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Pulmonary Embolism in Acute Pancreatitis: A Rare but Potentially Lethal Complication

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Introduction to Pancreatitis and Venous Thrombosis

Acute pancreatitis is an acute inflammatory process of the pancreas with local tissue injury and systemic inflammatory response. In the United States, out of gastrointestinal disease, acute pancreatitis was the most common reason for hospitalization [1]. Alcohol consumption, gallstones and idiopathic pancreatitis were the most common causes identified [2]. Cholelithiasis is the most common cause of acute pancreatitis in most areas of the world [3]. Serum amylase and multiple other biochemical tests are used in the diagnosis of acute pancreatitis and CT scan is the most important radiological test for diagnosing and to assessing complications of acute pancreatitis.

Pulmonary embolism results from obstruction of the pulmonary artery or one of its branches mostly by a thrombus and if untreated has a high mortality rate [4,5]. Most pulmonary emboli arise from thrombi in the lower limb deep venous system, iliofemoral veins being the most common source [6,7]. Immobilization was the major acquired risk factor for venous thrombosis and other risk factors include surgery within the last three months, stroke, paralysis, central venous instrumentation within the last three months, malignancy, chronic heart disease, autoimmune diseases, a history of venous thromboembolism, obesity, heavy cigarette smoking and hypertension [8-10]. Factor V Leiden mutation and the prothrombin gene mutation are the most frequent causes of an inherited hypercoagulable state leading to venous thromboembolism.

Splanchnic venous thrombosis and pancreatitis

Vascular complications in pancreatitis are well recognized and haemorrhage is the commonest usually due to erosion of a major pancreatic or peripancreatic blood vessel or due to the formation and subsequent rupture of an arterial pseudoaneurysm [11]. Splenic vein thrombosis [12] and less commonly portal and superior mesenteric vein thrombosis can also occur in pancreatitis [13,14]. In a Systematic Review and Meta-analysis done in 2015, pooled prevalence of splanchnic vein thrombosis was found to be 16.6% and 11.6% in patients with acute and chronic pancreatitis, respectively. Pooled prevalence of portal vein, splenic vein, and mesenteric vein thrombosis was 6.2%, 11.2%, and 2.7% respectively [15]. These venous thrombosis are related to the close proximity of the veins to pancreas [12,16]. In a prospective study done by Bernades et al. acute pancreatitis and pseudocysts were the probable cause of splenic vein thrombosis in 91.4% of cases [12]. According to Rebours V pseudocysts were associated with portal venous system thrombosis and local inflammation appears to be the major predisposing condition [14].

Extrasplanchnic venous thrombosis and pancreatitis

Even though the splanchnic venous thrombosis is well known in pancreatitis involvement of other veins are rare [17]. In 1988 Stringer, M.D. described a patient with acute pancreatitis who was found to have inferior vena caval thrombosis [18]. In 1994 Antony SJ and in 2014 Vinod KV reported inferior vena caval thrombosis in acute pancreatitis [19,20]. Renal vein and inferior vena cava (IVC) thrombosis in acute pancreatitis has also been reported [21]. Inferior vena cava thrombosis can also occur secondary to chronic pancreatitis [22,23] and Ohno et al. reported a 62 years old woman with complete obstruction of the inferior vena cava due to chronic relapsing pancreatitis [24]. Multiple vessel thrombosis involving superior vena cava, inferior vena cava, bilateral subclavian, internal jugular, axillary, iliac and renal veins in an adult male with alcoholic chronic pancreatitis was reported by Parikh et al.

Pulmonary embolism with deep vein thrombosis in pancreatitis is very rare. Few case reports are found in literature associated with chronic pancreatitis. In one case report of a patient with chronic pancreatitis a pancreatic cyst had penetrated into the inferior vena cava forming a thrombus and caused a pulmonary embolism [25]. Hanterdsith reported a case of sudden death from massive pulmonary thromboembolism due to an inferior vena cava thrombosis caused by chronic pancreatitis [26].

Pulmonary embolism in acute pancreatits

Pulmonary embolism in the setting of acute pancreatitis is even rarer. Goenka et al. reported a 35-year non-alcoholic male patient diagnosed with acute pancreatitis and pancreatic necrosis who developed inferior vena caval, right sided femoral and popliteal vein thrombosis complicated with pulmonary thromboembolism [27]. Zhang et al. reported a 38-year-old woman with acute pancreatitis who was found to have thromboembolism involving left pulmonary artery and a branch of right pulmonary artery in computer tomographic angiography of chest. She had expectoration with a little blood and progressive dyspnea [28]. Deiss et al. reported three cases of acute pancreatitis associated with pulmonary embolism in 2014 [29]. Two of them were females and two had a history of alcohol ingestion. The two patients who had a history of alcohol ingestion had pancreatic ascites and pleural effusions and had bilateral pulmonary embolism. Neither of them had shortness of breath and extensive pulmonary emboli were found incidentally. The other patient had evidence of choelithiasis without cholecystitis in the ultrasound. She presented with chest tightness and shortness of breath and had right-sided pulmonary embolism. She did not have ascites or pleural effusions. She had undergone emergent craniotomy one-week prior for rupture of a congenital arterio-venous malformation and prior to surgery, she had

been taking oral contraceptive hormones. Another case series reported four male patients with acute pancreatitis and pulmonary embolism [30]. All four patients had a history of alcohol consumption and all had dyspnea and pancreatic ascites. Three of them had bilateral pulmonary embolism. Another case report described a male patient with a history of heavy alcohol ingestion who presented with acute pancreatitis, pancreatic ascites and pleural effusion. CECT had revealed bilateral pulmonary embolism [31].

Acute pancreatitis and hypercoaguable state

Several explanations have been proposed for this venous thrombosis in pancreatitis. Firstly the systemic inflammatory response associated with severe acute pancreatitis results in a hypercoaguable state. This was demonstrated in many studies. Marked changes in coagulation parameters occur during acute pancreatitis and this was significantly higher in patients with initial amylase greater than 1,000 Somogyi units suggesting that enzyme-related intravascular coagulation may be implicated [32]. In acute pancreatitis, levels of fibrinogen and D-Dimer are raised, and the overall platelet level is increased [33]. Another suggested mechanism is trypsin converting prekallikrein to its activated form, sparking the kinin system leading to activation of factor XII and complements and disrupting the clotting pathway [26]. A combination of hepatic dysfunction, hypertrypsinaemia (resulting in raised fibrinogen and Factor VIII concentrations) and cachexia are also implicated for hypercoagulability in acute pancreatitis [34].

Year	Age years	Gender	Past history of pancreatitis	History of alcohol	Other etiology for pancreatitis	Symptoms of pulmonary embolism	Pulmonary artery involvement	Presence of lower limb DVT	Presence of IVC thrombosis	Amylase level (Units)	Presence of ascitis	Presence of pseudocyst
1994	35	Male	No	No	No cholelithiasis	None	N/A	Right femoral and popliteal	Present	500	No	Present
2012	35	Female	No	N/A	N/A	Cough and expectoration with a little blood, progressive dyspnea	Bilateral	No	No	1130	No	No
2014	28	Female	Present	Yes	No	None	Bilateral	N/A	N/A	N/A	Present	No
2014	32	Male	No	Yes	N/A	None	Bilateral	N/A	N/A	1105	Present	No
2014	21	Female	No	No	Cholelithisis	Dyspnea and chest tightness	Right	N/A	N/A	N/A	No	No
2016	46	Male		Yes	No	Dyspnea and cough	Bilateral	No	No	356	Present	No
2016	31	Male	Yes	Yes	No	Dyspnea	Bilateral	No	No	718	Present	No
2016	38	Male	Yes	Yes	No	Dyspnea	Left	Distal left saphenofemoral vein and popliteal vein.	No	1438	Present	Present
2016	35	Male	Yes	Yes	No	Dyspnea	Bilateral	Left sided greater saphenous vein and left anterior tibial vein	No	645	Present	present
2016	38	Male	Yes	Yes	No	No	Bilateral	Left common and internal iliac veins and both proximal external iliac veins	No	3570	Present	Present

Table 1: Summarizing the cases of 10 patients with acute pancreatitis and pulmonary embolism.

Secondly at microvascular level, inflammatory mediators cause intrinsic endothelial damage [35]. Pancreatic juice enters the vascular system and cause proteolytic damage or inflammation resulting in a vasculitic condition [28]. In rats submitted to experimental pancreatitis, the intense inflammatory response with high plasma nitrite/nitrate levels provoked deleterious effects in endothelium-dependent relaxing response for acetylcholine in mesenteric rings. Furthermore, the sub sensitivity of the contractile response to phenylephrine in both mesenteric and pulmonary rings might be due to the complications of this pathological condition in the early stage of pancreatitis [36]. Third cause is extrinsic damage of the veins from adjacent edema, fibrosis and cellular infiltration [12,16,37,38].

Fourthly compression of the vein by a psuedocyst or enlarged pancreatic parenchyma has been reported as the cause for venous thrombosis [38]. This was seen in one report where the pseudocyst was compressing the inferior vena cava [31]. In another case report pancreatic cyst had penetrated into the inferior vena cava, where it had triggered the formation of a thrombus [25]. Immobility may also contribute to venous thrombosis in acute pancreatitis.

Summarizing the Cases

The pathogenesis of pulmonary embolism is also multimodal. Here we describe 10 patients with acute pancreatitis and pulmonary embolism (Table 1). All were between the ages 30 and 50 years and 7 of them were males. 50% of them had a past history of pancreatitis. 7 out of 10 patients gave a history of alcohol consumption. 6 of the patients had developed dyspnea with pulmonary embolism and only one patient had mild heamoptasis, hypoxia and cyanosis [28]. 4 patients had evidence of lower limb deep vein thrombosis and only one patient had inferior vena caval thrombosis. 70% of the patients had ascites but a direct causal relationship of pancreatic ascites with pulmonary embolism is questionable. Patel et al. hypothesized that pancreatic enzymes released in the ascitic fluid could have caused severe inflammation in the systemic veins triggering cytokines to cause endothelial damage and venous thrombosis leading to pulmonary embolism [30].

Diagnosis and Treatment

Early recognition and diagnosis, of pulmonary embolisms is important. Diagnosis is based on the clinical manifestations in combination with laboratory tests and imaging studies. All the 10 patients described here were diagnosed using CECT and pulmonary embolism was an incidental finding in 4 of them. Early treatment with intravenous heparin followed by oral anticoagulation and radiological interventional procedures such as vascular filters reduce mortality in pulmonary embolism. No deaths have been reported in acute pancreatitis due to pulmonary embolism however a case of sudden death from massive pulmonary thromboembolism with inferior vena caval thrombosis is reported in chronic pancreatitis [26]. All the patients described here were started on heparin and later anticoagulated with warfarin. Only one patient developed bleeding into the peritoneal cavity requiring blood transfusion during enoxaparin and warfarin therapy and his INR was found to be high [31]. All the patients recovered well with anticoagulation. The ideal duration of anticoagulation is not known in this setting but some authors recommend a minimum duration of 12 months in inferior vena caval thrombosis [39,40].

Thromboprophylaxis in acute pancreatits

The place for thromboprophylaxis in acute pancreatits is not established. The American College of Chest Physicians 2008 guidelines recommend venous thromboembolism prophylaxis with low-molecular-weight heparin for patients undergoing major general surgery, major gynecological surgery, major open urologic procedures, and elective hip or knee arthroplasty, as well as for patients with major trauma and spinal cord injury and patients admitted to the hospital with an acute medical illness. On admission to the ICU, all patients should be assessed for their risk of venous thromboembolism, and most should receive thromboprophylaxis [41]. In acute pancreatitis anticoagulation prophylaxis is often not used because these patients may need intervention (pigtail catheter drainage or surgery) [31] and patients with acute pancreatitis has a risk of gastrointestinal bleeding [42]. It may be considered on a case-by-case basis in patients with pancreatitis who are acutely ill, immobilized, need ICU admission, and have multiple risk factors for deep vein thromboembolism. Thromboprophylaxis was used in one female in her second pregnancy who had a history of inferior vena caval thrombosis and acute pancreatitis following the first pregnancy. Thromboprophylaxis was continued for 8 weeks postnataly also [43].

Conclusion

In conclusion, deep vein thrombosis with a pulmonary embolism is a rare but life-threatening complication of acute pancreatitis. Multiple risk factors have been postulated for the prothrombotic state in acute pancreatitis. A high index of suspicion is warranted and if clinically suspected necessary investigations should be arranged. Most of the patients in literature who developed pulmonary embolism in acute pancreatitis were males with a history of significant alcohol ingestion and majority had pancreatic ascites. Once diagnosed early treatment with intravenous heparin followed by warfarin is effective but the duration of therapy in not known. Further studies must be undertaken to determine the place of deep vein thromboembolism prophylaxis in these patients.

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