91-200 iU/l	305	306		348	
Haptoglobin		578				
Urine Drug Screen		Negative				

Table 2: Laboratory results on admission for Case 2.

Discussion

"Multi-hit" theory has emphasized that aHUS is a consequence of both genetic predisposition to alternative complement pathway dysregulation as well as occurrence of events or conditions that can precipitate TMA [5]. These events/conditions are known as complement amplifying conditions (CACs). Common CACs include pregnancy, auto immune diseases (SLE, scleroderma), malignant

hypertension, infection and renal transplant [4]. The two cases presented in this report add to the existing literature that infection serves as a CAC in inducing thrombotic microangiopathy. It has been documented that a wide variety of systemic infections, including bacterial endocarditis, fungal infections, viral etiologies like HIV, CMV and even rickettsia diseases can precipitate TMA [6]. In recent research based on Oklahoma TTP-HUS Registry, 7% of the patients who initially presented with TTP-like features were finally attributed to underlying infections [6].

Case 1

This patient had microangiopathic hemolytic anemia, thrombocytopenia with end organ damage, thus preliminary diagnosis of TMA complicated by infection was made. ADAMTS 13 was found to be normal and hence the diagnosis of aHUS was made. We believe that infection with serratia marcescens (found on her blood culture) acted as a complemented amplifying condition and resulted in aHUS. However, our patient also had chronic hepatitis C and abused opioid drugs, both of which are associated with the development of TMA. We found multiple case reports highlighting the development of TMA in hepatitis C patients being treated with active interferon therapy [7]. There have also been reports of chronic hepatitis C patients who developed TMA (labeled as TTP) not associated with active interferon therapy [8]. More recently, however, TMA has been associated with intravenous opioid drug abusers especially OPANA ER [9]. Opana ER is an "oral only" form of oxymorphone, which is rapidly being implicated in the intravenous drug abuse reports from Tennessee[9]. Kapila et al, describe a TTP-like syndrome following opana intake. However, normal ADAMTS13 level in their case argues against the diagnosis of TTP.

Our patient had both chronic hepatitis C and was an active intravenous opioid abuser making her "at high-risk" patient for TMA. Nevertheless, TMA did not occur despite chronic opioid abuse and chronic hepatitis C until patient developed endocarditis with serratia marcescens. Importantly, once the offending CAC (endocarditis) was treated, TMA resolved and renal function recovered without the use of eculizumab.

Case 2

Our case number 2 also presented with TMA, as his presentation included the constellation of thrombocytopenia, anemia and end organ damage (both renal failure and liver damage). Once the requirement of TMA was met, differentiation between TTP and aHUS became essential in treatment of this patient. ADAMTS 13 levels returned normal, TTP was excluded and the diagnosis of aHUS was made. The CAC that precipitated the aHUS was most likely the leptospirosis infection.

It is important to mention that leptospirosis has been previously reported to be associated with TMA [10,11]. In their reports, both Sukran and Quinn et al. labeled the TMA as TTP [11,12]. However, ADAMTS 13 activity was either not reported or was not accurately interpreted [10]. Thus making a diagnosis of TTP unlikely (ADAMTS 13=43%) and aHUS more likely in the case by Quinn et al [12]. Also, for the case reported by Sukran et al, diagnosis is incomplete as ADAMTS 13 was not obtained [11].

The three important aspects that did not match with diagnosis of TTP in our case number 2 were the ADAMTS 13 level of greater than 80%, degree of thrombocytopenia [12] and advanced renal failure at presentation [13]. Just as in case number 1, our case number 2 demonstrated that once the patient's precipitating CAC recovered so did the renal function. The uniqueness in this case lies in the fact that leptospirosis has not been reported to be associated with aHUS. In this patient, thrombocytopenia, anemia and renal failure with normal ADAMTS 13 attest to the diagnosis of aHUS and not TTP. Just as in case number 1, this patient fully recovered once the CAC was appropriately treated without the need for eculizumab therapy.

Cac Treatment or Eculizumab?

Microangiopathic hemolytic anemia, thrombocytopenia, target organ injury (brought on due to microvascular thrombosis) in the context of normal ADAMTS 13 constitute a HUS and eculizumab is recommended for the treatment of this syndrome [13]. Eculizumab is a humanized monoclonal antibody that effectively blocks the cleavage of terminal complement protein C5 and blocks the generation of C5a and the Membrane Attack Complex (C5b-9) and results in improvement of thrombocytopenia, anemia and target organ injury [14]. In order to prevent ongoing damage to the target organs; at present, early diagnosis and prompt treatment with eculizumab administered indefinitely is recommended [15]. At the same time, CACs are emerging as important initiating factors. The two cases presented here and those reported in the literature are emphasizing that CACs must be identified and appropriately treated. TMA may resolve with appropriate treatment targeted to the CAC without the need for eculizumab.

Conclusion

Atypical HUS is a medical emergency that carries high mortality and morbidity. Thus, maintaining a high index of suspicion, accurate diagnosis and early treatment is of paramount importance. ADAMTS 13 is a vital test available to rule out TTP. Once an accurate diagnosis of aHUS has been established, one more step needs to be accomplished. A precipitating event (i.e. CAC) leading to the development of TMA must be investigated and appropriately treated. Our cases demonstrate successful resolution of aHUS with the treatment of CAC and without the use of monoclonal antibody. Eculizumab therapy should be employed only if the treatment of CAC does not resolve the aHUS.

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