CASE REPORT

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Nodular subcutaneous lesion – an alarming sign for an upcoming pancreatic disorder

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Abstract

Pancreatic panniculitis represents a rare dermatological manifestation mainly due to a pancreatic disorder, but other etiologies are possible. Even rarer, it can occur prior to the clinical signs of the underlying disease, and its presence must orientate the investigations especially towards pancreas, liver and neuroendocrine system. We report a rare case of a 47-year-old male patient who presented to the Emergency Unit complaining about a two weeks-long-persistent pain in the upper abdomen and biliary vomiting. The medical history included alcohol abuse. Several days prior to the onset of these symptoms, the patient has noticed the occurrence of a nodular inflammatory lesion of 5/3 cm on the right calf (this makes the case even rarer). Based on clinical aspect and high levels of pancreatic enzymes, acute pancreatitis was diagnosed. Contrast-enhanced abdominal computed tomography (CT) revealed a cystic pancreatic mass and dilated intrahepatic biliary ducts. Abdominal magnetic resonance imaging (MRI) revealed a cystic tumor of the pancreatic head and thrombosis of the portal vein, which increased the suspicion of pancreatic adenocarcinoma. Biopsy was performed from the calf nodular lesion, with the diagnosis of panniculitis. This case, besides its rarity, supports the clinical important value of a pancreatic workup in case of histologically proved panniculitis, even without pancreatic related symptoms.

Keywords: panniculitis, pancreatitis, ghost cell, adenocarcinoma.

Introduction

The occurrence of a subcutaneous nodule in a limb, without any other associated symptoms and signs, raises many problems of differential diagnosis. One of the rarest etiologies is pancreatic panniculitis [1].

Pancreatic panniculitis represents a dermatological manifestation mainly of pancreatic diseases, as acute or chronic pancreatitis, pancreatic carcinoma, neuroendocrine carcinoma, insulinoma, ischemic pancreatic disease, abdominal trauma, and pancreatic duct stenosis, fistulas of pancreatic pseudocyst in superior mesenteric vein or inferior vena cava [2–4], but other etiologies are possible: disorders of the liver, of the neuroendocrine system, connective tissue disorders, neoplasms [5, 6]. Clinically, the most frequently found association is the triad: pancreatitis, panniculitis and polyarthritis.

The lesions are erythematous or brown tender nodules, usually in the limbs (lower limbs more frequently), with tendency for spontaneous ulceration. While ulcerated, a yellow-brown, oily substance eliminates, consisting in liquefactive fat, probably necrotized by the excess of pancreatic enzymes. The exact mechanism of occurrence of these manifestations is not entirely known. Skin nodules can occur before, during or follow the clinical manifestation of the underlying disease and they can be found not only on the lower limbs but also on the buttocks, arms, face, abdomen, even scalp and trunk.

The importance of this clinical manifestation is that it can occur, usually associated with arthritis, weeks, even months, before other clinical signs of pancreatic distress [7], and it can be lifesaving if the clinician is aware of its implications. This was, in part, the case of our patient, also.

Aim

The aim of our paper is to get doctors' attention over a rare etiology of a subcutaneous nodule – pancreatic pathology, sometimes very severe as pancreatic carcinoma. Because of the incomplete clinical picture: only panniculitis (which did not motivate our patient to consult a physician), without any other signs, diagnosis was delayed up to the occurrence of typical signs of pancreatitis, with subsequent longer and more severe evolution of the disease.

Case presentation

We report the case of a 47-year-old male patient who presented to Emergency Unit complaining for two weeks persistent pain in the upper abdomen and biliary vomiting. Several days before the onset of these symptoms, he noticed on the anterior middle third of the right calf, a nodular inflammatory lesion of 5/3 cm (Figure 1). He

recognized alcohol abuse in the last 10 years: mostly beer (average of 1 L per day) and wine (7–8 glasses per week) and he is known with chronic gastritis.

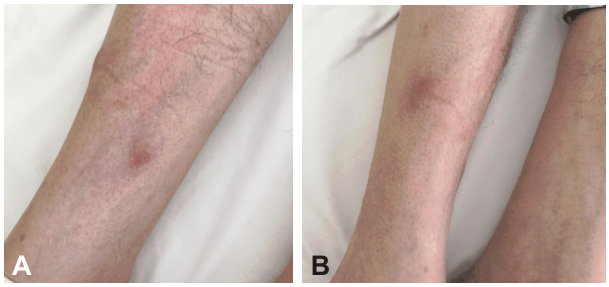

Figure 1 – ***(A and B) Nodular erythematous lesion of 5.3 cm on the right calf.***

Physical examination at admission was not significant except for the painful upper abdomen at palpation and the about mentioned nodular lesion in a patient with a normal body mass index (BMI) (23.9 kg/m^2).

Laboratory investigations at admission revealed elevated serum amylase, lipase, mild elevation of liver transaminases and mild leukocytosis with neutrophilia and elevated inflammatory tests [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)] (Table 1).

Contrast-enhanced abdominal computed tomography (CT) found a cystic pancreatic mass, dilatations of the intrahepatic biliary ducts (Figure 2) and recommended abdominal magnetic resonance imaging (MRI).

Because patient's clinical evolution was aggravating and the value of serum pancreatic enzymes abruptly increased, along with the unspecific CT aspect and with the ultrasound examination, which revealed important mesenteric adenopathy along with an isoechoic mass of 2 cm in the head of the pancreas, tumoral markers were performed: carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA), both within normal limits (Table 1).

Abdominal native MRI, performed six days after admission, revealed portal vein thrombosis and tumoral cystic mass of the head of the pancreas with the suspicion of adenocarcinoma (Figure 3).

Table 1 – ***Serum values of different parameters***

	Day 1	Day 4	Day 6	Day 25
WBC count (nv: 4–10×10^3/mm^3)	14.83			10.07
Neutrophils (nv: 2–8×10^3/mm^3)	9.18			5
PLT count (nv: 150–450×10^3/mm^3)	211			491
Hb (nv: 13.1–17.2 mg/dL)	15.6			14.4
CRP (nv <0.5 mg/dL)	3.88		10.93	1.13
ESR (nv <15 mm/h)	59			
Fibrinogen (nv: 200–400 mg/dL)	619			
ALAT (nv <41 U/L)	40.89		55	43
ASAT (nv <40 U/L)	66.91		42	38
Serum amylase (nv <100 U/L)	1539.63		>7500	112
Serum lipase (nv <60 U/L)	1516		2874	68
Urinary amylase (nv: 16–491 U/L)	3705			414
CA 19-9 (nv <27 U/mL)		16.1		
CEA (nv <3 ng/mL, in non-smokers)		3.9		
Serum creatinine (nv <1.2 mg/dL)	0.65		0.73	0.75
Glycemia (nv: 65–115 mg/dL)	104.31			98

WBC: White blood cells; PLT: Platelets; Hb: Hemoglobin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ALAT: Alanine aminotransferase; ASAT: Aspartate aminotransferase; CA 19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; nv: Normal values.

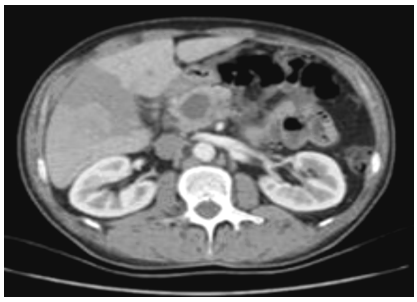

Figure 2 – ***Abdominal CT revealing a cystic pancreatic mass. CT: Computed tomography.***

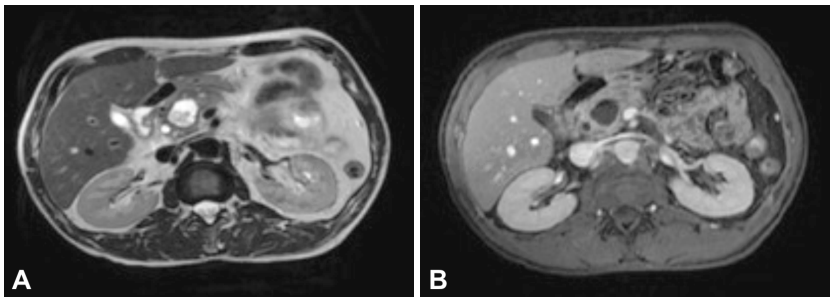

Figure 3 – ***(A and B) MRI examination confirming cystic pancreatic mass and portal vein thrombosis (day 6 from admission). MRI: Magnetic resonance imaging.***

Gastric aspiration was performed and treatment was initiated with i.v. inhibitors of the gastric proton pump (Pantoprazole), and antisecretory drugs (Octreotide), antispasmodic drugs (Drotaverine), antiemetics (Metoclopramide), i.v. fluids for volemic sustention, antibiotics (Meropenem, as the patient developed fever of 39.2ºC in the 12th day of hospitalization), non-steroid anti-inflammatory drugs (NSAIDs), major antalgic drugs (dilutions of Pethidine) and, due to portal vein thrombosis, low-molecular-weight heparin (Fraxiparine).

The moment the patient developed fever and his clinical evolution worsened, biopsy from the nodular lesion was considered and blood and urine cultures were taken. All cultures proved sterile.

A 4 mm skin punch biopsy was performed and histopathological examination [Hematoxylin–Eosin (HE) staining] revealed hypodermic lobular fibrosis and lymphohistiocytic inflammatory infiltrate, along with rare multinucleate giant cells (Figure 4).

The diagnosis of lobular panniculitis was established, in stage of resolution.

Immunohistochemistry was performed using Ventana BenchMark GX System, ready-to-use antibodies: cluster of differentiation (CD) 3, CD20 (clone L26), CD68 (clone klp1) and it revealed mainly histiocytes, B- and T-lymphocytes, with a T to B ratio of 2:1 (Figure 5).

The slides were examined with Leica DM750

microscope and image captured with Leica ICC50 HD camera, at high resolution.

Native and contrast-enhanced abdominal MRI was repeated in the 13th day of admission and the cystic tumoral mass was found in slight regression in comparison with the previous examination, most probably a pseudocyst but without excluding the possibility of a mucinous intraductal neoplasm, and with the persistence of portal vein thrombosis (Figure 6).

The right calf nodular lesion diminished significantly, along with the treatment of pancreatitis.

Patient's evolution under treatment finally improved and he was discharged after 26 days with slightly elevated serum pancreatic enzymes, mild inflammatory syndrome and normal blood count. Unfortunately, the patient did not return to the Clinic in order to reassess his pancreatic function and imagistic aspect of the pancreas.

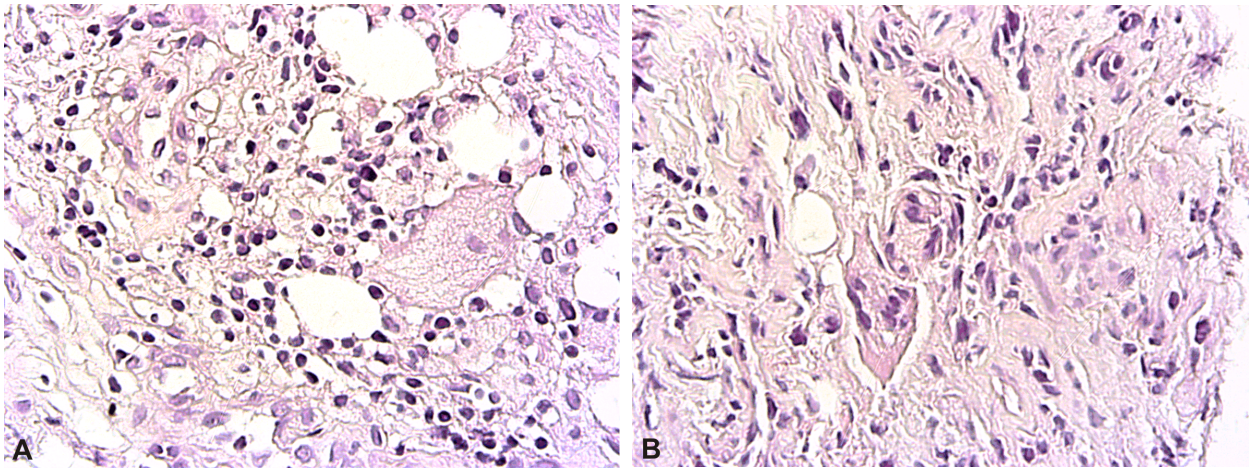

Figure 4 – ***Pathological aspects (HE staining, ×400): (A) A big cell with a small nucleus and fine granular cytoplasm – a necrotic adipocyte with a partially digested, shadowy cell membrane and basophilic granular material; (B) Giant multinucleate cell. HE: Hematoxylin–Eosin.***

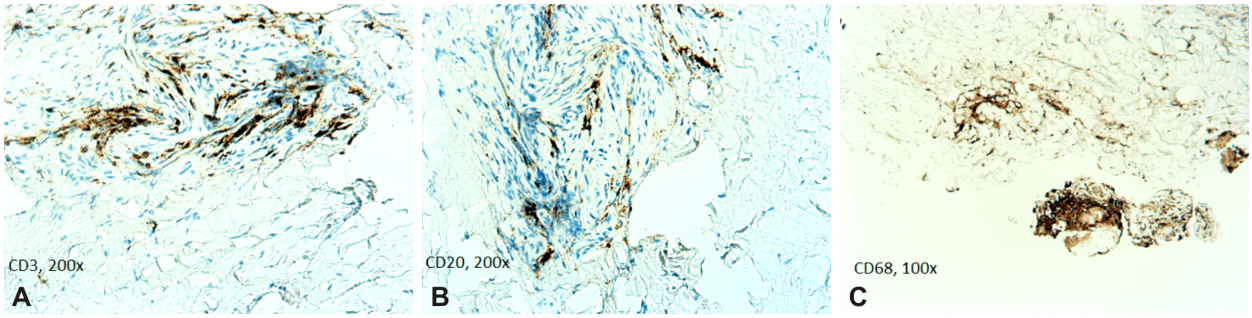

Figure 5 – ***IHC aspects of the specimen, revealing CD3-positive T-lymphocyte cells (A), CD20-positive B-lymphocyte cells (B), and CD68-positive macrophage cells (C), confirming lymphohistiocytic inflammatory infiltrate. Anti-CD3 antibody immunostaining: (A) ×200. Anti-CD20 antibody immunostaining: (B) ×200. Anti-CD68 antibody immunostaining: (C) ×100. IHC: Immunohistochemical; CD: Cluster of differentiation.***

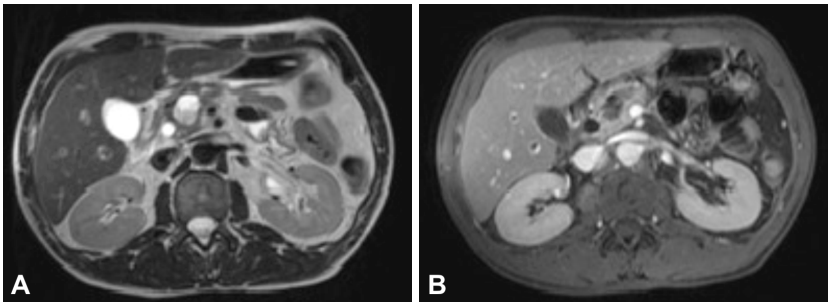

Figure 6 – ***MRI examination revealing persistent cystic pancreatic mass and portal vein thrombosis (day 13 from admission). MRI: Magnetic resonance imaging.***

Discussions

Pancreatic panniculitis represents a rare dermatological manifestation of different pancreatic disorders, with a prevalence of 2% to 3% [1, 8].

Even if the first description of this disorder was made in 1883, by Chiari, only in 1947 it was reported in the medical literature [9].

The exact mechanism implied in the occurrence of these nodular skin lesions is not entirely known. It seems that the high levels of pancreatic enzymes (amylase, lipase, phosphorylase and trypsin) travel to the blood stream and are accumulated inside fat lobules with the help of trypsin, which increases the permeability of the lymphatic vessels for the previous enumerated enzymes. The same mechanism happens in the in the intraosseous fat, the amylase and the lipase hydrolyze the neutral fat to free fatty acids and glycerol and the result is saponification

of fat and necrosis. In the necrotized fatty tissue, lipase was found and anti-lipase monoclonal antibodies, also [10]. This does not seem to be the entire mechanism because there is still controversial data: *in vitro* studies of human adipose tissue incubated along with high levels of pancreatic enzymes did not described the occurrence of panniculitis and, furthermore, cases of pancreatic panniculitis with normal values of pancreatic enzymes are described [6].

The clinical aspects of this phenomenon are the subcutaneous nodules and the inflammatory arthritis. To complete the picture of this pathology, pancreatitis, panniculitis and polyarthritis can occur [1].

In the majority of cases, panniculitis occur during or after the episode of pancreatic injury. Rarely, the onset of panniculitis and arthritis precede the signs of pancreatic disorders by days, even months [7, 10] and this is, in part, our patient's situation. Perhaps, if arthritis would have occurred also, it would have been easier to suspect the triad of pancreatitis, panniculitis, polyarthritis, as Jo & Song did [2].

The main pancreatic disorders that associate panniculitis are acute and chronic pancreatitis, pancreatic cysts [4], pancreatic neoplasm (mainly the acinar cell type) [11–13], but it can be also found along with hepatocarcinoma, cholangiocarcinoma, ampullary carcinomas, neuroendocrine tumors of the pancreas, even of the adrenal glands [14–17]. There are reported cases of panniculitis even in pregnant patient with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome [18], in an 18-month-old child with DiGeorge syndrome [19] and in a 10-year-old girl with systemic lupus erythematous (SLE) [20].

In our case, the physiopathological trigger seems to be acute pancreatitis but, as MRI revealed a pancreatic pseudocyst with the persistence of portal vein thrombosis, the possibility of a mucinous intraductal neoplasm cannot be excluded.

Even if medical literature comprises more than 100 cases of pancreatic panniculitis, the occurrence of subcutaneous nodular lesions in a patient, especially before pancreatic pathology is suspected, rises many differential diagnoses. These lesions can mimic erythema nodosum, lupus panniculitis, traumatic or infectious panniculitis, alpha-1 antitrypsin deficiency panniculitis, subcutaneous Sweet syndrome, factitial panniculitis, lipodystrophy, subcutaneous sarcoidosis [21].

The diagnosis is certain only after histopathological examination, which typically reveals the pathognomonic "ghost cells". "Ghost cells" are, in fact, anucleate necrotic adipocytes with a thick wall and with fine basophilic granular inclusions in their cytoplasm resulted from dystrophic calcifications. In early stages of the lesion, "ghost adipocytes" and neutrophilic infiltrate can be found but in late stages, they both diminish and are replaced by lipoatrophy with fibrosis.

Based on the macroscopically aspect, we expected a vascular nodular lesion, with positive immunostaining for CD10, CD34, which are markers for angiogenesis and hematopoietic neoplasms like acute lymphoblastic leukemia, follicular lymphomas or other malignancies [22]. However, in our case, the positive immunostaining for CD3, CD68 and CD20 differentiated the nodular lesion from subcutaneous panniculitis-like T-cell lymphoma (typical CD3-positive T-lymphocytes) [23], from the nodular lesions in Rosai–Dorfman disease (typical CD68-positive macrophage) [24], from erythema nodosum and skin lesions in SLE, even if SLE can be associated with pancreatic panniculitis, sometimes without the clinical or imagistic aspect of pancreatitis but only with elevated pancreatic enzymes [25].

There is no specific treatment for panniculitis. The treatment is supportive and the lesions usually diminish along with improvement of the pancreatic status.

The peculiarities of our case were the occurrence of pancreatic panniculitis prior to any symptom or sign of pancreatitis and the association of pancreatitis with portal vein thrombosis and a tumoral cystic mass of the head of the pancreas with the suspicion of adenocarcinoma, possible a gastrointestinal stromal tumor (GIST). GIST occurrence along with a pancreatic disorder was described by others, also [26, 27] but unfortunately our patient did not return in order to continue his investigations. Recognizing the nodular lesions as pancreatic panniculitis prior to the occurrence of acute pancreatitis may improve the patient's outcome at least by immediately modifying the alimentary habits and stopping alcohol consumption. In the meantime, pancreatic imagistic investigations must be started in order to diagnose a possible malignancy as Zundler *et al.* [28] revealed in 2016, on an analysis of more than 130 cases of pancreatic panniculitis, that nearly half of the cases were associated with an internal malignancy. More than that, in the same study, the percentage of patients developing panniculitis before the diagnosis of the underlying condition was by trend higher in patients with neoplastic disease than in patients with acute pancreatitis.

Conclusions

We present a rare case of pancreatic panniculitis occurring prior to typical clinical symptoms and signs of acute pancreatitis. The association of pancreatitis with portal vein thrombosis and a tumoral cystic mass of the head of the pancreas with the suspicion of adenocarcinoma, possible a GIST, represents another peculiarity of our case. This presentation is also relevant because it suggests an important change in clinical care: pancreatic workup in case of histologically proved panniculitis even without pancreatic related symptoms. We are in favor of considering pancreatic panniculitis as a facultative paraneoplastic syndrome and pancreatic or extrapancreatic appropriate tumor screening or biopsy procedures have to be undertaken.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Irina Tica and Costin Niculescu equally contributed to the manuscript.

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