Case Report

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A Case Report of Atypical Hemolytic Uremic Syndrome in the Setting of Idiopathic Acute Pancreatitis

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ABSTRACT

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy defined by the triad of sudden onset hemolytic anemia, thrombocytopenia, and acute kidney injury. We describe a rare case of atypical HUS secondary to acute pancreatitis with an unknown etiology in a 20-year-old male who presented with complaint of nausea, vomiting, and abdominal pain. On presentation, the patient's vitals were stable and physical exam was significant for epigastric abdominal tenderness. Abdominal imaging showed peripancreatic inflammatory changes consistent with acute pancreatitis and patient had an elevated lipase. Initial investigation reveals acute renal failure, thrombocytopenia and acute pancreatitis. Extensive work-up revealed low C3, and CH50 level, low haptoglobin, and elevated total bilirubin. Due to concern for thrombotic microangiopathy, particularly atypical hemolytic uremic syndrome, the patient was started on plasmapheresis. He remained unresponsive to treatment, thus was followed up with Eculizumab. The patient was also started on Hemodialysis due to worsening renal function and eventually recovered completely. Platelet count improved after initiation of eculizumab and remained stable throughout hospital stay.

Keywords: Anemia; Thrombocytopenia; TMA; Atypical Hus; AKI; Pancreatitis

Abbreviations: HUS: Hemolytic Uremic Syndrome; CFH: Complement Factor H; CFI: Complement Factor I; MCP: Membrane Cofactor Protein; THBD: Thrombomodulin

Introduction

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy defined by the triad of sudden onset hemolytic anemia, thrombocytopenia, and acute kidney injury [1]. Although most HUS cases are secondary to infection of *Escherichia coli* serotypes O157:H7 which produce Shiga-like toxin or less commonly *Streptococcus pneumoniae*, approximately 10% of cases are not caused by these bacteria and are classified as atypical HUS [2]. Atypical HUS is associated with primarily genetic or acquired defects in regulation of complement activation on host cells. Patients with atypical HUS have reduced complement fraction of C3 and normal levels of C4 which reflects complement activation and consumption during acute disease [3]. Genetic mutations within the complement pathway, namely those who do not produce complement factor H, account for 50-60% of these cases [4]. The complement pathway has been implicated in the pathogenesis of pancreatitis; however, its role is unclear [4]. Previous case reports of atypical HUS have been reported in the setting of alcohol induced pancreatitis [5]. Here we describe a rare case of atypical hemolytic uremic syndrome in the setting of recurrent acute pancreatitis who did not have a history of alcohol consumption.

Case Report

A 20 years old male with a history of autism, seizure disorder, and an episode of pancreatitis presented to the emergency room with vague complaints of nausea, vomiting, low grade fevers and increasing generalized abdominal pain for two days per his parents. The patient's parents noted that patient has had poor oral intake and has not been acting himself for almost a week. They reported that patient has had normal bowel movements prior to presenting to

the hospital and he did not have any recent diarrhea. Patient had no sick contacts, recent travel, or changes in diet or medications. They reported that patient had a previous episode of acute pancreatitis 18 months ago which was attributed to patient's Valproic acid that has since been discontinued. Further review of his labs from that admission shows he had low platelets (103K), anemia (9.9 gm/dl) along with elevated lipase (3895) at that time but he recovered without intervention. Since the patient's last episode of pancreatitis there had been no changes in his medications including THC and CBD products used for his seizures and behavioral issues.

On arrival his blood pressure was 146/112 mmHg, Pulse 79 bpm, Temp 98.9 F, RR 16 and spo2 98% on room air. On exam, he was ill appearing and had tenderness to the epigastric region without guarding or rebound. No ecchymosis around the umbilicus or flanks (negative Cullen's sign and Grey Turner sign) were noted. Laboratory investigation revealed a white blood cell count of 18.3, hemoglobin of 15.7 g/dl, and a platelet count of 40,000. His complete metabolic panel showed an elevated creatinine of 4.18 mg/dl (baseline of 0.5-0.7), BUN of 37, AST of 111, ALT of 51, ALP of 107, and total bilirubin of 4.5 (Direct bilirubin 0.5 mg/dl). The patient was noted to have an elevated lipase of 8771 u/l and CT of the abdomen and pelvis without contrast showed diffuse peripancreatic free fluid and edema surrounding the mesentery. A right upper quadrant ultrasound showed gallbladder sludge, however, no evidence of cholelithiasis or acute cholecystitis and fatty infiltration of the liver. A renal ultrasound was also unremarkable.

A diagnosis of acute pancreatitis was made and patient was started on intravenous fluids, analgesics and admitted to the intensive care unit. On admission, the patient's hemoglobin decreased to 11.8 g/dl, platelets were 9,000, and his creatinine increased to 5.32mg/dl. A repeat CBC showed a hemoglobin of 10.9 g/dl and platelets of 22,000. The patient was seen in consultation by gastroenterology. Patient's lipid panel was unremarkable and hepatic doppler was negative for portal vein thromboses. On the second day of admission, patient was noted to have significant drop in hemoglobin from 11.8 g/dl to 8 g/dl since admission without any signs of obvious bleeding. His platelet count remained low at 23,000. Few schistocytes were noted on the peripheral smear. The patient's LDH was elevated at 2521 and reticulocyte count was 1.68. The patient's haptoglobin decreased to 8 from 30 and fibrinogen was 311. The patient was seen in consultation by hematology and further workup was undertaken. A Coombs test and cryoglobulins were negative. Serum creatinine continued to trend upwards to 6.3 mg/dl and urinalysis was significant for protein and blood. Nephrology was consulted and urine microscopy showed isomorphic RBCs, occasional WBCs and some granular cast. (Figures 1 & 2) His creatinine kinase was noted to be elevated at 1,977. The patient was also negative for HIV and a hepatitis panle was also negative. A repeat CT abdomen repeated which was negative for retroperitoneal bleed. Due to concern for thrombotic microangiopathy in particular for HUS, he was started on Solumedrol and plasmapheresis. An ADAMTS13, PNH FLARE, and complement profile were sent.

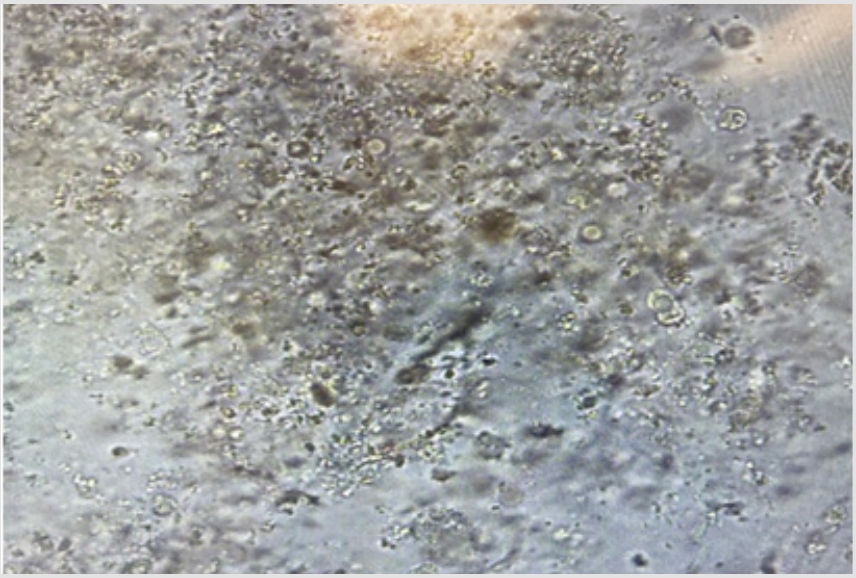

Figure 1: Urine microscopy with granular cast on hpf.

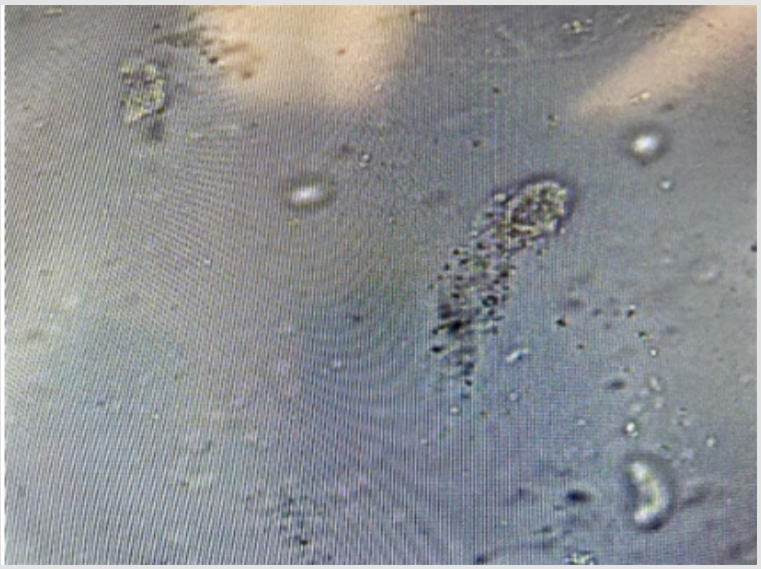

Figure 2: Granular Cast and isomorphic RBC's seen on urine microscopy.

The patient completed two treatments of plasmapheresis over the next two days but no improvement in platelet count was noted. During this time, he was transfused 1 unit of packed red blood cells and platelets due to continuous bleeding from the catheter site insertion. The patient's PNH FLARE test returned negative. The patient's complement profile returned with a low C3 of 72, normal C4 of 21.4, and low CH50 of 38. At that point our concern was atypical HUS and complement factor H was sent. The patient was promptly started Eculizumab based on his presentation and diagnostic data available at that time. The patient was placed on prophylactic Amoxicillin and given the meningococcal vaccine prior to being started on his first dose of Eculizumab. On the fifth day of admission, the patient started to experience hiccups, poor appetite, and increasing generalized edema. Serum creatinine rose to 7.06 mg/dl, BUN to 113 mg/dl and he remained oliguric despite IV diuretics. He was eventually started on hemodialysis. On day 7 of admission, the patient's hemoglobin and platelet count improved. Parvovirus result returned IgG positive however quantitative PCR was negative. On day 9 of admission, patient appeared jaundice and his total bilirubin was 11.5 mg/dl while his direct bilirubin was 9.3 mg/dl. A right upper quadrant ultrasound showed hepatic steatosis however no biliary duct dilation. The patient's hemoglobin decreased to 6.9 g/dl and he was transfused 1 unit of packed red blood cells. On the 10th day of admission, the patient's bilirubin improved to 5.1 from 11.1mg/dl and his hemoglobin and platelets remained stable. He received a total of 4 hemodialysis sessions throughout admission.

The patient was noted to have renal recovery with decreasing creatinine in inter-dialysis phase with increasing urine output. Over the ensuing days, serum creatinine continued to improve down to 0.9 mg/dl and his platelets remained stable. (See Graphs 1 & 2) (Table 1) The patient's Complement factor H returned with a value of less than 4.0. Unfortunately, his hospital course was complicated by second episode of pancreatitis with peak lipase of 1365 and elevated ALT(273), AST(264), and ALP (295). MRCP which could not be performed due to presence of a Vagus nerve stimulator. Patient underwent endoscopic ultrasound which revealed CBD sludge material. He underwent ERCP for CBD stent placement and sphincterotomy due to features of papillary stenosis. The patient was seen by surgery who recommended cholecystectomy. The post procedure was complicated by shock however the patient completely recovered after supportive measures. The patient received his 3rd dose of Eculizumab on admission day 18. Eventually he was discharged on day 26 after his 4th dose of Eculizumab. The patient was set up with close outpatient follow up with gastroenterology and hematology-oncology for further surveillance and Eculizumab doses. The patient was recommended to undergo genetic testing to further evaluate the etiology of his atypical HUS.

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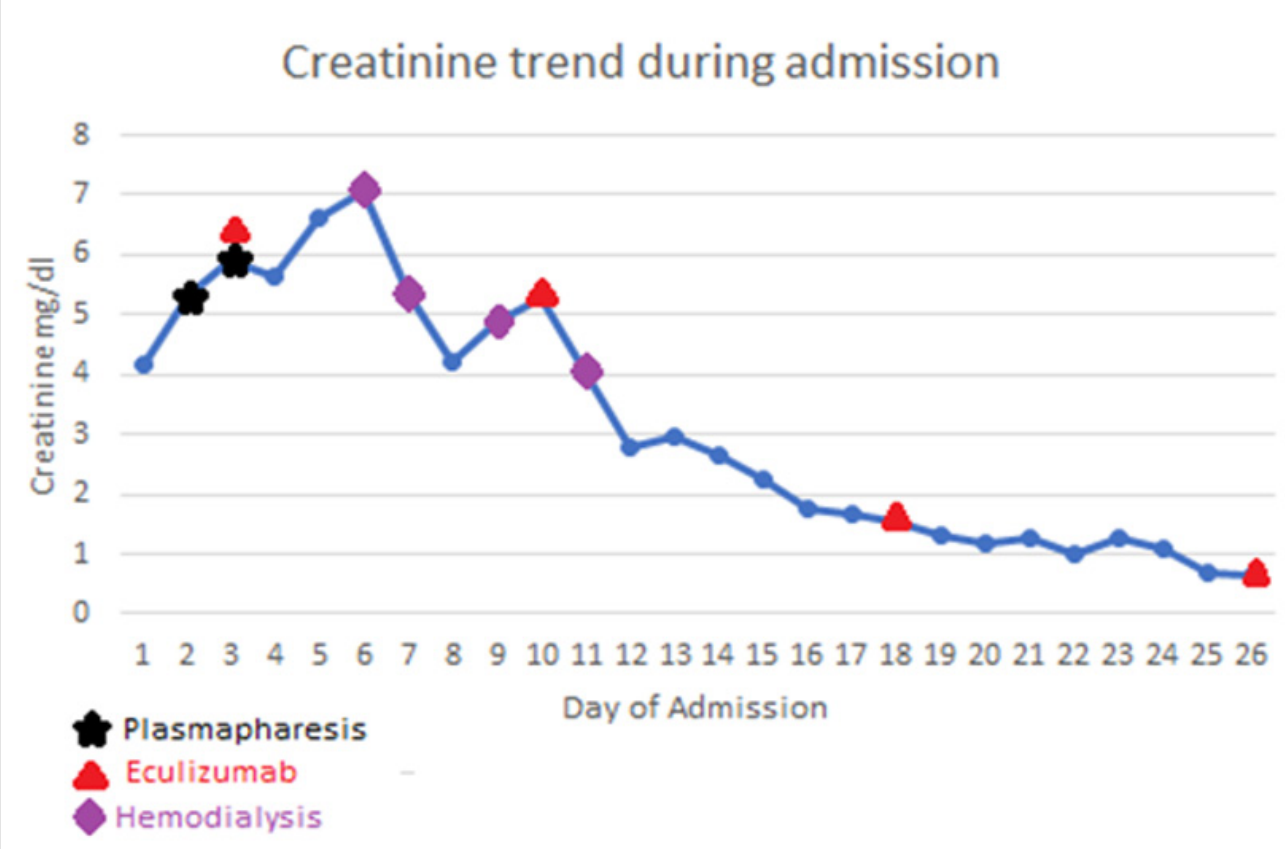
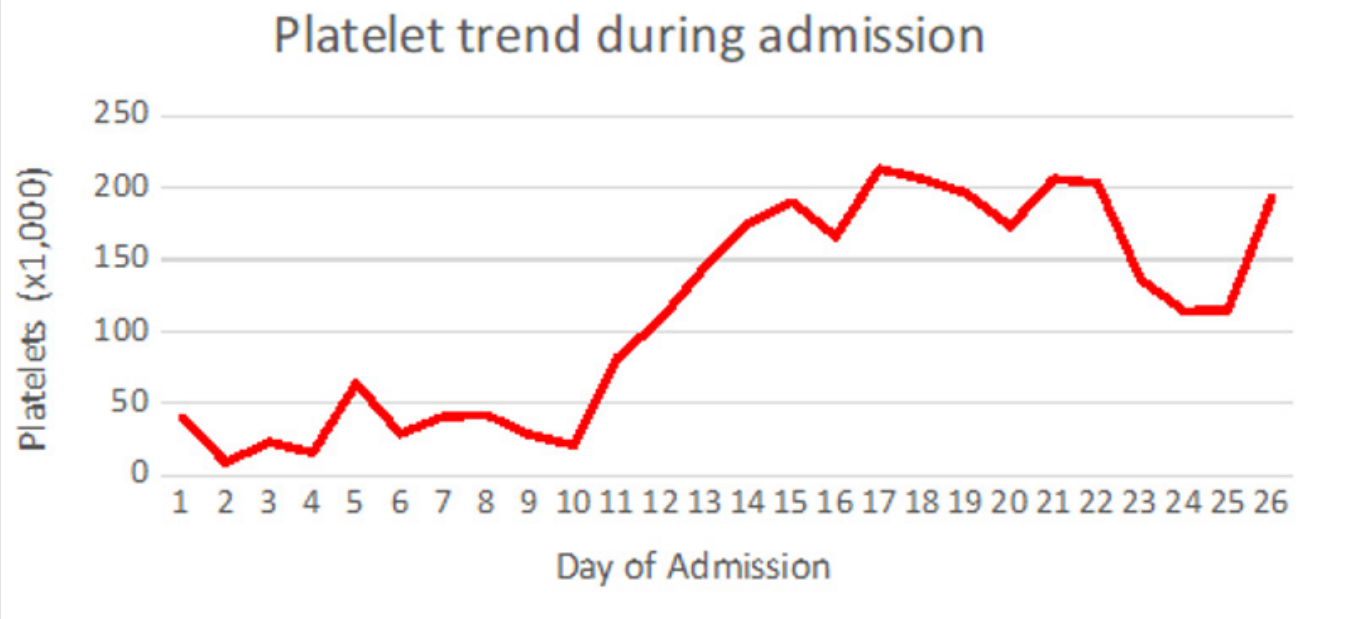


Graph 1: Patient's creatinine trend during admission.



Graph 2: Patient's platelet trend during admission.

Table 1: Patient's creatinine and platelet values during admission.

Admission Day	Creatinine mg/dl	Platelets
1	4.18	40
2	5,32	9
3	5.92	23
4	5.63	16
5	6.60	64
6	7.06	29
7	5.37	41
8	4.19	42
9	4.86	28
10	5.30	21
11	4.04	82
12	2.80	109
13	2.98	145
14	2.65	175
15	2.23	190
16	1.76	166
17	1.66	213
18	1.54	206
19	1.32	196
20	1.17	173
21	1.28	206
22	0.98	203
23	1.26	136
24	1.07	114
25	0.70	115
26	0.64	193

Discussion

Atypical hemolytic uremic syndrome in the context of pancreatitis is a rare life-threatening disorder that requires prompt recognition for timely treatment. Previous case reports describe the development of pancreatitis from various etiologies including alcohol use, biliary disease, and endoscopic retrograde cholangiopancreatography occurring prior to the atypical HUS [6-7]. Patients presenting with elevated creatinine, thrombocytopenia, and hemolytic anemia in the setting of pancreatitis should raise clinical suspicion for atypical hemolytic uremic syndrome. Additional testing such as ADAMTS23 and complements should be ordered. The role of complements have been suggested in the pathogenesis of pancreatitis however the exact underlying mechanisms and their role have yet to be clear [8]. The cause of this case remains unclear however the initial trigger of patient's condition was suspected due to CBD sludge secondary to pigment gallstone from hemolysis although but no gallstones were identified. Our hypothesis is pancreatitis could be idiopathic and a trigger factor for atypical HUS which is very unusual as patient did have similar presentation almost year and a half prior but he recovered on his own. He will be undergoing further evaluation to rule out familial/genetic etiology of atypical Hemolytic uremic syndrome and pancreatitis (Table 2). This case also remains unique as the patient's findings of low C3 as compared to C4 despite having negative complement factor H (CFH) suggests an alternative pathway.

Table 2.

Variable	On Presentation	2nd day of admission	Reference range
Hemoglobin	15.7 g/dl	11.8 g/dl	12.5 –17.0 g/dl
Platelets	40000 thou/cmm	9000 thou/cmm	140 - 350 thou/cmm
WBC	18.3 thou/cmm	14.8 thou/cmm	4.0-10.5 thou/cmm
Creatinine	4.18 mg/dl	5.32 mg/dl	0.5-1.3 mg/dl
Lipase	8771 U/L	-	80-360 U/L
Total bilirubin	4.5 mg/dl	-	0.2-1.0 mg/dl
LDH	2521 U/L	1786 U/L	100-250 U/L
C3	72 mg/dl	-	90-180 mg/dl
C4	21.4 mg/dl	-	10-40 mg/dl
CH50	38 U/ml	-	42-95 U/ml
AST	111	-	
ALT	51	-	
ALP	107	-	
Haptoglobin	8 mg/dl	9 mg/dl	34-200 mg/dl
Retic Count	1.68 milli/cmm	-	0.018-0.108 milli/cmm

CFH mutations account for approximately 25% of the genetic predisposition to HUS [9]. Derangements in the C-Terminal domains of the CFH gene in transgenic mice spontaneously developed atypical hemolytic uremic syndrome confirming the importance of local endothelial cell complement regulation [10-11]. Complement factor I (CFI) accounts for 5%-10% of acute hemolytic uremic syndrome [12]. Functional analysis performed on mutations of CFI showed loss of both alternative and classical pathway regulatory activity [13]. Membrane Cofactor Protein (MCP) acts as a cofactor for CFI mediated cleavage of C3b and C4b [14]. MCP mutations are found in 10% of patients with atypical hemolytic uremic syndrome and approximately 75% result in a qualitative defect while the remaining result in a secreted, non-functional protein [15]. Thrombomodulin (THBD) mutations accounts for 3-5% of atypical hemolytic uremic syndrome patients in the United States and Italy [16-17]. THBD mutations are less effective in enhancing CFI mediated inactivation of C3b. 50% of patients with THBD mutations have decreased C3 levels due to mutant THBD having the reduced capacity to degrade C3b and to generate thrombin activable fibrinolysis inhibitor that cleaves C3a and C5a [18]. Given the patient's history of autism, this patient likely has genetic haploinsufficiency leading to inactivating mutations in CFH, CFI, MCP, and THBD or activating mutations of CFB or C3. It is highly likely the patient from this case report had a genetic etiology with delayed phenotype. Ideally the patient will need to undergo genetic testing to confirm these suspicions.

As testing may take time to process, prompt treatment with Eculizumab should be considered based on clinical grounds and laboratory data. Eculizumab is a recombinant humanized monoclonal antibody directed against C5 which blocks cleavage of C5 into C5a and C5b [19]. Prompt initiation of Eculuzimab is associated with significant time dependent improvement in renal functions in patients with atypical hemolytic syndrome, reducing the morbidity and mortality [20]. Approximately 85% of patients become disease free with Eculizumab in both plasma-resistant and plasma dependent atypical hemolytic uremic syndrome [20]. In this case report, the patient completed two rounds of plasmapheresis and eventually transitioned to Eculizumab monotherapy prior to the return of his confirmatory labs due to the high suspicion of atypical hemolytic uremic syndrome. He began to show steady improvement of platelets after the second dose of Eculizumab and continued to improve throughout his admission. Individuals with genetic atypical hemolytic uremic syndrome frequently experience relapse despite having a full recovery from a previous episode [21]. In the case where the patient's genetic testing returns positive for CFH or CHI mutations, a kidney transplantation should be considered to reduce the risk of recurrence. Recurrence rates are greater than 80% in patients CFH mutations while initial studies of CFI carried a poor prognosis [22]. Ultimately, understanding the complement genetic mutation will facilitate successful treatment of atypical hemolytic uremic syndrome.

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