CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 31 (2017) 170–175

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Pancreatitis, panniculitis and polyarthritis (PPP-) syndrome caused by post-pancreatitis pseudocyst with mesenteric fistula. Diagnosis and successful surgical treatment. Case report and review of literature

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ARTICLE INFO

Article history:
Received 11 October 2016
Received in revised form 15 January 2017
Accepted 16 January 2017
Available online 18 January 2017

Keywords:
Pancreatitis
Arthritis
Fat tissue necrosis
Pancreatic pseudocyst
Lipase
Osteonecrosis

ABSTRACT

INTRODUCTION: Pancreatitis, panniculitis and polyarthritis syndrome is a very rare extra-pancreatic complication of pancreatic diseases.
PRESENTATION OF CASE: While in most cases this syndrome is caused by acute or chronic pancreatitis, we report a case of a 62-year-old man presenting with extensive intraosseous fat necrosis, polyarthritis and panniculitis caused by a post-pancreatitis pseudocyst with a fistula to the superior mesenteric vein and extremely high blood levels of lipase. This became symptomatic 2.5 years after an episode of acute pancreatitis and as in most cases abdominal symptoms were absent. Treatment by surgical resection of the pancreatic head with the pseudocyst and mesenteric fistula led to complete remission of all symptoms.
DISCUSSION: A review of the literature revealed that all publications are limited to case reports. Most authors hypothesize that an unspecific damage can cause a secretion of pancreatic enzymes to the blood-stream leading to a systemic lipolysis and fat tissue necrosis, especially of subcutaneous tissue, bone marrow, inducing panniculitis, polyarthritis and osteonecrosis. Even if caused by an acute pancreatitis abdominal symptoms are often mild or absent in most cases leading to misdiagnosis and poor prognosis.
CONCLUSION: While symptomatic treatment with NSAR and cortisone showed poor to moderate response, causal treatment can be successful depending on the underlying pancreatic disease.

1. Introduction

Pancreatitis, panniculitis and polyarthritis syndrome (PPP-syndrome) is a very rare symptom complex of extra pancreatic manifestations of pancreatitis with lobular panniculitis and (poly-) arthritis with intraosseous fat necrosis. Although the pancreatic pathology with exceptional high blood levels of pancreatic enzymes (in particular lipase) is widely considered causative, abdominal symptoms are often mild or absent. This leads to misdiagnosis, delay of appropriate therapy and worsening of prognosis [1]. Here we report a case of PPP-syndrome with extensive intraosseous fat necrosis in multiple bones and polyarthritis. Outstanding in this case was the extremely high blood level of up to 600-fold elevated lipase caused by a pancreatic pseudocyst with contact and fistula to the superior mesenteric vein. While in most cases acute or chronic pancreatitis were present at the onset of the PPP-syndrome, this patient became clinically apparent 2.5 years after an acute pancreatitis and was successfully treated by surgical resection of the pancreatic head with the pseudocyst and mesenteric fistula. Furthermore, we review the literature and summarize the characteristics of this syndrome. This report is in line with the SCARE guideline [2].

2. Case report

A 62-year-old Caucasian male with a history of alcohol abuse and acute pancreatitis 3 years ago, was admitted to University Hospital because of progressive, spreading joint and bone pain for 3–4 weeks. He reported that initially both cubital joints, then both ankle joints, finger joints and wrists on both hands were affected. The patient also mentioned a heavily painful and reddened swelling of his left wrist. Previously the patient was treated under the suspicion of reactive arthritis based on positive titer for chlamydia pneumoniae IgA and IgG and absent signs of a systemic rheumatologic disease with 20 mg/d prednisolone and antibiotics (doxycycline). In addition, there was a high level of lipase noticed, but in absence of

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http://dx.doi.org/10.1016/j.ijscr.2017.01.037

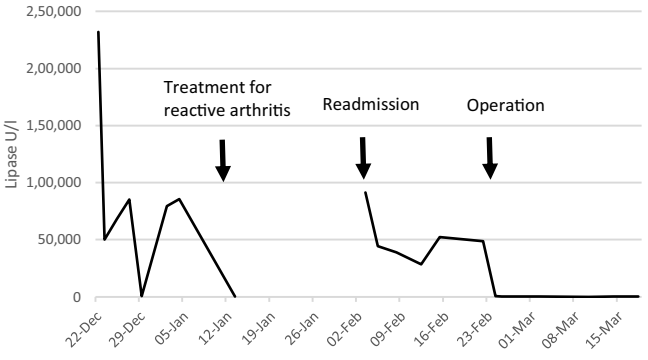

Fig. 1. Development of lipase levels. Normal: 73–393 U/l. Treatment for reactive arthritis was 20 mg prednisolone + doxycycline. Operation: Surgical resection of pancreatic pseudocyst.

signs of pancreatitis in clinical symptoms, computed tomography and ultrasound it was not related with the other symptoms. By this treatment, the elevated lipase levels and CRP-values were normalized, but joint pain was only partially reduced. After 2 weeks, the patient was readmitted with heavy pain in his left knee joint with distinct swelling and reddening. In minor extent, he suffered also from pain in the left shoulder, wrists, cubital and both ankle joints. He added that 9 months ago, he suffered from similar symptoms with multiple joint pain. The patient had a history of acute, necrotizing head-pancreatitis caused by heavy alcohol abuse 3 years ago, but now he clearly negated any abdominal symptoms and was plausibly abstinent of alcohol. A cystic lesion of the uncinate process of the pancreas with constant size was described in imaging for 3 years.

On physical examination, the left knee joint showed clear signs of inflammation with reddening, massive pressure pain and swelling. Abdominal status was inconspicuous. There were no signs of skin lesions typical for psoriasis, but "sausage toes" on the fifth left toe and third and fifth right toe were noticed.

Laboratory tests showed extremely high levels of plasma lipase up to 232.000 U/l (normal: 73–383 U/l) and alpha-amylase up to 11920 U/l (normal: 25–115 U/l) (Fig. 1). C-reactive protein was 147 mg/l (normal: 0–5 mg/l). Further laboratory tests were negative for rheumatoid factor (RF), antibodies to citrullinated protein antigens (ACPAs), anti-neutrophil cytoplasmic antibodies (ANCAs), antinuclear antibodies (ANAs), immunoglobulin G1-4, complement factor C3/C4, protein electrophoresis, procalcitonin, differential blood count, LDH, ACE, sIL2, HIV and screening for hepatitis B and C. The puncture of a pretibial fluid accumulation revealed a sterile, bloody material.

2-phase bone scintigraphy showed symmetric polyarthritis with pathological nuclide uptake of left proximal tibia, both patellae, cubital joints, wrists, ankle joints and metatarsus as well as calcaneus and all the interphalangeal joints of hands and feet. There was also a striking intense uptake in the clinically highly affected left proximal tibia with a central gap (mark in Fig. 2) which is not typical for arthritis. Magnetic resonance imaging revealed multiple necrotic bone lesions in proximal tibia and both patellae with circumscribed, garland-like T1-hypointense, T2-hyperintense lesions with marginal contrast agent uptake. Further examination showed similar lesions in both distal tibiae, calcaneus, talus and all tarsal bones (Fig. 3). In addition, there was an articular effusion in the left knee with contrast agent uptake of the synovia. A malignant process was excluded by CT-guided puncture. Histology showed unspecific bone necrosis consistent with fat tissue necrosis. Magnetic resonance and computed tomography of pancreas and biliary tract showed a cystic lesion in the pancreas head with a diameter of 1.3 cm and a partial thrombosis of the superior mesenteric vein adjacent to the cyst (Fig. 4).

Diagnosis of pancreatitis, panniculitis and polyarthritis syndrome due to a post pancreatitis pseudocyst with pseudocystomesenteric fistula was made. On surgical exploration, the pancreas presented with heavy post-inflammatory alterations of the uncinate process with a pseudocyst adjacent to the superior mesenteric vein (Fig. 5). We performed a pylorus-preserving partial pancreaticoduodenectomy with resection of the mesenteric fistula, removal of the mesenteric thrombus and reconstruction of the vein by direct suture. Postoperative plasma levels of lipase dropped immediately and permanently to normal levels, which confirmed the diagnosis (Fig. 1). In the further course no more signs of inflammation or active disease were detectable, but the patient still suffered from pain and mobility restriction due to the distinct bone necrosis for some weeks. Afterwards he was completely free of symptoms. Follow-up computed tomography of tibia head showed bone densification, but no osteolysis or fractures.

3. Literature review and discussion

Pancreatic panniculitis can occur in 2–3 % of patients with pancreatitis, first described by Chiari in 1883 [3,4]. Much rarer the triad of pancreatitis, subcutaneous tissue inflammation (panniculitis) and polyarthritis, often referred to as "Pancreatitis-Panniculitis-Polyarthritis-Syndrome" or "PPP-syndrome" could be observed. In addition to our case we found 32 well-documented cases in current literature [1,5–11]. Reports are limited to case-reports and speculations about pathogenesis. The pathogenesis is unknown, but most authors consider that direct secretion of pancreatic enzymes to the bloodstream causes systemic fat necrosis especially in subcutaneous fat tissue, bones and joints [10]. In all cases an exceptional high level of lipase was found though other pancreatic enzymes such as amylase, phosphorylase and trypsin may play a role [3]. Notably, in all cases lipase was considerably elevated, but in two amylase was not [11–13]. Additionally elevated amylase alone cannot cause panniculitis [11]. Also while the level of lipase does not indicate the severity of acute pancreatitis, it seems to correspond with the extent of extra pancreatic fat tissue necrosis in PPP-syndrome [1,14,15]. Some authors hypothesize that arthritis is caused by free fatty acids that are released into the joint, after the lipolytic pancreatic enzymes have hydrolyzed triglycerides in the joint near bone marrow [1,16].

PPP-syndrome can occur at any age (range: 6–88), although the typical patient is a middle-aged male with a history of heavy alcohol abuse (past or present) [1,7,11,17]. It can precede (1/3), coincide or succeed the pancreatic disease [1]. In all cases the authors saw an underlying pancreatic pathology as the main etiological factor, which can be acute or chronic pancreatitis, pancreatic carcinoma, neuroendocrine carcinoma, insulinoma, ischemic pancreatic disease, abdominal trauma or pancreatic duct stenosis [5–7,11,18–21]. Some authors described the presence of a pseudocyst, others detected a fistula between the pseudocyst and the superior mesenteric vein [8]. While the usually tiny fistulas are difficult to visualize in preoperative imaging, presence of mesenteric vein thrombosis can be an indirect sign and should always lead to surgical exploration. It is important to emphasize that in most cases abdominal symptoms were mild or absent, despite high levels of lipase [1].

The panniculitis presents with sometimes painful, erythematous red-brown nodules (0.5–5 cm), which are typically located on the lower extremities, but can spread to the entire body if the disease progresses. The cutaneous manifestation can precede the pancreatic disease several weeks [12]. Spontaneous rupture of the skin lesions can occur and secretion of a sterile "oily, brown, viscous" material is described [7,11]. In the beginning these lesions