Secondary Atypical Hemolytic Uremic Syndrome Triggered By Acute Pancreatitis

Triston Berger, MD[1]; Jaspreet Suri, MD[2]; Daniel Boxer, MD[3]
1. Department of Internal Medicine, Norwalk Hospital, affiliated with Yale School of Medicine
2. Division of Gastroenterology and Hepatology, Norwalk Hospital, affiliated with Yale School of Medicine
3. Division of Hematology and Oncology, Norwalk Hospital

Introduction

- Hemolytic Uremia Syndrome (HUS) is a thrombotic microangiopathy defined by hemolytic anemia, thrombocytopenia, and acute kidney injury.
- Categorized as 'Typical' in the presence of Shiga Toxin producing Escherichia coli.
- 'Atypical' HUS (aHUS), also known as complement mediated thrombotic microangiopathy, is the result of dysregulation of complement pathways from inherited or acquired abnormalities in complement proteins, or secondary to systemic disease.
- aHUS is exceptionally rare with incidence of approximately 1 in 1,000,000.
- aHUS secondary to pancreatitis has been reported in few cases in literature, and the pathologic mechanism remains elusive.
- Pancreatitis can also present as a rare extrarenal manifestation of aHUS. It can be difficult to differentiate between the two, but genetic evaluation and timings can provide some insight.
- This case presents a rare case of secondary aHUS from pancreatitis with negative genetic workup.

Case

35-year-old male with no medical history was brought in by ambulance after being found unresponsive. He was last heard from 3 days prior. His brother stated that the patient had been experiencing diarrhea and taking loperamide, but was unable to provide more information.

Physical
T: 102.4 °F **HR:** 130 bpm **RR:** 30 br/min **BP:** 94/52 mmHg **SpO2:** 97% RA
General: Age appropriate male, lethargic but arousable, oriented x3
HEENT: Anicteric sclera. EOMI, dry mucus membranes
Heart: RRR, no m/r/g
Lungs: CTABL
Abdomen: +BS x4, soft, nondistended, mild tenderness over RUQ
Neuro: no focal neurologic deficits

Imaging:
CT Brain: No acute intracranial abnormality
Chest XR: No cardiopulmonary disease
CT AP: Findings consistent with pancreatitis with trace peripancreatic free fluid and without definite drainable collection and redemonstrated hepatic steatosis.

Labs:

20.8	19.8 / 66	388	165 / 3.9	119 / 21	61 / 2.25	1375

ALP 264 U/L
AST 154 U/L
ALT 314 U/L
Total Bilirubin 0.6 mg/dL

Lactic acid 4.8 mmol/L
Beta hydroxybutyrate 6.9 mmol/L
Lipase 1636 U/L
Triglycerides 528 mg/dL

Ethanol level not detected
Creatinine kinase 260 U/L
COVID PCR negative

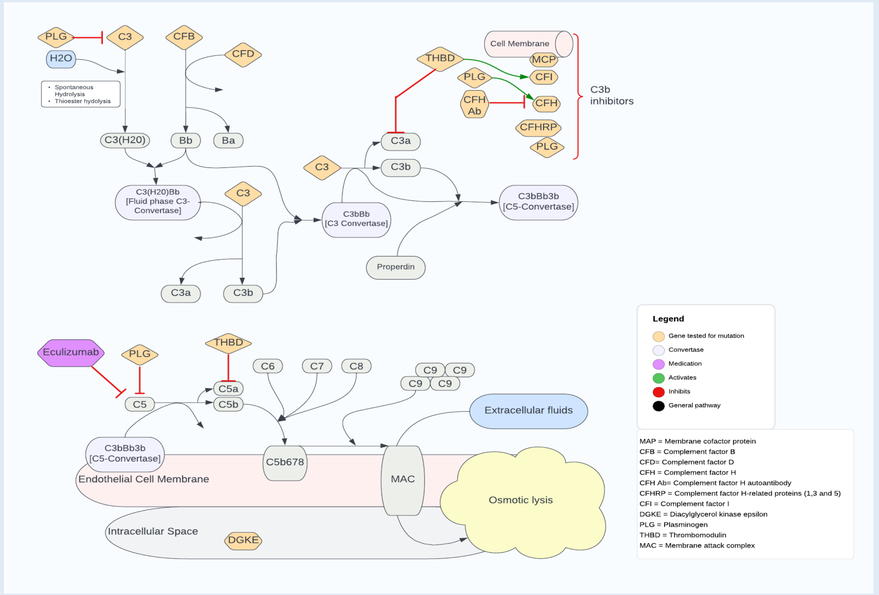

Figure 1. Alternative complement pathway involved in the pathophysiology of atypical hemolytic uremic syndrome (aHUS). Genetic abnormalities predisposing to aHUS are highlighted.

Hospital Course

- Initially treated for severe dehydration with electrolyte abnormalities, pancreatitis, and hyperosmolar hyperglycemic syndrome.
- Significant improvement over first 3 days. On day 4, he had a rapid drop in platelets to $12x10^9$/L with worsening renal function (Creatinine 9.65mg/dL).
- Further workup reveled significantly elevated D-Dimer, fibrinogen, and LDH with indirect hyperbilirubinemia and low haptoglobin, concerning for hemolytic process. PTT and PT/INR was normal.
- Peripheral Smear was obtained (Figure 2). Coombs test returned negative.
- Hematology was consulted – Leading differential included microangiopathic hemolytic anemia from thrombotic thrombocytopenic purpura (TTP) vs typical or atypical HUS.
- Dialysis and plasma exchange were initiated, as well as methylprednisolone 1000mg daily for possible TTP while further workup was pending.
- A few days later, ADAMTS13 activity level returned normal, and patient was found negative for Shiga toxin. These results allowed for the diagnosis of atypical HUS to be made.
- He was started on eculizumab (C5 complement inhibitor) for treatment, and saw resolution of aHUS with restoration of renal function.

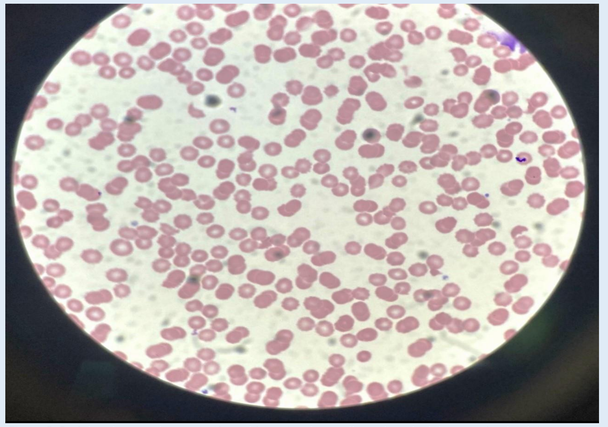

Figure 2. Peripheral smear demonstrating schistocytes, burr cells, and marked decrease in platelets.

Discussion

- The complement system serves a critical role in the innate immune system, including formation of membrane attack complex (MAC), propagation of anaphylatoxins, and opsonization of pathogens.
- Three pathways: classical pathway (activated by microbial bound IgG), lectin pathway (recognition of foreign particles via mannose binding lectin and ficolin), and alternate pathway (antibody independent and spontaneously activated in the serum. Involves regulatory factors in serum and cell surfaces to prevent activated complement system attack on host cells).
- In aHUS, the alternate pathway is continuously made active by the imbalance of activated C3 and regulatory factors.
- Genetic testing includes genes involved in the alternative pathway. Mutations result in over-activation of the complement system and formation of microvascular thrombi.
- Genetic panel used to test our patient was the "Complement-Mediated Atypical Hemolytic-Uremic Syndrome(aHUS)/Thrombotic Microangiopathy (TMA) Gene Panel [Test ID: AHUSP]" by Mayo Clinic in Rochester, MN. Next generation or Sanger sequencing was performed to test for the presence of a variant in all coding regions and intron/exon boundaries of the genes tested.
- Genes tested included: von Willebrand factor-cleaving protease, Complement component 3, Membrane Cofactor Protein, Complement factor B, Complement factor D, Complement factor H, Complement factor H-related protein 1, 3, and 5, Complement factor I, Diacylglycerol kinase epsilon, Plasminogen, and Thrombomodulin (THBD). Factor H autoantibody was also tested and returned negative.
- Genetic variants in complement regulatory proteins account for 50-60% of aHUS cases, with 30-50% having no identifiable mutation.
- Direct damage on the vascular endothelium from drugs, autoimmune diseases, infections, and cancer are well-known causes of secondary aHUS. aHUS secondary to pancreatitis has been described few times in literature.
- The underlying mechanism in the setting of acute pancreatitis remains elusive, but may be related to release of activated enzymes causing endothelial damage and subsequent activation of proinflammatory cascades, with subsequent complement dysregulation and end-organ damage.
- Eculizumab, a C5 complement inhibitor, is considered first line therapy and has been shown to prevent multi-organ damage

Contact
Triston Berger, MD
Nuvance Health
Email: triston.berger@nuvancehealth.org

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