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Spinal Cord Ischemia Because of Microvascular Thrombosis in a Patient with Necrotizing Pancreatitis. Case Report and Literature Review

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 37-year-old
Final Diagnosis: Acute pancreatitis • thrombotic microangiopathy
Symptoms: Epigastric pain • paresis
Medication: —
Clinical Procedure: Computed tomography • ERCP • hemodialysis • magnetic resonance imaging • omentectomy
Specialty: Critical Care Medicine • Gastroenterology and Hepatology • Radiology • Surgery

Objective: Unusual clinical course
Background: Central nervous system ischemia in acute pancreatitis is rare with only a handful of cases reported in the literature. We report a case of spinal cord ischemia due to microvascular thrombosis complicating acute on chronic pancreatitis.

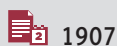
Case Report: A 37-year-old male was transferred to a university hospital intensive care unit with a diagnosis of acute onset chronic pancreatitis, paraplegia, and multi-organ failure. Laboratory studies showed elevated serum amylase activity and leukocytosis. The patient deteriorated quickly and anemia with thrombocytopenia and coagulation abnormalities developed. Computed tomography showed large pancreatic pseudocyst and ischemic lesions in abdominal organs. Symptoms of paraplegia preceded by the bilateral paresis were noted 7 days from the onset of his disease and magnetic resonance imaging showed ischemia involving the central part of the medullary cone resulting from microvascular thrombosis. The patient underwent endoscopic retrograde cholangiopancreatography and repeated surgery with a number of complications but 2 months later was discharged to rehabilitation center due to persistent neurologic deficit.

Conclusions: Patients with severe pancreatitis and multiorgan failure requiring intensive care should undergo routine neurological examination to identify and treat deficits early.

MeSH Keywords: Disseminated Intravascular Coagulation • Pancreatitis, Acute Necrotizing • Spinal Cord Ischemia • Thrombotic Microangiopathies

Abbreviations: AP – acute pancreatitis; DIC – disseminated intravascular coagulation; TTP – thrombotic thrombocytopenic purpura; HUS – hemolytic uremic syndrome; TMAs – thrombotic microangiopathies; FFP – fresh frozen plasma; RCC – red cell concentrate; ERCP – endoscopic retrograde cholangiopancreatography

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Background

Acute pancreatitis is an inflammatory process of the pancreas, which presents with epigastric pain and increased serum amylase [1]. Up to 70% of cases in the USA are triggered by alcohol overuse or common bile duct gallstones [2,3]. Apart from local complications, acute pancreatitis may result in serious systemic complications, such as systemic inflammatory response syndrome, gastrointestinal bleeding, and multi organ failure [4]. While overall mortality in acute pancreatitis approximates 5%, in severe necrotizing cases it may reach 17% to 30% [5]. Most of the fatal cases (up to 80%) result from bacterial infection of necrotic tissue and septic complications [6]. Significant complications may arise from hematologic disturbances related to acute pancreatitis. Disseminated intravascular coagulation (DIC) or thrombotic microangiopathies (TMAs) accompanying pancreatitis may lead to ischemic injury of multiple organs, however, neurologic sequelae are rarely reported [7–11]. We present a case of spinal cord ischemia in a patient with necrotizing pancreatitis complicated with microvascular thrombosis.

Case Report

A 37-year-old male was transferred to our tertiary care intensive care unit (ICU) from a local hospital with a diagnosis of complicated acute on chronic pancreatitis. Three days earlier (day 0), the patient presented to the local hospital emergency department complaining of severe epigastric pain and progressive lower limbs paresis. His medical history included one episode of alcohol-related acute pancreatitis. On admission, the patient's vital signs were heart rate 70 beats/minute; blood pressure 126/76 mmHg; saturation 99% at $\text{FiO}_2=0.21$; and body temperature 38°C. Examination of the abdominal wall revealed bruising around the umbilicus (Cullen's sign). The abdomen was tender to palpation, with no signs of peritonitis. Neurological examination showed absent deep tendon reflexes and weakened middle and lower cutaneous reflexes with attenuation of all kinds of sensation below the umbilicus and complete loss of sensation below the knees. Apart from increased amylase level (234 U/L) and leukocytosis ($12 \times 10^3/\mu\text{L}$), admission laboratory tests were normal. The patient underwent abdominal computed tomography (CT) and magnetic resonance imaging (MRI) of the lumbar spine. CT revealed a giant pancreatic pseudocyst (20×14×18 cm), impaired contrast enhancement of the left kidney and small subcapsular ischemic foci in both kidneys. MRI showed a central hyperintense signal on T2-weighted images in the thickened medullary cone sparing the thin rim of tissue on the periphery of the medulla. Acute onset chronic pancreatitis was diagnosed and since medullary infarction was suspected, the patient was given a prophylactic dose of low-molecular-weight

heparin (LMWH), and empiric antimicrobial therapy (ertapenem and vancomycin). Within a few hours, mild anemia (hemoglobin 11.7 g/dL) and thrombocytopenia ($146 \times 10^3/\mu\text{L}$) developed. On day 2, the patient's general condition deteriorated. He progressed to acute renal failure requiring hemodialysis and acute liver failure. Paresis transformed into a complete paraplegia. Laboratory tests showed anemia (6.5 g/dL), thrombocytopenia ($61 \times 10^3/\mu\text{L}$), decreased fibrinogen (135 mg/dL), increased D-dimers (29.1 ug/mL) and international normalized ratio (INR, 2.1) values, and prolonged activated partial thromboplastin time (aPTT, 40.7 seconds). Unenhanced CT showed hyperdense content in the pancreatic cysts consistent with intracystic bleeding. Fresh frozen plasma and packed red blood cells were administered.

On day 3, the patient was transferred to our hospital in critical condition: he was hypotensive with blood pressure maintained with vasopressors, and he was in septic shock. All cultures on admission (blood, urine, tracheal aspirate, throat and rectal swabs) were negative. The decision to perform an emergency laparotomy was made. The surgery included omentectomy and cholecystectomy due to their necrosis and external drainage of pancreatic cyst. Histopathological examination of the gallbladder revealed multifocal, bile stained, demarcated coagulative necrosis of mucosa accompanied by active inflammatory infiltrate. In deep layers of the wall, especially between muscle bundles, small vessels with fresh thrombosis were noticed (Figure 1). A CT on day 7 revealed ischemic foci in the liver and spleen and necrotic tissue in the pancreatic head and body and was followed by relaparotomy with pancreatic necrosectomy and lesser sac and rectovesical pouch drainage (Figure 2). After surgery, a mixed pancreatobiliary fistula was observed with an output of up to 500 mL of amylase-rich ($50\text{--}90 \times 10^3$ U/L) fluid per day. The next 2 weeks of conservative treatment included total parenteral nutrition, somatostatin, 8 sessions of hemodiafiltration, 4 hemodialysis sessions, and 4 packs of red cell concentrate transfusion, packed platelets, and fresh frozen plasma transfusion. Platelets count normalized on day 9 and hemoglobin level on day 12 and the patient was transferred from the ICU to the surgical ward on day 13. He underwent a follow up MRI on day 21 that showed persistent hyperintense signal on T2-weighted images in the central part of the medullary cone accompanied with patchy contrast enhancement (Figure 3). Due to persistent pancreatic fistula, the patient was scheduled for an endoscopic retrograde cholangiopancreatography (ERCP). Atrial fibrillation and cardiac arrest complicated the first ERCP on day 26, however, at the second attempt on day 40, 2 stents were introduced to the common bile duct and Wirsung duct. On day 57, the patient was discharged from the hospital in good general condition and without fistula symptoms and referred for intensive rehabilitation. A year later, the patient remained severely disabled: he developed lower-limb muscle atrophy and contractures in

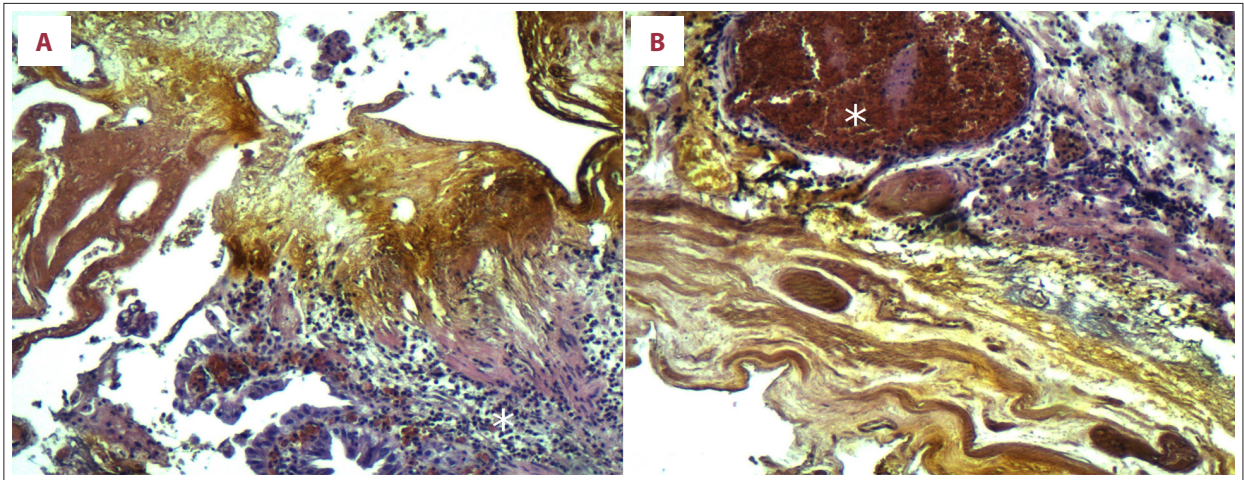


Figure 1. Hematoxylin and eosin histopathology. Coagulative necrosis of the gallbladder mucosa with active inflammatory infiltrate (A) and fresh thrombosis in the intramuscular vessel (B).

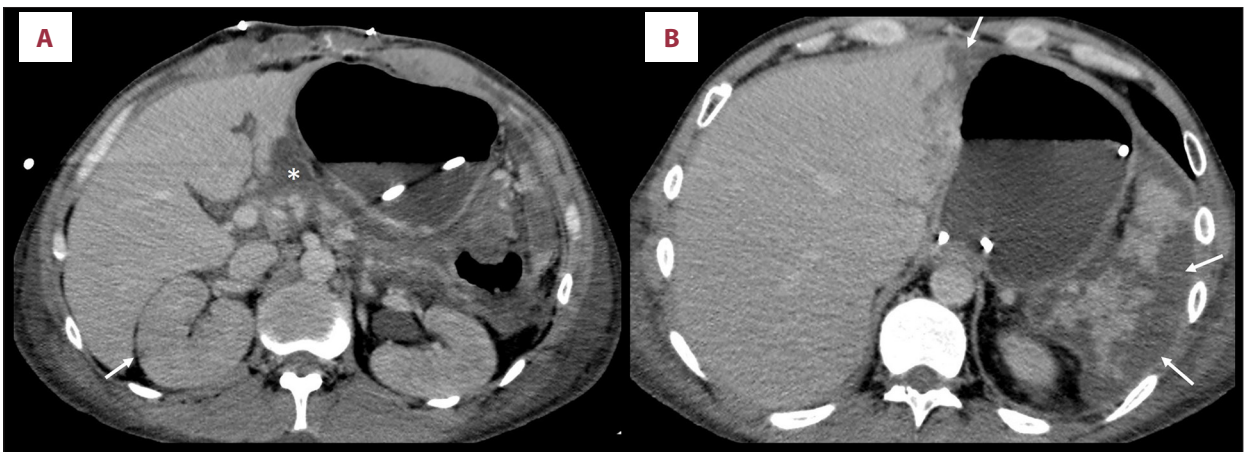


Figure 2. Computed tomography from day 7. The pancreas shows a diffuse edema with formation of acute necrosis collections in the head and body (A, asterix). The kidneys are edematous with small subcapsular ischemic foci (A, arrow). Large ischemic areas can be noticed in the left lobe of the liver and in the spleen (B, arrows).

the talocrural regions, had no deep tendon reflexes and middle and lower cutaneous reflexes and did not have any kind of sensation below the knees. He regained moderate flexion and extension in the hips, which allowed him to change body position and sit without arm support. He also moved from a wheelchair to a bed and opposite freely. The patient could walk by a wall with orthosis or with therapist help. He developed urinary retention requiring intermittent self-catheterization, suffered from erectile dysfunction, but had no problems with defecation. An MRI at 4.5 months after the incident showed severe atrophy of the medullary cone with central gliosis (Figure 3).

Discussion

Central nervous system ischemia complicating acute pancreatitis is extremely rare with only a handful of cases reported

in the literature. Wei et al. were the first to report on spinal cord infarction in a patient with acute pancreatitis, pseudocyst formation, and splenic infarction [11]. Soumian et al. presented a case of acute paraplegia in a patient with a ruptured hemorrhagic pancreatic pseudocyst, however, an exact cause of paraplegia was not explained with imaging or during autopsy [7]. Henin et al. described an MRI-confirmed medullary cone infarction during septic shock in a patient with choledocholithiasis-related cholangitis [9]. The patient had a history of a recent episode of acute onset chronic alcoholic pancreatitis with transient acute renal failure. Brain ischemia in the course of acute pancreatitis has also been reported [8,10]. Ludwig et al. reported scattered left cerebral hemisphere cortical infarctions in a patient with necrotizing acute onset chronic pancreatitis, splenic and left renal vein thrombosis. Imaging showed the thrombus in internal carotid artery without underlying atherosclerosis [8]. In our patient ischemia seems to

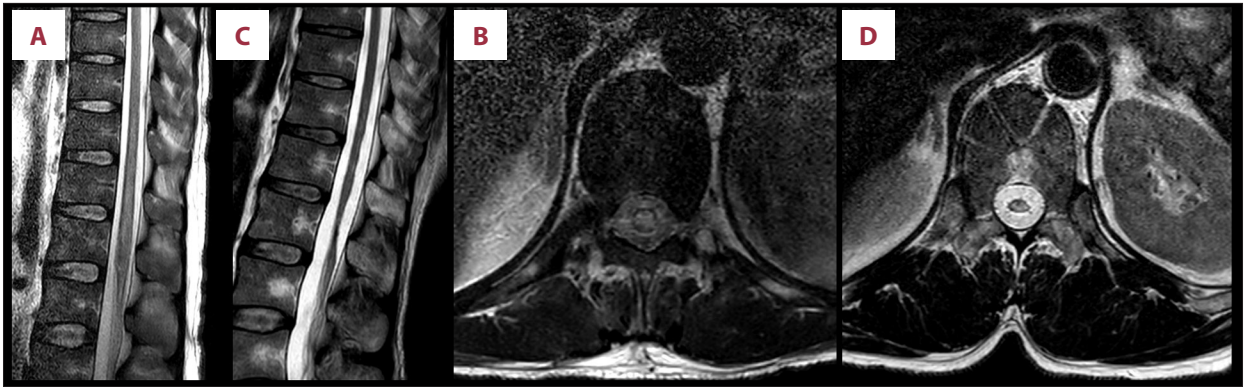


Figure 3. Evolution of magnetic resonance imaging (MRI) findings. MRI from day 21 shows edematous medullary cone with hyperintense signal on T2-weighted images sparing the periphery of the cord (**A, B**). Follow-up study 4.5 months later reveals atrophy of the conus medullaris with central gliosis (**C, D**). Our standard medullary trauma MRI protocol does not include FLAIR images; gradient echo (GRE) blood-sensitive images are included instead. Since follow-up MRI showed a marked atrophy of the medullary cone with intermediate hyperintensity on T2-weighted images (signal of lower intensity than cerebrospinal fluid in the dural sac), we consider gliosis more probable than myelomalacia, however both processes often coexist.

have risen from a small vessel thrombosis. While most cases of spinal cord ischemia are due to anterior spinal artery syndrome, which affects anterior two-thirds of the thoracic cord, in our patient ischemic lesion was within the medullary cone, usually surrounded by arterial circulation arising from both anterior and posterior spinal arteries [12,13]. Sparring of the periphery of the cone suggests that ischemia occurred in the territory of small vessels located further away from the arterial circulation. Findings in other organs confirm this supposition: imaging showed scattered ischemic foci in the kidneys, liver, and spleen and surgical exploration revealed ischemic necrosis of the omentum and gallbladder with microvascular thrombosis seen in histopathology. Other factors might have contributed to the neurologic outcome of our patient. The patient had neurologic symptoms before he deteriorated and became hypotensive, however, considering a well-known susceptibility of lumbar spinal cord to global ischemic events, hypotension might have had a role in aggravating the ischemic insult [14]. The presence of very large (20×14×18 cm) pancreatic pseudocyst and inflammatory process in the abdominal cavity most likely increased intra-abdominal pressure, which might have caused congestion in the valveless spinal veins [15].

The constellation of microvascular thrombosis, anemia, thrombocytopenia, and organ failure found in our patient may occur both in disseminated intravascular coagulation (DIC) and thrombotic microangiopathies (TMAs) such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) [16]. DIC is much more common than TTP and HUS and changes in laboratory studies showing fibrinogen depletion, increased D-dimers, and prolonged aPTT were typical of DIC, however, they occurred a few days after neurologic symptoms [16,17]. Initially, our patient had mild anemia

and thrombocytopenia without coagulopathy, suggestive of TMA [16,18,19]. Acute pancreatitis and TMAs are mutually related: there are reports of TTP/HUS both preceding pancreatitis and occurring in the course of it [20–24]. In our patient, lack of preceding diarrhea and melaena/hematochezia and the presence of neurologic complications make TTP more probable than HUS [16,18,19]. Pancreatitis in TMAs results from a disruption of pancreatic blood supply from microvascular thrombosis [21]. The key pathophysiological mechanism in TTP is a deficiency of ADAMTS13, a metalloproteinase that cleaves ultra large von Willebrand Factor (UL-vWF) multimers [25]. Those multimers bind to, activate, and aggregate platelets, therefore low ADAMTS-13 activity promotes the formation of platelet-rich thrombi in small vessels throughout the body causing organ failure [25]. The kidneys are prone to injury in TTP from low expression of CD36 transmembrane protein [23,25]. Idiopathic TTP is caused by protease-directed autoantibodies [26]. The exact mechanism of TTP development in patients with acute pancreatitis is still not established clearly, however, apart from antibodies, multiple factors that may disturb ADAMTS13/vWF balance in the setting of systemic inflammation either by inhibition of ADAMTS-13 or increased vWF production have been identified (e.g., interleukins, cytokines, coagulation factors, enzymes) [20,22,25,27–29]. Low ADAMTS-13 activity has been also observed in DIC [30,31]. Patients with sepsis-induced DIC who have a severely reduced ADAMTS13 activity have a clinical profile indistinguishable from that of patients with primary TMA [30]. Low ADAMTS13 activity is associated with risk of renal failure and worse outcome in patients with DIC or sepsis irrespective of DIC [30]. The reports on coexistence of DIC and TMA are not uncommon [25,32]. Based on the clinical course and laboratory test results, we believe that it was also the case in our patient and that overlapping of DIC and

TTP leading to microvascular thrombotic occlusion in different mechanisms was responsible for bulky systemic thrombosis. The treatment in our patient was therefore aimed to both remove the cause of DIC (antibiotic therapy, pancreatic cyst drainage, necrosectomy) and limit the effects of TTP (hemodiafiltration, fresh frozen plasma administration, hemodialysis) [33].

Several diagnostic algorithms for DIC and TMA have been published [34–36]. Recently, Vincent et al. proposed a practical approach for interventionists to distinguish DIC from TMA [16]. In patients with thrombocytopenia, microangiopathic hemolytic anemia and organ dysfunction diagnostics should start with coagulation profile (prothrombin time, aPTT, D-dimers). If findings in coagulation profile are not specific for DIC, the next steps should include assessment of ADAMTS13 activity and stool culture/PCR for Shiga-toxin-producing *Escherichia coli* to rule out TTP and HUS. However, ADAMTS-13 activity testing is not available routinely.

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Due to very few cases reported in the literature, there is no proven treatment that could prevent or limit the progression of the spinal cord ischemia associated with TMAs.

Conclusions

Coagulation abnormalities in the form of TMA and/or DIC may aggravate the course of pancreatitis. Considering serious consequences of this complication, a high index of suspicion is recommended, and blood morphology and coagulation profile should be observed with caution in patients with pancreatitis.

Conflict of interest

None.

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