Case Report

Pancreatic Panniculitis: A Cutaneous Presentation as an Initial Clue to the Diagnosis of Pancreatic Cancer

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Background: *Pancreatic panniculitis is a rare complication of pancreatic diseases, including pancreatic carcinoma. It is clinically manifested by erythematous subcutaneous nodules typically located on the legs which can occur before or at the onset of pancreatic disease.*
Case Report: *An 81-year-old woman presented with painful subcutaneous nodules at both shins, recurrent epigastric pain, anorexia and significant weight loss. Physical examination revealed mild pallor, palpable epigastric mass and multiple tender erythematous subcutaneous nodules discrete to both lower extremities. The skin biopsy showed lobular panniculitis with marked subcutaneous fat necrosis and ghost adipocytes compatible with pancreatic panniculitis that was an important clue for further investigations. Elevations of serum amylase and serum lipase were then noted. Computed tomography of the abdomen revealed pancreatic cancer with duodenal involvement and multiple liver metastases.*
Conclusion: *Pancreatic panniculitis is associated with pancreatic cancer and represents an important clue to the diagnosis.*

Keywords: *Pancreatic panniculitis, Pancreatic cancer*

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Pancreatic panniculitis belongs to the category of panniculitis, a group of heterogeneous inflammatory diseases of the subcutaneous fat. It has been reported in many pancreatic diseases including acute[1] and chronic pancreatitis[2], pancreatic pseudocysts[3], congenital abnormalities such as pancreas divisum[4], and most importantly, pancreatic cancer[5]. The condition usually presents as erythematous subcutaneous nodules that sometimes become ulcerative with oily brown exudates. They are predominantly located on distal part of the lower extremities, especially around the ankles and knees. The diagnosis is made by the presence of histologic findings including lobular panniculitis without vasculitis, and basophilic granular material-containing ghost adipocytes[6]. The skin lesion can present concurrently with, or even precede the pancreatic pathology. In this report, we describe a patient with pancreatic panniculitis which led to further investigations and diagnosis of pancreatic cancer.

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Case Report

An 81-year-old woman presented with recurrent painful subcutaneous nodules on her both shins. Her underlying diseases were well-controlled hypertension and dyslipidemia. The first episode of painful nodules developed 4 months ago and resolved spontaneously within 1 month. Two months later, she complained of recurrent dull-aching pain in the epigastric area, anorexia and significant weight loss. Non-ulcerated subcutaneous nodules appeared on her shins and calves again and brought her to the hospital three weeks later.

On her visit, she had no fever, arthralgia or chronic cough. Her bowel habits were normal. Physical examination revealed mild pallor without jaundice. A non-tender, poorly circumscribed mass, rubbery in consistency, extending 5 cm below the epigastrium, was noted on palpation. There were multiple discrete, tender, ill-defined, erythematous to brownish

subcutaneous nodules without ulceration, varying from 2-5 cm in diameter, confined to distal parts of the lower extremities bilaterally (Fig. 1). Investigations revealed hemoglobin of 8.5 g/dL, total leukocyte of 6,800 cells/mm^3 (66% neutrophil, 30% lymphocyte and 4% eosinophil) and platelet count of 326,000 cells/mm^3. Total bilirubin was 0.4 mg/dL (normal 0.3-1.2) and direct bilirubin was 0 mg/dL (normal 0-0.5). Aspartate aminotransferase (AST) was 24 U/L (normal 0-37), alanine aminotransferase (ALT) was 12 U/L (normal 0-40), albumin was 3.8 g/dL (normal 3.5-5), globulin was 4.8 g/dL (normal 1.5-3.5) and alkaline phosphatase was 119 U/L (normal 39 -117).

The differential diagnoses of the cutaneous manifestation were cutaneous metastasis, deep cutaneous vasculitis and deep cutaneous infection. The skin biopsy was done. The skin biopsy revealed lobular panniculitis with marked subcutaneous fat necrosis and characteristic ghostlike fat cells with basophilic material. Neutrophils, lymphocytes and foamy histiocytes are noted around necrotic area. These findings are compatible with pancreatic panniculitis (Fig. 2).

Further investigation showed serum amylase was mildly elevated to 297 U/L (normal 0-220) and serum lipase to 931 U/L (normal 13-60). Computed tomography (CT) of the abdomen showed advanced pancreatic neoplasm with duodenal involvement and liver metastasis, most likely pancreatic ductal adenocarcinoma (Fig. 3).

Three weeks later, the patient complained of progressive jaundice and progressive abdominal

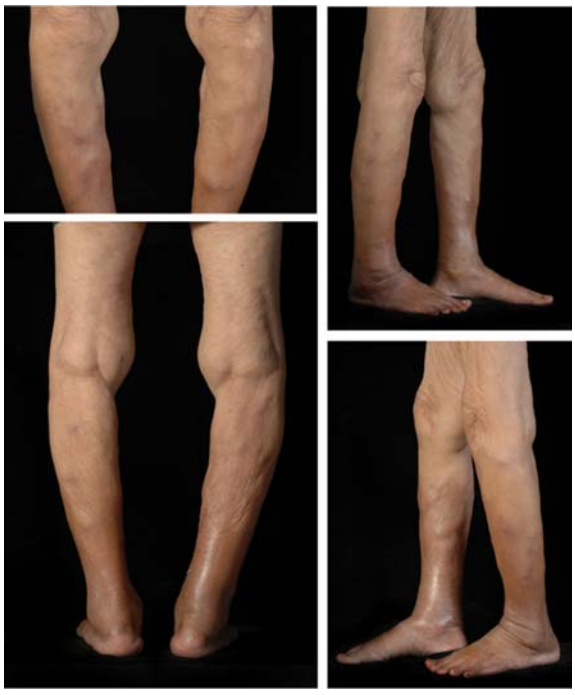

Fig. 1 Bilateral ill-defined, tender, erythematous nodules on the lower extremities

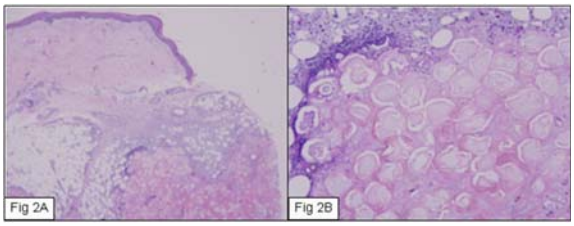

Fig. 2 A. The skin biopsy showed lobular panniculitis (H&E x 40). B. Ghost adipocytes with basophilic material (H&E x 400)

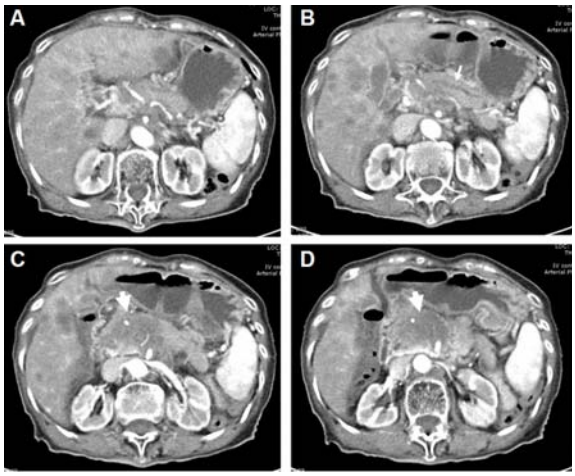

Fig. 3 Computed tomography (CT) with contrast of the abdomen, A-D was the images from cephalic to caudal showed the features of ill-defined heterogenous hypodensity mass at proximal body and head of pancreas, sized about 3.5 x 5.2 cm (large arrows), which encasement of celiac axis and superior mesenteric artery, extended downwardly to involve mesenteric root of small bowel. Dilatation of pancreatic duct was noted (small arrow). The involvement with thrombosis of splenic vein, superior mesenteric vein and proximal main portal vein were also detected. Multiple hypodensity heterogenous enhancing lesions, varying in size, scattered at both lobes of liver suggestive of liver metastasis. Multiple small lymphadenopathy at paraaortic, celiac plexus and aortocaval regions.

pain. Physical exanimation revealed mild pallor with marked jaundice. Abdominal examination showed marked distension. The liver function tests showed total bilirubin of 14 mg/dL, direct bilirubin of 12.9 mg/dL. AST was 62 U/L, ALT was 33 U/L, alkaline phosphatase was 434 U/L. Albumin was 2.9 g/dL and globulin was 3.7 g/dL. The endoscopic retrograde cholangiopancreatography (ERCP) with stent was initially planned for palliative biliary drainage, but it could not be done due to the presence of an infiltrative duodenal mass causing severe luminal narrowing precluding the performance of ERCP. The final diagnosis was pancreatic cancer with duodenal involvement and multiple liver metastases. Due to the very aggressive nature of the disease, the patient was treated palliatively with pain and symptom control. She rapidly deteriorated and expired 3 months after her diagnosis.

Discussion

Pancreatic panniculitis is a rare condition associated with pancreatic disease, in which fat necrosis occurs in subcutaneous tissue and elsewhere. It appears in approximately 2% to 3% of all patients with pancreatic diseases[7], mostly been described in association with acute and chronic pancreatitis which usually result from alcohol abuse[1], trauma[8] or cholelithiasis[9]. However, this condition has also been found in patients with pancreatic cancer, more frequently with acinar cell carcinoma[10-12] and less commonly with ductal adenocarcinoma[5], islet cell carcinoma[13], acinar cell cystadenocarcinoma[14]. Other less frequent pancreatic abnormalities that have been described in association with pancreatic panniculitis include pancreas divisum, pancreatic pseudocysts, pancreatic-vascular fistula[15] and drug-induced pancreatitis[16].

In our case the diagnosis of pancreatic ductal adenocarcinoma was made by the clinical features of aggressive tumor extension involving bile duct and duodenum. The CT evidences of heterogenous hypodensity pancreatic mass encased the arteries with thrombosis of splenic, superior mesenteric and portal vein were also very suggestive of pancreatic ductal adenocarcinoma. Unfortunately, tissue biopsy of the mass that invaded into the duodenum was not done due to extreme friability and contact bleeding of the mass. Nevertheless, all the clinicians and endoscopist involved with this patient agreed that pancreatic ductal adenocarcinoma was very likely.

The exact pathogenesis of pancreatic panniculitis is uncertain. There is a proposed hypothesis that pancreatic enzymes, mostly lipase, from inflammatory pancreas are released into the bloodstream and necrotized subcutaneous tissue to enzymatic panniculitis. The pathogenic role of pancreatic lipase was supported by the finding of pancreatic lipase in the areas of subcutaneous necrosis, and the immunohistochemical demonstration with anti-lipase monoclonal antibodies within the necrotic adipocytes[7]. However, pancreatic lipase can not entirely explain the pathogenesis because there is a contrast between the relative frequency of pancreatitis with high serum levels of lipase and the fact that pancreatic panniculitis is a rare disorder[13]. Furthermore, *in vitro* investigations failed to reproduce pancreatic panniculitis when normal human subcutaneous fat was incubated with the serum of a patient with high levels of pancreatic lipase, trypsin, and amylase[11]. Well-documented examples of pancreatic panniculitis have been described in patients with normal serum levels of all pancreatic enzymes[7]. Other suggested pathogenic mechanisms of this syndrome are immunologic processes[17,18]. In the pancreatic panniculitis associated with malignant condition, there is a proposed pathogenesis of direct effect of tumor deposits, most evidence implicates direct physicochemical injury by reflux of pancreatic lipase from functional pancreatic tumor cell[19]. In this patient, serum levels of pancreatic enzymes are also elevated but there were little abdominal pain and no radiological evidence of acute pancreatitis. Therefore, the cause of panniculitis is more likely from pancreatic carcinoma rather than release of pancreatic enzyme from pancreatitis.

The clinical manifestation of pancreatic panniculitis presents with ill-defined, tender, edematous, erythematous, or red-brown nodules that may spontaneously ulcerate and drain an oily brown, sterile and viscous substance that results from liquefactive necrosis of adipocytes. The most frequently involved sites are the distal parts of the lower extremities and around the ankles and knees. Also the nodules can, less commonly, spread over the thighs, buttocks, arms, abdomen, chest and scalp. Often the onset of subcutaneous fat necrosis in pancreatic diseases is accompanied by acute arthritis that results from necrosis in periarticular fat tissue.

The course of pancreatic panniculitis associated with pancreatitis usually has resolution when the inflammatory episode is improved. In contrast, in patients with pancreatic panniculitis associated with pancreatic carcinoma, the nodules tend to be more persistent with frequent recurrences,

ulceration, and involvement of cutaneous areas beyond the lower extremities[20] and the tumor usually in advanced stage by the time cutaneous lesions appear[21]. When associated with a pancreatic tumor, the combination of panniculitis, polyarthritis and eosinophilia is known as Schmid's triad, and it is associated with poor prognosis[22].

The subcutaneous nodules of pancreatic panniculitis have many clinical differential diagnose, including other forms of panniculitis, such as erythema nodosum, erythema induratum, alpha 1 antitrypsin deficiency panniculitis, infectious panniculitis and subcutaneous metastasis. However, these conditions rarely produce discharge of oily material. Typically, pancreatic panniculitis has the characteristic feature of ghost adipocytes with basophilic granular material from the process of saponification. This feature is a pathognomonic finding of pancreatic panniculitis. However, histologic findings might vary from septal panniculitis, lobular panniculitis with ghost cells or lobular panniculitis with granulomatous reaction which depend on the stages of lesion[11].

Treatment of pancreatic panniculitis is mainly supportive and primarily directed to the underlying pancreatic disease which usually not possible with pancreatic cancer. In the case of pancreatic cancer, the surgical excision of the tumor[10] and chemotherapy[21,23] may resolve the skin lesions, while the administration of octreotide, a long acting octapeptide of somatostatin analogue that inhibit pancreatic enzyme production, show benefit only in one patient[23]. In acute pancreatitis, the skin lesion usually disappear when the inflammation subsides[24]. In patient with chronic pancreatitis, cholecystectomy and removal of pancreatic duct stone could also treat the panniculitis[24] and in the case of pancreatic fistula or cyst, a resolution of nodule occurs after successful surgical correction of anatomical duct anomaly[25]. Other treatment modalities for pancreatic panniculitis included nonsteroidal anti-inflammatory drugs, corticosteroid and immunosuppressive medication are usually not effective[26].

In conclusion, the illustrated patient was found to have pancreatic cancer that was initially signaled by the presence of pancreatic panniculitis. Pancreatic panniculitis may precede the detection of pancreatic cancer by several months and represents an important clue to the diagnosis.

Potential conflicts of interest

None.

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Pancreatic panniculitis อาการแสดงทางผิวหนังเบื้องต้นซึ่งนำไปสู่การวินิจฉัยโรคมะเร็งตับอ่อน

เศารยะ เลื่องอรุณ, พนิตตา สิทธินามสุวรรณ, บุษกร มหรรฆานุเคราะห์, เพ็ญวดี พัฒนปรีชากุล, สุพจน์ พงศ์ประสบชัย

ภูมิหลัง: *Pancreatic panniculitis เป็นภาวะที่พบได้น้อยในผู้ป่วยที่เป็นโรคของตับอ่อนชนิดต่างๆ รวมถึงมะเร็งตับอ่อน ส่วนใหญ่มีรอยโรคเป็นก้อนใต้ผิวหนัง สีแดง กดเจ็บบริเวณขา โดยอาจพบรอยโรคที่ผิวหนังก่อน หรือพร้อมกับอาการแสดงอื่นของโรคของตับอ่อน*

รายงานผู้ป่วย: *หญิงไทยอายุ 81 ปี มีก้อนแดงกดเจ็บบริเวณหน้าแข้งทั้งสองข้าง ปวดท้องบริเวณใต้ลิ้นปี่เรื้อรัง เบื่ออาหารและน้ำหนักลด ตรวจร่างกายพบซีด คลำได้ก้อนบริเวณลิ้นปี่และก้อนใต้ผิวหนังสีแดง กดเจ็บที่ขาทั้ง 2 ข้าง จำนวนมาก ผลพยาธิวิทยาบริเวณก้อนที่ขาแสดงให้เห็นการอักเสบของ fat lobule บริเวณกลาง lobule และชั้นไขมันใต้ผิวหนัง และพบมี ghost adipocyte ซึ่งเข้าได้กับภาวะ pancreatic panniculitis ซึ่งเป็นข้อมูลสำคัญที่นำไปสู่การสืบค้นเพิ่มเติม โดยพบเอนไซม์ amylase และ lipase เพิ่มสูงขึ้นผลเอกซเรย์คอมพิวเตอร์ช่องท้องพบมะเร็งตับอ่อนซึ่งลุกลามไปยังลำไส้เล็กส่วนต้นและมีการแพร่กระจายไปยังตับ*

สรุป: *ภาวะ pancreatic panniculitis ซึ่งเกิดจากมะเร็งตับอ่อน เป็นอาการทางคลินิกเบื้องต้นที่สำคัญซึ่งนำไปสู่การวินิจฉัยโรคดังกล่าว*