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CASE REPORT

E.P.C.M.S.

Pancreatitis leading to Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome

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DISCLOSURES
This work was previously presented as a poster at the Annual Meeting of the American Society for Apheresis in Galveston, Texas, April 2008.

ABSTRACT
The prevalence of acute kidney injury (AKI) in patients with acute pancreatitis (AP) has been reported to be 15%, with mortality from cases complicated by AKI close to 80% compared with 7% among patients with acute pancreatitis but without AKI. Hemolytic Uremic Syndrome (HUS) is a disorder consisting of AKI accompanied by non-immune hemolytic anemia and thrombocytopenia most commonly seen in children. Thrombocytopenic Thrombotic Purpura (TTP) shares many clinical similarities with HUS but affects mainly adults. TTP/HUS among adults is associated with infections, transplants, autoimmune diseases, drugs and neoplastic diseases. Pancreatitis as a result of TTP/HUS is rare, affecting only 2% of adults with TTP/HUS. Pancreatitis as the cause of TTP/HUS has only been described in a few case reports. We describe the case of a 25-year-old man with history of alcohol abuse who was readmitted with a diagnosis of AP and who developed progressive worsening of his renal function, despite fluid resuscitation, associated with thrombocytopenia. Further laboratory evaluations confirmed findings of microangiopathic hemolysis consistent with the diagnosis of TTP/HUS. The patient was started on therapeutic plasma exchanges with improvement of his renal function 24 to 48 hours after initiating therapy. In this patient with AP, the renal failure was part of TTP/HUS spectrum. The exact mechanism that leads to the development of TTP/HUS in patients with AP is not clear, some hypotheses point toward endothelial injury as the inciting factor that leads to the microangiopathic process mediated by pancreatic autoantibodies, interleukin-1, tumor necrosis factor-α or modified Von Willebrand factor. Exchange transfusion of fresh frozen plasma remains the cornerstone of treatment for classic TTP/HUS. Among adult patients, it is important that physicians recognize TTP/HUS as one of the potential causes of AKI in cases of AP, especially when there is concomitant thrombocytopenia, because the early initiation of plasma exchange has a major impact on survival and long term renal function.

INTRODUCTION AND BACKGROUND
Hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation are classified into a group of disorders called thrombotic microangiopathies (TMA) (1). The term HUS was coined by Gasser et al. in 1955 and describes an illness consisting of acute renal failure accompanied by non-immune hemolytic anemia and thrombocytopenia (2). The first case of TTP was described in 1924 by Dr. Eli Moschcowitz in a young woman who presented with microangiopathic hemolytic anemia, fever, bleeding, neurologic and renal abnormalities(1). HUS is most commonly seen in children, but cases among adults have also been described associated with infections, transplants, autoimmune diseases, drugs and neoplasms (1,3,4). Pancreatitis as a result of TTP or HUS is rare, affecting only 2% of adults with TTP/HUS (5). Pancreatitis causing TTP/HUS has only been described in a few case reports (5-8). Here we report a case of TTP/HUS that developed as a complication of acute pancreatitis (AP) and which was treated successfully with plasma exchange after early recognition.

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A 25-year-old was admitted to the hospital with epigastric pain, nausea and recurrent vomiting. The patient reported being hospitalized two months prior with similar symptoms diagnosed as acute alcohol-related pancreatitis. He denied having any other pre-existing medical conditions or prior surgeries. The patient drank large amounts of alcohol daily. Hypoactive bowel sounds and epigastric tenderness were found on physical exam. The admission laboratory examinations are shown in Table 1.

The patient was admitted with a diagnosis of recurrent pancreatitis secondary to alcohol abuse, dehydration secondary to oral intolerance and acute pre-renal azotemia. Intravenous fluid hydration was started and the patient was placed on bowel rest. Medications were given to control his pain, nausea and vomiting. In the next two days his renal function progressively deteriorated and on the third hospital day the blood urea nitrogen was 77 mg/dL and the serum creatinine was 7.1 mg/dL with associated oliguria that did not respond to further fluid challenges. It was also noticed that his hemoglobin and platelet count dropped to 10.4 g/dL and 26 x103/uL, respectively, without clinical evidence of bleeding. At that time the diagnosis of disseminated intravascular coagulation was considered, however his clotting profile remained normal. Further laboratory investigations revealed a raised reticulocyte count of 3.3%, schistocytes on the peripheral blood smear, LDH of 1774 IU/L (reference range: 94 – 172 IU/L), haptoglobin less than 14 mg/dL (reference range: 30 – 200 mg/dL) and a negative Coombs' test. The patient was therefore diagnosed with TTP/HUS.

The patient was started on daily therapeutic plasma exchanges (1.5 plasma volumes per treatment) on the third hospital day. His

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renal function and platelet count improved as shown in Figure 1. The therapeutic plasma exchanges were stopped after the fourth exchange and the patient was discharged to his home on the twelfth hospital day.

DISCUSSION

The prevalence of acute kidney injury in patients with acute pancreatitis has been reported to be approximately 15%, usually in association with multiple organ failure. Only 3% of patients with acute pancreatitis have isolated renal failure (9,10). The prevalence of acute kidney injury varies depending on the severity of the pancreatitis, with some reports being as high as 42% (11) and as low as 5% (12). The mortality from acute pancreatitis complicated by acute kidney injury can reach 70% to 80% compared with 6% to 7% in patients with pancreatitis but without acute kidney injury (9-11). Most of the deaths are in patients with multiple organ failure rather than with isolated acute kidney injury. In this case of acute pancreatitis, the decline in renal function appeared to be part of the hemolytic uremic syndrome.

HUS and TTP are two different and rare entities with similarities in clinical presentation, laboratory findings (thrombocytopenia/microangiopathic hemolytic anemia/renal dysfunction) and in the fundamental mechanism of endothelial cell damage (3). Increasingly, the two syndromes are described in tandem as TTP/HUS (13).

Two types of HUS have been described (3). The first is a self-limited, diarrhea-associated HUS that occurs mostly in children and is caused by verotoxin-producing E. Coli 0157:H7 (4,14,15). The second type of HUS is sporadic, not associated with diarrhea, and is most commonly seen in adults (1,16). Many of these cases are considered idiopathic, but in some instances have been found to be associated with infections, bone marrow transplants, autoimmune diseases, drugs and neoplastic diseases (16-18).

In our patient, the rapid deterioration of kidney function and the development of systemic symptoms within two days of admission led us to consider the possibility of a causal relationship between acute pancreatitis and the subsequent development of TTP/HUS. Other cases of acute pancreatitis preceding a thrombotic microangiopathy by 2 to 3 days have been reported in the literature (7). In most cases, the thrombotic microangiopathy became clinically apparent while the pancreatitis was clinically improving (7). Another case report in which acute pancreatitis was associated with TTP/HUS described the resolution of TTP/HUS following pancreatectomy (19).

Some hypotheses point toward endothelial injury, in acute pancreatitis, as the inciting factor that sustains the microangiopathic process. The mechanism of endothelial injury could be mediated by pancreatic autoantibodies, interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) or modified Von Willebrand factor (vWF) (5,6). Genetic predisposition is clearly important considering that most cases of acute pancreatitis do not result in TTP/HUS (20). It is difficult to identify risk factors for the development of TTP/HUS among patients with acute pancreatitis (1,3), because there have been only a few cases reported in the literature, and the pathophysiologic mechanism that leads to the development of TTP/HUS in patients with acute pancreatitis is not sufficiently understood (6,7).

Unusually large multimers of VWF (ULvWF) have been implicated in the pathogenesis of TTP/HUS. Aggregation of the large VWF multimers with platelets occludes terminal arterioles and capillaries (21). Recently, serum measurement of von Willebrand factor cleaving protease, called ADAMTS-13, has been used to differentiate between Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura. Patients with TTP may have either a deficiency in the activity of ADAMTS-13 enzyme or they have an inhibitor such as anti-ADAMTS-13, therefore patients with TTP typically have little or no ADAMTS-13 activity in their plasma compared to patients with HUS (3,16, 22-25), although TTP-like illness without identifiable ADAMTS-13 dysfunction has also been recognized (26).

Therapeutic plasma exchange, using donor fresh frozen plasma as the replacement fluid, remains the cornerstone of treatment for classic TTP (16,21). Although plasma-based therapies are being used first-line for HUS, there is no evidence from clinical controlled trials (20). It is thought that the donor plasma infusion replaces the missing metalloproteinase, while the removal of the patient's plasma depletes the ADAMTS-13 inhibitor and possibly also the vWF polymers (3). In our case, the patient's renal function improved after 24 to 48 hours of initiating the therapeutic plasma exchange. In his report of 20 cases, Boyle describes a 100% survival rate in patients that received plasma (7), other reports also describe renal recovery within 24 hours after initiating plasma exchange (5,6,8).

Other possible therapies that can be considered in refractory patients include splenectomy and the use of corticosteroid with variable success rates reported (1). Recently, in isolated case reports, the anti-CD20 monoclonal antibody rituximab has been used successfully in treatment refractory cases of TTP (27).

CONCLUSION

Acute kidney injury is a common complication of patients with acute pancreatitis. Most of these cases are associated with multiple organ dysfunction and are usually seen in the setting of severe pancreatitis. It is important that physicians recognize TTP/HUS as one of the potential causes of acute renal failure among adult patients with acute pancreatitis, especially when there is concomitant thrombocytopenia. While the pathophysiologic mechanism is not clear, direct or indirect endothelial damage is thought to play a major role. Early diagnosis and plasma exchange therapy have been reported to improve survival and preserve renal function.

Table 1. Laboratory results on admission

WBC (X103/uL)	Hb (g/dL)	PLAT (X103/uL)	PT/PTT	Na (mmol/L)	K (mmol/L)	HCO3 (mmol/L)	BUN (mg/dL)	CREAT (mg/dL)	AST (IU/L)	ALT (IU/L)	Lipase (IU/L)
17.6	16.9	233	Normal	135	3.3	21	10	1.8	56	88	1554

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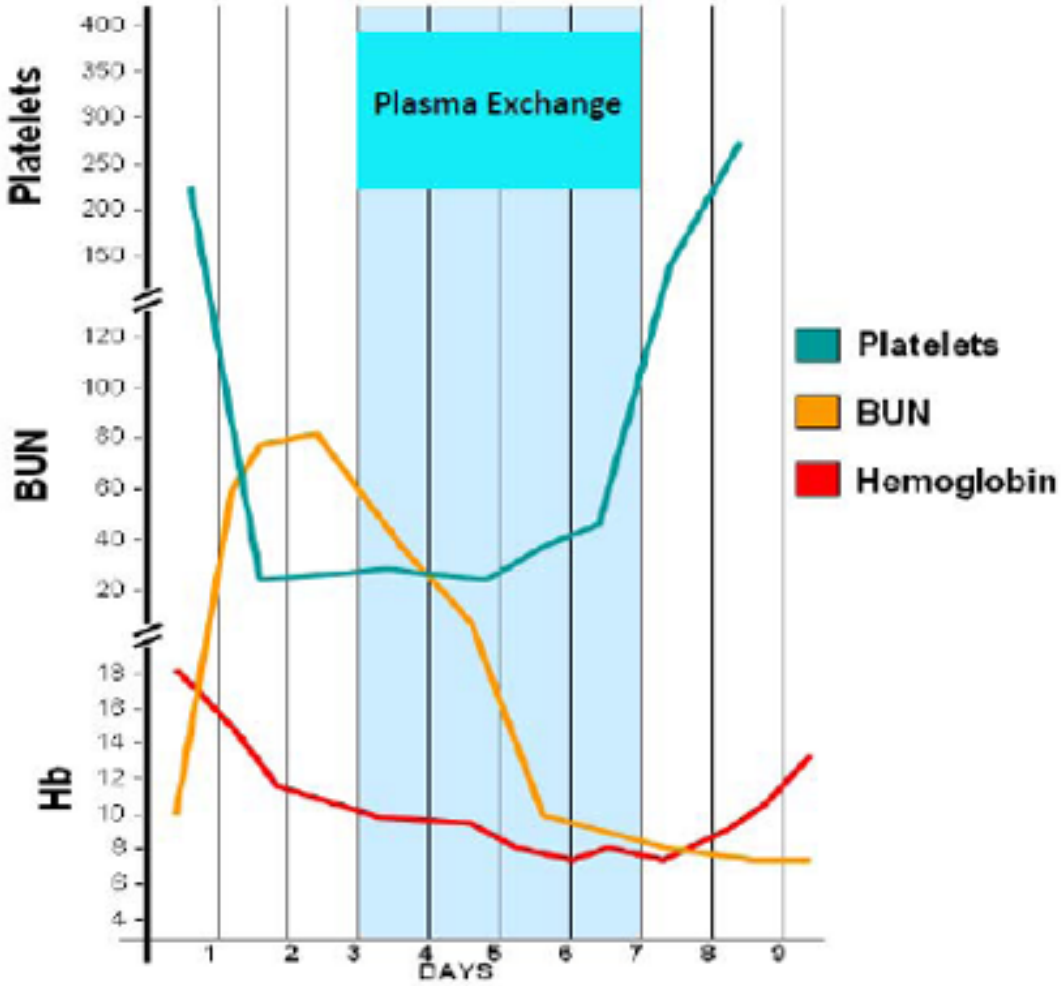
Pancreatitis leading to Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome
(Continued)

Figure 1



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