An unusual complication of acute pancreatitis – To treat or not to treat?

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The case

A 16-year-old girl presented with 1 week of epigastric pain and emesis and was diagnosed with acute pancreatitis complicated by splanchnic vein thrombosis (SVT).

History

A 16-year-old girl with a history of abnormal uterine bleeding on oral contraceptive pills (OCPs) presented with 1 week of epigastric pain and 1 day of nonbilious, nonbloody emesis. The epigastric pain was burning in quality, radiated to her back, and was described as 9 out of 10 in intensity. It improved with sitting up and leaning forward and was exacerbated by leaning backward. Her symptoms were preceded by rhinorrhea and sore throat. One week prior to presentation, she was evaluated by her primary care physician and received a course of antibiotics for presumed urinary tract infection. Two days later, due to continued pain, she presented to an outside hospital emergency department (ED) and was admitted for presumed gastritis. Her laboratory tests and imaging studies at the time were within normal limits. She was discharged home after a 1-day hospitalization on an acid suppression agent. Following a symptom-free period of 4 days, she developed acute onset epigastric pain radiating to the back and 1 episode of nonbilious vomiting, prompting a return ED visit.

Physical examination

On presentation, she was afebrile, tachycardic to 98 beats per minute, and tachypneic to 26 breaths per minute. She appeared to be in acute distress due to pain and diaphoretic. Her abdominal exam was significant for tenderness in the epigastrium and right upper quadrant. There was guarding but no rigidity or rebound tenderness. Bowel sounds were audible. She had a positive Murphy's sign. Her blood pressure was elevated at 130/80 mmHg. Her oxygen saturation was 97% on room air.

Differential diagnosis

Given her presenting symptoms of acute onset severe epigastric pain radiating to the back and nonbloody, nonbilious emesis, acute pancreatitis was the leading diagnosis. The differential diagnoses also included peptic ulcer disease, cholecystitis, cholangitis, acute mesenteric ischemia, hepatitis, inflammatory bowel disease, small bowel obstruction, pyelonephritis or cystitis, ureteric colic, pregnancy, pelvic inflammatory disease, ovarian torsion, or ectopic pregnancy.

Diagnostic evaluation

Studies done in the ED revealed a serum lipase of 5017 U/L. Her complete blood count was within normal limits with a white blood cell (WBC) count of 9K/uL. Comprehensive metabolic panel was unremarkable. C-reactive protein (CRP) was 8.4 mg/L. Lipid panel showed cholesterol of 271 mg/dL; high density lipoprotein of 71 mg/dL; low density lipoprotein of 160 mg/dL; and triglycerides (TGs) of 198 mg/dL. Her alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were elevated to 141 and 153 U/L, respectively. However, her total and direct bilirubin, alkaline phosphatase, and albumin were within normal limits. Coagulation profile showed normal D-dimer, prothrombin time, partial thromboplastin time, and international normalized ratio. Her troponin was normal. Urinalysis was significant for leukocyte esterase, >50 red blood cells/high power field (HPF), and 6 WBCs/hpf. Respiratory viral panel (RVP) was positive for adenovirus. Her COVID-19 polymerase chain reaction (PCR) was negative but COVID-19 antibody positive. Abdominal ultrasound demonstrated enlarged hypoechoic pancreas with trace peripancreatic fluid. Abdominal computed tomography (CT) was significant for enlarged liver measuring 21.7cm and few, tiny, non-obstructive gallstones in the gallbladder. Of note, it demonstrated prominent pancreas with peripancreatic fluid suggestive of acute pancreatitis. The splanchnic circulation was patent (**Figure 1**).

Diagnosis

The patient was diagnosed with acute pancreatitis and admitted for intravenous hydration and pain control. On hospital day (HD) 2, when she became febrile, tachycardic, and tachypneic, fulfilling the systemic inflammatory response syndrome (SIRS) criteria, laboratory tests were repeated. At this point, significant findings included leukocytosis (WBC count 15K/uL increased from 9K/uL) with neutrophilia of 82%, and elevated CRP to 217 mg/L (increased from 8.4mg/L). Serum lipase decreased from 5017 U/L to 1093 U/L. Magnetic resonance cholangiopancreatography showed newly demonstrated thrombosis of the splanchnic vasculature (splenic vein extending into the main portal vein) as seen in **Figure 2.** Doppler ultrasound revealed that the thrombus was non-occlusive. A diagnosis of pancreatitis complicated by SVT was made.

Discussion

SVT is a rare, but well-documented complication of acute pancreatitis. In adults, SVT complicates 16%-22% of acute pancreatitis cases.[1,2] There is a dearth of data on the presentation of pancreatitis-induced SVT in the pediatric population. Particularly, the efficacy of anticoagulation in improving outcomes and

facilitating thrombus resolution in pediatric patients remains largely unexplored. Data from adults are conflicting. Some studies show no difference in splenic vein recanalization with systemic anticoagulation[2,3] whereas others show improved clinical outcomes including lower mortality and lower incidence of new-onset organ failure.[4] Further research on the therapeutic benefit of systematic anticoagulation for SVT in pediatric acute pancreatitis is needed.

The etiology of pancreatitis in this case was most likely viral given the positive RVP for adenovirus. Estrogen is a rare cause of drug-induced pancreatitis with case reports demonstrating an increased risk of pancreatitis with prolonged use of estrogen OCPs.[5] The mechanism of action is secondary to the hyper-triglyceridemic effects of estrogen, and most cases described in the literature had TG levels exceeding 1000mg/dL.[5,6] However, our patient had only been on OCPs for 2 months, and her TG levels were within normal limits at presentation.

Another potential explanation is that OCP use predisposed our patient to a hypercoagulable state that contributed to the SVT. The first case of SVT associated with contraceptives was described by Reed et al in 1963.[7] Most case studies have demonstrated SVT occurring after at least 2 years of OCP use.[8-10] All of these patients were treated with anticoagulation.

Acute and past COVID-19 infection have also been associated with increased hypercoagulability.[11] Case reports of pancreatitis secondary to COVID-19 infection with positive COVID-19 PCR have been described in the literature. The mechanism of action is thought to be due to the expression of angiotensin converting enzyme II (ACE II) receptors in the pancreatic islet cells.[12] Studies have shown that ACE II expression is higher in the pancreas than the lungs, indicating that SARS-CoV-2 might also bind to ACE II receptors in the pancreas causing pancreatic injury.[12] The consequences of pancreatic injury include systemic inflammation, acute respiratory distress syndrome, and chronic pancreatitis.[13] Other mechanisms of pancreatic injury that have been hypothesized include the direct cytopathic effect of SARS-CoV-2 as well as well as indirect systemic inflammatory and immune mediated cellular responses, resulting in organ damage.[14] Similarly, COVID-19 infection has also been shown to be associated with hypercoagulability predisposing both adult and pediatric patients to micro- and macrovascular thrombosis.[11,15,16] SVT has also been reported as a rare sequela of COVID-19 infection.[17,18] The patient in this case was COVID-19 PCR negative making acute infection unlikely. However, she was positive for the COVID-19 antibody, indicating a past infection. Multi-systemic inflammatory syndrome (MIS-C) is a hyperinflammatory syndrome that occurs as a sequela to COVID-19 infection particularly in children and adolescents and is characterized by multiorgan involvement.[19] Gastrointestinal manifestations of MIS-C have been reported including mesenteric lymphadenopathy and edema, ascites, bowel wall thickening, ileus, hepatomegaly, and gallbladder wall thickening.[20] To the best of our knowledge, no reports of pancreatitis associated with MIS-C have been published.

Treatment and patient outcome

With the clinical deterioration on HD 2, the patient was transferred to the pediatric intensive care unit for management of possible septic shock versus complicated pancreatitis. She received respiratory support with continuous positive airway pressure and was started on broad spectrum antibiotics

(meropenem) for possible intraabdominal infection. Vancomycin was added on HD 5 due to continued fevers and concern for possible septic thrombi resulting from SVT. CT angiography was negative for pulmonary embolism. She defervesced on HD 6 and antibiotics were discontinued on HD 10 after all blood and urine cultures returned negative and her inflammatory markers were down-trending.

Pediatric hematology was consulted for management of SVT. The patient was initially started on an unfractionated heparin drip. Unfractionated heparin was chosen primarily for easy reversibility in anticipation of possible surgical intervention. Repeat doppler ultrasound on HD 9 showed resolution of the SVT (**Figure 2**). Unfractionated heparin was switched to low molecular weight heparin (enoxaparin) and then to apixaban for discharge home. Apixaban is a novel oral anticoagulant and was chosen because of its predictable pharmacologic profile which allows for use without the need for routine coagulation monitoring. She continues to follow up with pediatric hematology as an outpatient. She was discharged home on HD 20.

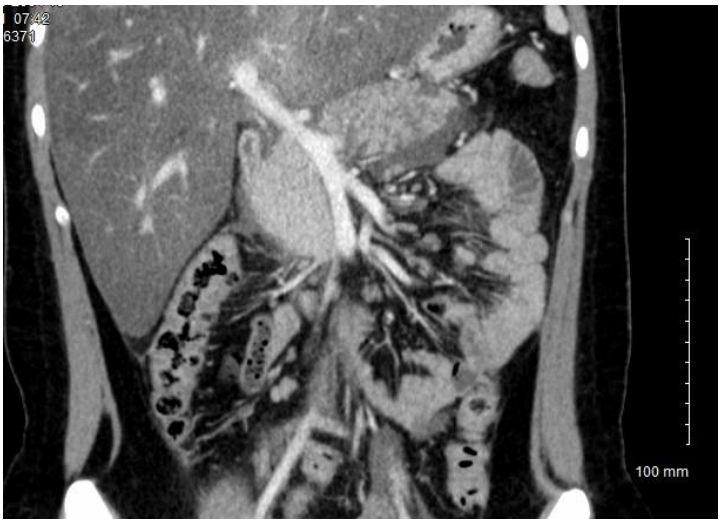

Figure 1 Hospital Day 0 – Patent splanchnic circulation

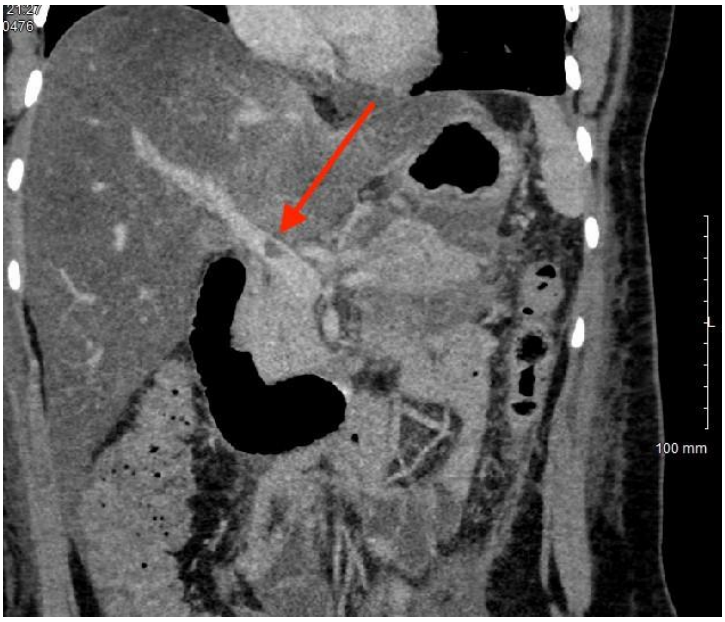

Figure 2 Hospital Day 5 - Persistent thrombus in the portal vein

BIOS

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