Int J Clin Exp Med 2016;9(2):3621-3627
www.ijcem.com /ISSN:1940-5901/IJCEM0016802

Original Article

Occult portal venous system thrombosis complicating acute pancreatitis: three case reports and a literature review

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Received September 24, 2015; Accepted December 17, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Portal venous system thrombosis (PVT) is a relative rare complication of acute pancreatitis (AP), especially in China, and the incidence thereof in published studies may be overestimated. The management of PVT complicating AP by the use of anticoagulation therapy remains controversial due to the lack of standardized treatment. We herein report three cases of occult PVT complicating AP. Referring to the literatures and our clinical experiences, if the thrombosis detected recently and lack of evidence of bleeding tendencies, anticoagulation therapy is safe and is not associated with an increase in major complication. Since the study was done only in three cases, the necessity of implementing anticoagulation therapy in PVT complicating AP will require more supportive data in future as more evidence-based data emerges.

Keywords: Acute pancreatitis, portal venous system, thrombosis, anticoagulation therapy

Introduction

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas characterized by local or systemic complications. The 2012 revision of the Atlanta Classification recognizes three grades of disease severity: mild, moderately severe, and severe [1]. In most patients, the clinical course is mild and self-limiting, but in moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP) patients, a range of complications develop. PVT is a rare complication, which is often an incidental finding on contrast-enhanced computed tomography (CECT) which is performed to assess symptoms or local complications, involving the portal vein (PV), the splenic vein (SV), and the superior mesenteric vein (SMV) either alone or in combination [2]. Previous studies on PVT complicating pancreatitis focused principally on chronic pancreatitis (CP) patients, and the incidence varying from 1% to 24% [3]. As the spontaneous recanalization rate was high, the implementation of anticoagulation therapy still remains controversial [2]. Most patients' symptoms are atypical, or overlaps with those of AP. If the diagnosis and treatment is not timely it may result in serious clinical consequences which includes hepatic failure, hypersplenism, bowel ischemia, and gastrointestinal hemorrhage [3]. In the present article, we report three cases of occult PVT complicating AP and review the literature with a hope of raising awareness of this complication.

Typical case presentation

A 56-year-old male patient was admitted to our emergency department 20 hrs after a bout heavy drinking with gradually progressive pain in the upper abdomen, abdominal distension, nausea, and vomiting. He had no significant past medical history except for a 30 pack-year smoking and chronic heavy alcohol intake. His vital signs were normal. On physical examination, he exhibited epigastric and left upper quadrant tenderness. Murphy's sign and peritoneal signs were negative. Laboratory test results were: white blood cell (WBC) count

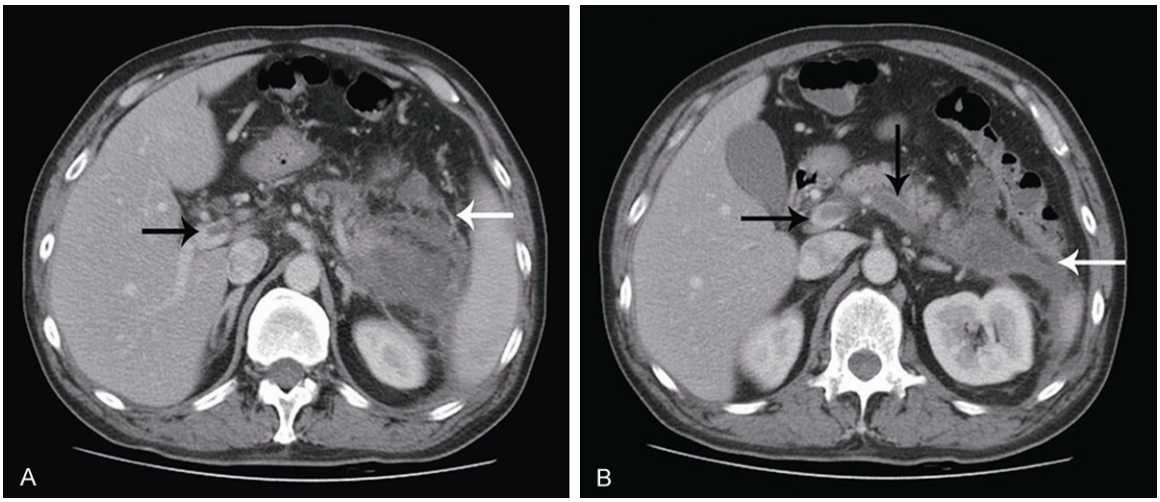

Figure 1. The male patient with acute interstitial edematous pancreatitis and acute peripancreatic fluid collection (APFC) (white arrow). A. A filling defect in the contrast-filled right branch of the portal vein (black arrow) was caused by a thrombus. B. Filling defects in the contrast-filled splenic and portal veins (black arrow) were caused by a thrombus.

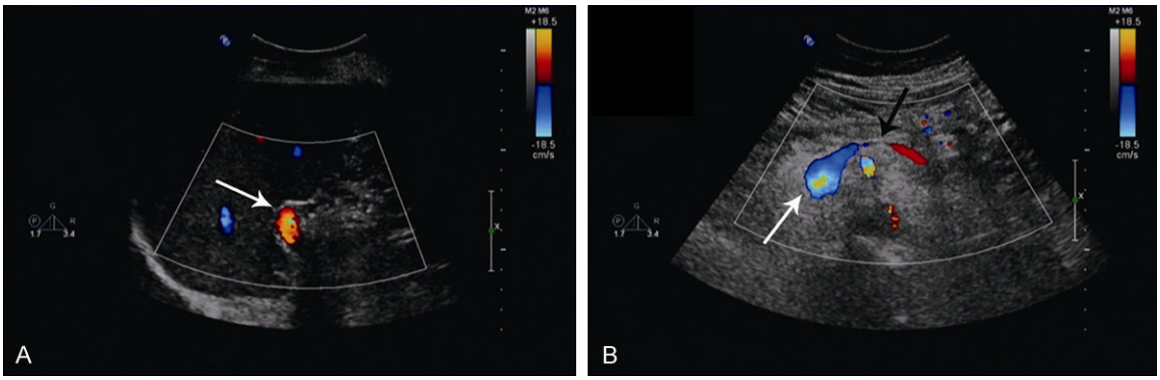

Figure 2. Outpatient color Doppler ultrasonography (CDUS) performed 6 months after initiation of anticoagulation therapy showed complete resolution of the clot. A. There was no thrombus in portal veins (white arrow). B. There was no thrombus at the confluence of the portal vein and splenic veins (black arrow).

10.33×10^9/L with 90.81% neutrophils; hemoglobin (HB) 181.10 g/L (Normal range: 115-150); amylase (AMY) 1137 U/L (Normal range: 30-110); lipase (LPS) 1479 U/L (Normal range: 23-300); calcium (Ca) 1.99 mmol/L (Normal range: 2.1-2.55); alanine aminotransferase (ALT) 43 U/L (Normal range: 7-40); r-glutamyl transpeptidase (r-GT) 314 U/L (Normal range: 7-45); cholesterol (CHOL) 5.71 mmol/L (Normal range: 0-5.2); triglycerides (TG) 4.2 mmol/L (Normal range: 0-1.7); and blood glucose (GLU) 10.19 mmol/L (Normal range: 3.89-6.11). Coagulation blood test and other laboratory data were normal. Chest CT revealed bilateral pleural effusion. Abdominal CT was conclusive to the diagnosis of AP. After 10 days of conventional treatment (bowel rest, intravenous fluids, antibiotics, and Chinese medical therapy), his abdominal pain was gradually ameliorated. We performed CECT to evaluate pancreatic necrosis and found thrombosis of the portal and splenic veins (**Figure 1**). He had no symptoms caused by PVT. Early anticoagulation therapy was implemented as the thrombosis was detected. We administered subcutaneous injections of low molecular-weight heparin with a subsequent transition to oral warfarin. Outpatient color Doppler ultrasonography (CDUS) performed 6 months post initiation of anticoagulation therapy which resulted in complete resolution of the clot (**Figure 2**) with no related complication.

Discussion

As the standardized CT scan protocols used for detection of thrombosis have increased in sensitivity, the incidence of PVT has risen gradually in recent years, being reported in 1.8-24% of AP patients [2-5]. In our retrospective study, we collected data from the First Affiliated Hospital of Dalian Medical University, focusing on patients diagnosed with PVT complicating AP during the period from May 2010 to May 2014. A total of 446 AP patients were treated during this time, of which 163 were MSAP and SAP patients. PVT was detected in three patients (in 0.67% and 1.8% of MSAP and SAP patients). All three cases in our study had a history of heavy alcohol intake (which is generally considered to be > 50 g per day and over 5 years) [6]. They were in accordance with the diagnosis of acute alcoholic pancreatitis and accompanied by a long-term smoking history (**Table 1**). This incidence is much lower than what is noted in English literatures (**Table 2**). The three principal reasons for this may be briefly summarized. First, Dorffel et al [7] and Rebours et al [8] found that PVT was significantly more frequent in patients with alcohol- rather than gallstone-induced pancreatitis, and in most developed countries alcohol is the other major cause of AP [9]. Nevertheless in our country gallstone-induced disease is dominant, with alcohol-induced disease being relatively less common. Secondly, asymptomatic patients may have been missed because diagnostic imaging may not have been performed thus decreasing the reported incidence. Lastly, before the advent of 2012 revision of the Atlanta Classification the published studies were not consistent in terms of inclusion criteria; some literatures calculated the incidence in MSAP and SAP as denominator and so the incidence of PVT may have been overestimated. All our cases were alcohol-induced AP, consistent with literature reports. Therefore, a CECT examination has to be performed in patients with acute alcoholic pancreatitis, to ensure that a relevant diagnosis is not missed. A more detailed understanding of the features and severity of the disease would allow a uniform categorization of the system to be established worldwide, and we recommend the 2012 revision of the Atlanta Classification. A remarkable fact is that heavy drinkers are more likely to be smokers. Smoking alone may induce pancreatitis, or smoking and alcohol may exert additive effects. A recent study found that smoking was independently associated with an increased risk of pancreatitis [10], but it is difficult to assess the effects of smoking on PVT development.

In the cited studies, 58-100% had pancreatic necrosis or peripancreatic fluid collections (PFCs) [2, 3, 5, 7], suggest that MSAP and SAP patients are more prone to develop PVT. Several local or systemic features may play important roles in PVT pathogenesis. Rebours et al [8] recently reported that PVT in patients with acute alcoholic pancreatitis was caused by local inflammation and not thrombophilia. A clear association was evident between the sites of necrosis or PFCs, and the vessels that were thrombosed [2]. As the pancreas and the portal venous system share a close anatomical relationship, PV, SV, SMV were often involved, and the most commonly involved vessel is the SV [2-5, 7]. It is noted that complication of AP such as pancreatic necrosis, PFCs, or an enlarged pancreatic parenchyma which can lead to the venous compression and progressive edema with cellular infiltration. Inflammatory process can involve the vein directly and cause intimal injury leading to thickening of the wall and narrowing the lumen of the vessel. The outcome progresses to blood flow disturbance resulting in stasis and occlusion [3]. Occlusion of major vessels and its branches due to PVT may result in collateral circulation channel. Once the SV and the distal portal vein are obstructed the blood flows to short gastric veins diverting excessive blood into stomach in the form of gastric varices (GVs) [11].

Symptoms of PVT complicating AP always depend on the formation of clot, the site and the extent of the thrombosis; along with the formation of the collateral circulation. It is a challenge for clinicians to determine whether abdominal pain is caused by a thrombus or AP progression. In a few patients clinical presentation is severe with sudden-onset of abdominal pain, intestinal necrosis, perforation, peritonitis, shock and even death from multiorgan failure [12]. Most patients with occult thrombi of the portal venous trunk have partially blocked vessels presenting with symptoms of gastrointestinal dysfunction such as low grade fever, mild abdominal pain or distention, diarrhea, nausea, vomiting, and anorexia. They may also have ongoing symptoms of AP. Thus, because of early misdiagnosis, PVT develops to the subacute stage. As the thrombus progresses, vis-

Table 1. Comparative clinical analyses of three cases

Case	Sex/age (years)	Etiology	Smoking	PFCs or Necrosis	Time (PVT detected)	Vessel thrombosed	Peritoneal lavage	Anticoagulated	Recanalized	Collateral formation	Follow up	Outcome
1	M/56	Alcohol	YES	PFCs	10 days	PV, SV	No	Long-term anticoagulation	YES	No	1 year	Well
2	M/52	Alcohol	YES	Necrosis	8 days	PV	YES	Short-term anticoagulation	YES	No	2 year	Well
3	M/38	Alcohol	YES	Necrosis	12 days	PV, SV	No	Long-term anticoagulation	YES	No	6 month	Well

Table 2. Previous data on PVT complicating AP reported in the English-language literature

Reference	Incidence	Sex		Age (mean)	Etiology			Collection or necrosis	Time (PVT detected)	Vessel thrombosed		
		Male	Female		Biliary	Alcohol	Other			PV	SV	SMV
Dorffel et al [7]	24% (45/189)	60%	40%	43 yr	32%	54%	14%	87%	10-14 days (average)	25%	62.5%	12.5%
Vege et al [4] (abstract)	4.3% (50/1155)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	26%	74%	20%
Gonzelez et al [2]	18.9% (20/127)	45%	55%	53.5 yr	45%	55%	0	80%	at the time of their admission	70%	50%	15%
Harris et al [3]	1.8% (45/2454)	69%	31%	58 yr	51%	11%	38%	58%	Onset: 18% <1 month: 42% <1 year: 40%	44%	67%	38%
Easler et al [5]	14% (22/162)	64%	36%	54 yr	50%	23%	27%	100%	17 days (average)	36%	86%	27%

Reference	Recanalization rate		Bleeding complications		Collateral formation	Follow up (mean)	Outcome*
	AC group	Non-AC group	AC group	Variceal bleeding			
Dorffel et al [7]	N/A	N/A	N/A	0	60% (27/45)	7 month	Survival 45/45 (100%)
Vege et al [4] (abstract)	62.5% (5/8)	19% (8/42)	0	2% (1/50)	N/A	N/A	N/A
Gonzelez et al [2]	50% (2/4)	25% (4/16)	0	0	50% 10/20	18 month	Survival 19/20 (95%) One death 1/20 (5%)
Harris et al [3]	12% (2/17)	11% (3/28)	12% (2/17)	2% (1/45)	43% (21/45)	N/A	Survival 42/45 (93%) Three death 3/45 (7%)
Easler et al [5]	9% (2/22)		25% (2/8)	0	86% (19/22)	12.3 months	Survival 21/22 (95%) One death 1/22 (5%)

PV: portal vein, SV: Splenic vein, SMV: Superior mesenteric vein, AC: Anticoagulation, N/A: Not available. *Deaths were due to severe AP, not severe bleeding complications.

ceral venous collateral circulation becomes well-established, and cavernous transformation of the portal vein marks the beginning of the chronic phase. Such patients present with portal hypertension as revealed by rupture of esophageal GVs, hemorrhage, splenomegaly, and ascites. In our present study, the symptoms were non-specific, being similar to those of AP, hence we should pay more attention to this complication.

Rebours et al [8] reported that thrombosis occurred a median of 5 (0-19) years after the diagnosis of CP. Easler et al [5] reported that the median time to detection of PVT complicating AP was 17 days (interquartile range, 11-40 days). The difference between CP and AP is worthy of our attention, early CECT not only aids in evaluating the prognosis but also allows screening for PVT. In our present study, the time period from onset of symptom to confirmation (by CECT) of thrombosis were 8, 10, and 12 days, thus an average of 10 days, which was consistent with the literature reports, suggesting that CECT should be performed about 10 days after the onset of symptom. Laboratory tests are of limited utility in the diagnosis of PVT; diagnosis is principally achieved via CDUS, CECT, and magnetic resonance imaging (MRI) [13-15]. CECT is one of the most common radiological imaging techniques used to assess the extent of pancreatic necrosis, and to evaluate vascular structures, the bowel wall, and the adjacent mesentery. The sensitivity attains at least 90% [14, 15].

Management includes treatment of AP per se, and anticoagulant therapy. Therapeutic strategies for AP include correction of water and electrolyte imbalance, nutritional support, and prevention of local and systemic complications. Gonzelez et al [2] recently reported that recanalization was evident in almost one-third of PVT complicating AP patients, irrespective of whether or not systemic anticoagulation therapy was prescribed. AP alleviation, with absorption of PFCs and reductions in pancreatic necrosis, may explain this outcome. Upon release of compression, and decreased perivascular inflammation, blood clots dissolves and vascular recanalization is achieved. This also suggests that the most effective way to treat PVT complicating AP is probably to drain PFCs and reduce pancreatic necrosis in a timely manner. Percutaneous drainage (PCD) and peritoneal lavage are the most frequently used minimally invasive methods for management of fluid collections complicating necrotizing AP, and are to be preferred to open necrosectomy [6]. In one patient of our study, symptom onset was characterized by acute hemorrhagic necrotic pancreatitis, and timely peritoneal lavage played crucial role in successful treatment and better prognosis. Also, the thrombus disappeared in this particular patient and was discharged without oral warfarin. These observations support the aforementioned view. Subcutaneous injections of low-molecular-weight heparin with a subsequent transition to oral warfarin is the most common approach to anticoagulation therapy, maintaining the prothrombin time (PT) in the range of 13-26 and the international normalized ratio (INR) between 2 and 3 [16], but whether or not such therapy given remains controversial. Gonzelez et al [2] and Samar et al [3] recently reported that no significant differences in PVT recanalization rates were evident between patients given anticoagulation therapy or not, but such therapy was advocated because it is not associated with an increased bleeding risk in AP patients within the appropriate indications. The duration of such therapy is 3-6 months depending on the speed of recanalization. The European Network for Vascular Disorders of the Liver (EN-Vie) recommends early anticoagulation therapy for patients with acute PV thrombosis unrelated to cirrhosis or malignancy and recanalization was seen in one-third of the patients [17]. Anticoagulation therapy is safe both in patients with a healthy liver and in patients with cirrhosis [18]. Most of the patients who fails to achieve the recanalization were noted for gastroesophageal varices during the follow-up [19]. Based on the EN-Vie recommendation, two of our cases received long-term anticoagulation therapy, and one received short-term therapy. The thrombi disappeared and no related complication was evident during follow-up, supporting early diagnosis of PVT and treatment with anticoagulant therapy, especially when thrombosis is recent and with no evidence of bleeding tendencies. Our studies have limitations. We studied only three cases, and the spontaneous recanalization rate was high so we cannot state that early anticoagulation is a necessity. We did not screen all patients who developed PVT for thrombophilic states, but a recent study reported that there is no indication for screen-

ing of thrombophilia in a patient with no past medical history of blood related disorders [8]. Patients on long-term oral warfarin require regular monitoring of the INR; this not only increases the medical burden but also the mental pressure on patients. The prescription of anticoagulant therapy may confirm in future as more evidence-based data emerges.

Conclusion

The incidence of PVT complicating AP in China is much lower than noted in English literatures, although the true incidence could be higher because asymptomatic patients with AP and PVT may have been missed when diagnostic imaging were not performed, and we should pay attention to the application of CECT. PVT was significantly more frequent in patients with acute alcoholic pancreatitis and is caused by local inflammation and not thrombophilia. Referring to the literatures and our clinical experiences, if the thrombosis detected recently and with lack of bleeding tendencies, anticoagulation is safe and is not associated with an increase in related complications. Because we studied only three cases, the role for anticoagulation therapy for patients with PVT complicating AP needs to be confirmed in a larger prospective, multicentric study.

Acknowledgements

We thank Prof. Dong Shang for assisting in the preparation of this manuscript. This study was supported by the National Natural Science Foundation of China (Grant No. 81373875).

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Disclosure of conflict of interest

None.

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