Pancreatitis, Panniculitis, and Polyarthritis

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Background and Objective: Lobular panniculitis, together with polyarthritis and intraosseous fat necrosis, may occasionally complicate pancreatic disease. This triad is known in the literature as the pancreatitis, panniculitis, and polyarthritis (PPP syndrome). We describe a case of the PPP syndrome and review the available literature to summarize the clinical characteristics of patients with this condition.

Methods: A patient with the PPP syndrome, with evidence of extensive intraosseous fat necrosis in the joints involved revealed by magnetic resonance imaging, is described and the relevant literature based on a PubMed search from 1970 to February 2008 is reviewed. The keywords used were pancreatitis or pancreatic disease, panniculitis, arthritis, and intraosseous fat necrosis.

Results: Including our case, 25 well-documented patients with the PPP syndrome have been reported. Our patient had few abdominal symptoms despite high serum levels of pancreatic enzymes. In our review of the literature, almost 2/3 of patients had absent or mild abdominal symptoms, leading to misdiagnosis. The delay in diagnosis and specific treatment of the underlying pancreatitis worsens the prognosis of this condition, which has a mortality rate as high as 24%. In nearly 45% of the patients, the arthritis follows a chronic course with a poor response to nonsteroidal anti-inflammatory drugs and corticosteroids, and the rapid development of radiographic joint damage.

Conclusion: Certain forms of pancreatic disease can very occasionally cause arthritis and panniculitis. Although uncommon, physicians should be alert to the possible presence of this syndrome for 2 reasons: first, unrecognized pancreatic disease can be fatal if not treated promptly; second, to avoid inappropriate and risky therapy to improve joint symptoms.

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Patients with pancreatitis may develop extrapancreatic manifestations. Lobular panniculitis, which appears in 2 to 3% of patients, may predate the identification of pancreatitis by days or several weeks (1). More rarely, these patients can also develop arthritis with intraosseous fat necrosis, thus forming the triad of pancreatitis, panniculitis, and polyarthritis, referred to in the literature as the PPP syndrome (2-24). The absence or mild nature of the abdominal symptoms raises the risk of misdiagnosis of the pancreatic disease (3,5-9,12-15,21,22). In addition, in some of these patients the arthritis follows a chronic course with a poor response to treatment and the rapid development of radiographic lesions (6,7,9,16,22,23).

We report a case of the PPP syndrome with evidence of extensive intraosseous fat necrosis in the involved joints, as revealed by magnetic resonance imaging (MRI). We also review the available literature and summarize the clinical characteristics of patients with this condition.

METHODS

In addition to our case, a literature search (PubMed database, National Library of Medicine, Bethesda, MD) for

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articles published between January 1970 and February 2008 was performed using the Medline subheadings and key words "pancreatitis" or "pancreatic disease," "panniculitis," "arthritis," and "intraosseous fat necrosis." Only English-, French-, and Spanish-language reports were selected for review. The references of the studies obtained were then examined to identify additional reports. We included only those cases that were sufficiently detailed to be analyzed individually.

RESULTS

Case Report

A 45-year-old man with a 30-year history of heavy alcohol abuse was admitted to our center for alcohol detoxification. On admission, the patient reported that he had experienced mild upper abdominal pain, without nausea or vomiting, for 1 week.

On physical examination the abdomen was soft, tender in the epigastrium and left hypochondrium, with nontender hepatomegaly; joint and skin examination at that time were normal. Laboratory examination revealed an elevated erythrocyte sedimentation rate (84 mm/h), C-reactive protein of 254 mg/L (normal, <5), hemoglobin of 10.9 g/dL, mean corpuscular volume of 102, white blood cells of 16.5×10^9/L (82% neutrophils), platelet count of 543×10^9/L, serum amylase of 83 U/L (normal, ≤ 1.32), lipase of 64.5 ukat/L (normal, ≤ 1), aspartate transaminase of 0.7 ukat/L (normal, ≤ 0.5), alkaline phosphatase of 2.8 ukat/L (normal, ≤ 1.5), and gamma glutamyl transpeptidase of 5.7 ukat/L (normal, ≤ 1.16). Bilirubin, alanine aminotransferase, albumin, total proteins, cholesterol, triglycerides, serum calcium, and renal function test were all normal. Amylasuria was 409 UI/24 hours (normal, ≤ 6.68). Prothrombin ratio and activated partial thromboplastin time, antithrombin, protein C, and protein S were also normal; antiphospholipid antibodies were negative. Screening for hepatitis B and C was negative and $\alpha 1$-antitrypsin was normal.

Computed tomography of the abdomen confirmed the suspicion of acute pancreatitis and revealed segmental inflammation of the uncinate process of the pancreas, with irregular contour and obliteration of peripancreatic fat and partial thrombosis of the portal vein. There was no evidence of pseudocysts, biliary stone disease, or pancreatic stones. The patient was initially treated with bowel rest and nutritional support, analgesia (meperidine), and anticoagulation therapy (initially heparin followed by acenocumarol), with progressive resolution of the abdominal pain.

However, 3 days after admission the patient developed multiple painful erythematous nodules of 1 to 3 cm in diameter on both legs. Biopsy of the skin nodules showed subcutaneous fat necrosis consistent with a nodular panniculitis. Over the next 5 days he also developed pain and marked swelling involving the left ankle, both wrists, and several small joints of both hands. Joint examination revealed diffuse swelling, redness, and tenderness over both wrists and all metacarpophalangeal (MCP) joints. The left ankle was tender, warm, grossly swollen, and fluctuant. Arthrocentesis of the left ankle revealed a thick, yellowish, creamy fluid. Leukocyte and differential cell counts could not be performed accurately in this fluid because of the high viscosity. Sudan and oil-red-O stains of the synovial fluid were positive, indicating high lipid content. Cultures were sterile and no microcrystals were found. Plain radiographs of hands, wrists, and ankles revealed only soft-tissue swelling. Rheumatoid factor and antinuclear antibodies were negative.

Treatment with 30 mg/d of prednisone and nonsteroidal anti-inflammatory drugs (NSAID) was started, with complete resolution of the panniculitis lesions but without apparent improvement of the joint symptoms. Over the next few days the right wrist and, subsequently, the left ankle and left wrist began to drain spontaneously. These joints were incised with evacuation of abundant creamy yellowish material. Histopathological examination showed necrotic fat and connective tissue with low levels of lymphocyte and macrophage infiltration. Gram staining and serial cultures of this material were negative. MRI of the involved joints (hands and left ankle) showed multiple foci of abnormal signal, with ill-defined low signal intensity on T1-weighted images and high signal intensity on fat-suppressed T2-weighted and short tau inversion recovery (STIR) images, within the marrow of the affected bones (distal radius, scaphoid, base of the metacarpals, distal tibia, peroneal malleolus, calcaneus and talus), compatible with the diagnosis of fat necrosis and accompanying marrow edema. These bone lesions showed diffuse contrast enhancement. Other MRI features were concomitant synovitis, more pronounced in the right wrist, and panniculitis of periarticular soft tissues (identified as thickening and signal intensity alteration of the subcutaneous fat) (Fig. 1).

During subsequent follow-up, with topical therapy (daily wound cleaning using saline followed by the application of iodine), NSAID (diclofenac), and analgesics, the surgical incisions healed and the joint inflammation subsided over the next 8 weeks without relapses. A new computed tomography of the abdomen showed resolution of the portal thrombosis and marked improvement of the inflammatory changes, without evidence of pancreatic pseudocyst or phlegmons/abscesses. On day 28 of hospitalization, the pancreatic enzyme levels normalized. Although remaining systemically well, the patient continued to suffer persistent mechanical joint pain and functional sequelae, affecting the right wrist in particular. A radiograph performed 5 weeks after the onset of arthritis showed the rapid development of joint damage in both wrists (particularly the right) and left ankle, with loss of joint space and multiple osteolytic lesions, with a pattern of bone destruction and endosteal erosion (Fig. 2).