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Acute Pancreatitis Unmasks Complement-Mediated TMA in a Patient with Heterozygous CFHR1–CFHR3 Deletions: A Two-Hit Model Informing Diagnosis and Therapy

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Abstract

Introduction
Thrombotic microangiopathy (TMA) is a syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ injury due to microvascular thrombosis. Causes include thrombotic thrombocytopenic purpura (TTP), Shiga toxin-associated hemolytic uremic syndrome (STEC-HUS), and complement-mediated TMA (cm-TMA). CM-TMA results from dysregulation of the alternative complement pathway, mainly terminal complement activation.
We report a patient who developed cm-TMA following acute pancreatitis. The patient improved with plasma exchange (PLEX) and the terminal complement inhibitor eculizumab. Genetic testing revealed heterozygous deletions of CFHR1 and CFHR3, variants considered risk modifiers of uncertain significance.
This case supports a two-hit hypothesis, in which genetic susceptibility to complement dysregulation remains clinically silent until triggered by an inflammatory stressor such as infection, pregnancy, surgery, or malignancy. Clinicians should consider cm-TMA in patients with pancreatitis who have disproportionate cytopenias or kidney injury, as early recognition and complement-targeted therapy may improve outcomes and guide treatment decisions. This flips the clinical script: TMA is not an adverse event of pancreatitis; rather, the TMA is the main disease, and pancreatitis is the trigger.

Case Description
A 42-year-old woman with hepatic steatosis, gallstones, and prior pancreatitis presented with acute epigastric pain and lipase elevation. Imaging demonstrated peripancreatic edema without biliary obstruction. She was admitted for acute pancreatitis and treated with IV fluids and analgesia. On her third day of hospitalization, she developed melena, progressive cytopenias, and elevated LDH. Creatinine peaked at 7.88 mg/dL. She received transfusions and PLEX before transfer for further management.

Discussion
Evaluation included ADAMTS13 activity, Shiga toxin assay, complement levels, renal biopsy, and a complement-related genetic panel.
A low C4, normal C3, and elevated C3b suggested activation of the alternative pathway. Renal biopsy was consistent with TMA. Genetic testing identified heterozygous deletions of CFHR1 and CFHR3 within the CFH-CFHR cluster. Platelets improved after PLEX, though renal function remained impaired. After initiation of eculizumab, creatinine decreased to 4.5 mg/dL.
CM-TMA can be attributed to a broad spectrum of genetic changes, with incomplete penetrance. Heterozygous CFHR1-CFHR3 deletions are designated not pathogenic on their own but may contribute to disease under the two-hit model. In this patient, acute pancreatitis served as the inflammatory trigger unmasking her complement dysregulation disorder. This case highlights the importance of considering cm-TMA as a primary diagnosis when cytopenias and kidney injury are more severe than expected in the setting of inflammatory conditions that can act as triggers. It influences evaluation and therapeutic decisions, including whether to pursue early complement inhibition versus PLEX. Prompt recognition and targeted therapy may improve outcomes in cm-TMA.
Further management for patients with this diagnosis requires genetic counseling, vaccination against encapsulated organisms, and follow-up to monitor for common complications.