Thrombotic microangiopathy as a complication of recurrent pancreatitis

P. Malleshappa, A. P. Chaudhari, M. Aghariya, A. Siddiqui, R. Ranganath, A. B. Shah
Department of Nephrology, Lilavati Hospital and Research Centre, Mumbai, India

ABSTRACT

Acute pancreatitis as a cause of thrombotic microangiopathy is very rare. We report a case of 40-year-old woman with idiopathic recurrent pancreatitis, who presented with acute pancreatitis complicated by thrombotic microangiopathy. Although thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) has been reported as causing acute pancreatitis, the induction of TTP/HUS by pancreatitis is rare. As far as we are aware this is the first reported case of TTP/HUS in association with pancreatitis in India. Our patient had a complete recovery of her thrombotic microangiopathy following plasma exchange therapy.

Key words: Pancreatitis, plasma exchange therapy, thrombotic microangiopathy

Introduction

The symptom complex of fever, neurologic manifestations, thrombocytopenia, and renal dysfunction with microangiopathic hemolytic anemia characterizes thrombotic thrombocytopenic purpura (TTP).[1] Morphological studies show widespread hyaline microthrombi in the terminal arterioles and capillaries of heart, kidneys, and central nervous system. It is generally accepted that the pancreas can be affected by TTP. But the induction of TTP by pancreatitis is rare. Previously published case reports suggest that the acute inflammatory response to pancreatitis may trigger the onset of TTP.[2] The short interval between the diagnosis of pancreatitis and the diagnosis of TTP, a median of 3 days, raises the hypothesis that the inflammatory consequence of pancreatitis has a direct impact on the pathogenesis of TTP. Our patient developed TTP two days after the diagnosis of pancreatitis and recovered completely following plasma exchange.

Address for correspondence:
Dr. Pavan Malleshappa, Department of Nephrology, A-791, Lilavati Hospital and Research Centre, Bandra Reclamation, Bandra West, Mumbai - 400 050, India. E-mail: dr_pavanm@yahoo.co.in

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Case Report

A 40 year-old-female presented to us with an episode of sudden onset of severe upper abdominal pain. She denied any history of fever, vomiting, loose stools, or blunt trauma to her abdomen. She had two episodes of acute pancreatitis in the past. She had hypertension for 5 years and was recently detected to have diabetes. Following the second episode of pancreatitis, she was thoroughly investigated. Work-up did not reveal any metabolic causes like hypertriglyceridemia, hypercalcemia, toxic causes like heavy alcohol consumption, chronic drug intake, mechanical causes like gall stones, tumors of the pancreatic duct system or any other anatomical conditions associated with obstructive mechanisms of the pancreatic duct, and miscellaneous causes such as vascular disorders, tuberculosis, viral and parasitic infections, and tropical pancreatitis.

On the day of admission, she was afebrile with stable hemodynamics. Systemic examination was unremarkable except for severe guarding and rigidity of her abdomen. Her investigation results on admission were as follows: hemoglobin 10.5g/dL, total leukocyte count 8,800/cmm, platelet count 194,000/cmm, BUN 28mg/dL, creatinine 1.7mg/dL, amylase 1394 U/L, lipase 4275 U/L, total bilirubin 1.1mg/dL, direct bilirubin 0.6 mg/dL, AST 59 IU/L, ALT 17 IU/L, ALP 40 IU/L, albumin 4.2g/dL, calcium 8mg/dL. Sonography of the abdomen revealed bulky pancreas with peripancreatic collection, and no evidence of pancreatic cyst or stone in the pancreatic and common bile duct [Figure 1]. Her lipid profile and

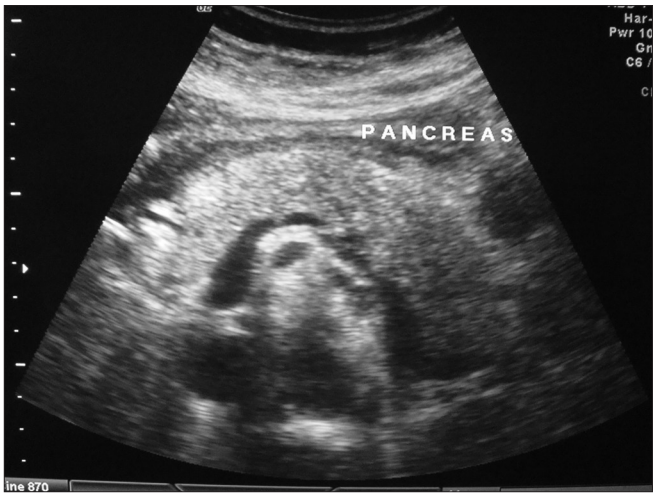

Figure 1: Bulky, edematous, hypoechoic pancreas with peripancreatic fluid collection

urine examination were unremarkable. She was kept nil by mouth and treated with intravenous antibiotics and other supportive measures.

Over the next 2 days, she became jaundiced, oliguric, and developed spontaneous bruises, epistaxes, and hematuria. She had an abrupt decrease in hemoglobin from 10.5 to 7.2 g/dL and platelet count from 194,000/cmm to 22,000/cmm. Further evaluation revealed the following: serum creatinine 2.79 mg/dL, total bilirubin 3.2 mg/dL, direct bilirubin 1.2 mg/dL, AST 160 IU/L, ALT 50 IU/L, ALP 52 IU/L, amylase 186 U/L, lipase 304 U/L, LDH 4288 U/L, reticulocyte count 5%, haptoglobin 3.9 mg/dL. Her PT, APTT, D-dimer, and fibrinogen levels were normal. Her peripheral blood film revealed numerous fragmented red cells and schistocytes. The coomb's test and vasculitis work-up were negative and serum complement levels were within normal limits.

In view of abrupt drop in hemoglobin and platelet count, worsening renal function, and fragmented red cells in blood film, a diagnosis of thrombotic microangiopathy (TTP/HUS) was made. She was initiated on plasma exchange as follows: 2 L of plasma exchange per cycle (35mL/kg), blood flow of 100 mL/min, heparin anticoagulation, and fresh frozen plasma, and albumin as the replacement fluid. The day after initiating plasma exchange, she had a further drop in her hemoglobin to 5.9 g/dL and platelet count to 11,000/cmm, which then stabilized. Her renal function also worsened with a raise in serum creatinine to 5.7 mg/dL. She received five cycles of plasma exchange daily followed by five cycles on alternate days. Her renal function, blood counts, and LDH levels were monitored. There was a dramatic improvement with the resolution of her bleeding tendency and significant improvement in urine output. The microangiopathic hemolysis and thrombocytopenia resolved (LDH 400 U/L, platelet count 200,000/cmm). Renal function returned to normal and she was discharged.

Discussion

TTP has been reported in association with a range of conditions including bacterial and viral infection, malignancy, pregnancy, and drug therapy. The clinicopathological features of TTP have been well documented but the pathophysiology remains to be elucidated. It is probable that the clinical syndrome can be precipitated by a number of different mechanisms depending on the underlying pathological condition. TTP has been reported to cause pancreatitis in about 2% of cases.[3] This is likely to be a result of ischemic damage caused by deposition of platelet thrombi in pancreatic arterioles. However, precipitation of the condition by acute pancreatitis is uncommon.

The mechanism by which pancreatitis induces TTP is not known. Several hypotheses have been put forward including the role of TNF-α and IL-1, which are important mediators for pancreatitis and might induce widespread vascular endothelial injury.[4] Karen and colleagues suggested that the acute inflammatory response to pancreatitis, mediated by IL6, IL8, and TNF-α, and other cytokines, contributes to the onset of an acute episode of TTP.[2] Circulating pancreatic proteases have previously been shown to interact with a number of components of the coagulation system. They can directly induce clotting factor activation precipitating disseminated intravascular coagulation and also proteolyse the alpha chains of fibrinogen resulting in dysfibrinogenemia. It is possible that in cases of TTP associated with pancreatitis, circulating proteases may modify circulating Von Willebrand factor (vWF) molecules enabling spontaneous binding to platelet membrane glycoproteins with subsequent platelet aggregation. This is analogous to the action of cysteine proteinases, which have been identified in the circulation of some patients with TTP.[5] Acquired or congenital deficiency of vWF has been shown to be the underlying cause of thrombotic angiopathies. Recently serum measurement of vWF cleaving protease (ADAMTS-13) has been used to differentiate between TTP and HUS, as patients with TTP have little or no ADAMTS-13 activity in plasma compared to patients with HUS. It has also been suggested that patients with ADAMTS-13 activity might have better prognosis than patients without ADAMTS-13.[6] However, in our patient serum levels of ADAMTS-13 could not be measured. In the absence of this definitive test, diagnosis of TTP/HUS

was entertained. Camilleri and coworkers detected a missense mutation (*C3178T*) in exon 24 of ADAMTS-13 in 11% of adult onset TTP. Such missense mutation have not been identified in childhood congenital TTP and may, therefore, be a factor in the development of late onset adult TTP.[7] A recent review by Thachil stressed that patients who develop TTP secondary to acute pancreatitis do not always have the characteristic low levels of ADAMTS-13, suggesting the involvement of other pathophysiological factors.[8]

A total of 21 patients have been reported to develop TTP following pancreatitis. Among these 21 patients, 14 were men, opposite to gender disparity of TTP but consistent with the great frequency of acute pancreatitis among men. Etiology of pancreatitis among these patients included chronic severe alcohol use, gall bladder disease, vasculitis, or idiopathic. TTP was diagnosed 2–15 days after the diagnosis of pancreatitis. Treatment modalities in these patients included were plasma exchange, plasma infusion, splenectomy or just a supportive therapy. Our patient had an excellent response to plasma exchange with complete resolution of her microangiopathy and complete recovery of her renal function.

Conclusion

Thrombotic microangiopathy is an important, treatable complication of recurrent pancreatitis and plasma exchange is a safe and effective modality in the treatment of thrombotic microangiopathy.

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