Pancreatic Neuroendocrine Tumor Presenting with Arthritis and Panniculitis

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Pancreatic neoplasm is complicated and can be preceded by extra-pancreatic manifestations, such as cutaneous and musculoskeletal symptoms. Awareness of these associations is important for timely diagnosis and appropriate treatment. We report a case of pancreatic neuroendocrine tumor (NET) presenting with arthritis and panniculitis. The patient had a two month history of right knee pain and subcutaneous nodules in both legs. Synovial fluid analysis from the right knee joint revealed a mildly increased white blood cell count without crystallization. A skin biopsy of a subcutaneous nodule revealed lobular panniculitis. The initial treatment with empirical antibiotics did not alleviate the symptoms; however, the right knee arthritis and skin nodules improved with steroid treatment. On the eighth day of hospitalization, the patient complained of abdominal discomfort. Abdominopelvic computed tomography scanning revealed a 14-cm sized pancreatic mass with peritoneal metastasis. Percutaneous needle biopsy confirmed the diagnosis of pancreatic NET. (J Rheum Dis 2017;24:313-317)

Key Words. Pancreatic neoplasms, Neuroendocrine tumors, Arthritis, Panniculitis

INTRODUCTION

Pancreatic cancer is one of the highly lethal malignancies, worldwide. Even in Korea, pancreatic cancer is fifth cause of death, according to cancer sites [1]. Curative modality is surgical resection; however, only 15 to 20% of patients are eligible for surgery. Moreover, even after complete resection, the overall 3- and 5-year survival rates were 29.5 and 18.3%, respectively, with a median survival period of 20.6 months [2].

The most common symptoms of pancreatic cancer are pain, jaundice, and weight loss; however, it does not always present with these classical symptoms. In certain rare cases, pancreatic cancer has been found to be complicated and is preceded by extra-pancreatic manifestations such as cutaneous and musculoskeletal symptoms. Awareness of these symptoms is important for timely diagnosis and appropriate treatment. In this report, we describe a case of pancreatic neuroendocrine tumor (NET) presenting with arthritis and panniculitis.

CASE REPORT

A 71-year-old man visited our hospital presenting with a 2-month history of right knee pain. He also had subcutaneous nodules on both lower legs that developed 2 months prior. He was diagnosed with small cell lung cancer 4 years ago, which had been in complete remission for 3.5 years after chemotherapy and radiation therapy. He was an ex-smoker of 40 pack-years, who had quit smoking 4 years ago. He was a social drinker, but stopped drinking 4 years ago.

On admission, the patient’s blood pressure was 125/72 mmHg, heart rate was 95 beats/min, body temperature was 36.3°C, and respiratory rate was 14 breaths/min. Physical examination revealed swelling and tenderness in the right knee joint, with limited motion. The left knee joint was also swollen, although to a lesser extent and
without tenderness. There were tender subcutaneous nodules on both lower extremities that were movable and rubbery (Figure 1A). Laboratory tests revealed the following: serum white blood cell count, 14,010 per mm$^3$; C-reactive protein, 15 mg/dL; erythrocyte sedimentation rate, 82 mm/hr; D-dimer, 6.57 μg/mL; blood urea nitrogen, 17.7 mg/dL; serum creatinine, 17.7 mg/dL; estimated glomerular filtration rate, 49 mL/min; aspartate transaminase, 25 IU/L; alanine transaminase, 11 IU/L; total bilirubin, 0.5 mg/dL; direct bilirubin, 0.2 mg/dL; uric acid, 2.2 mg/dL; a negative result for rheumatoid factor; and a negative result for anti-cyclic citrullinated peptide antibody. Urinalysis result was within the normal range. Synovial fluid (40 mL) was aspirated from the right knee joint and exhibited a turbid appearance (Figure 2A). In analysis of the synovial fluid, the white blood cell count was 24,800 per μL (neutrophil, 98%), and no visible crystals were observed under the polarized microscope. The gram stain and culture revealed no microorganisms. Furthermore, an acid-fast bacillus stain and polymerase chain reaction results for mycobacterium tuberculosis from the synovial fluid were also negative. A skin punch biopsy was conducted from the subcutaneous nodule on the left lower leg, which revealed lobular panniculitis with fat necrosis on the specimen (Figure 1B).

There were no specific findings from a simple knee radiography. However, magnetic resonance imaging indicated enhanced fluid collection around the right knee joint (Figure 2B). Although empirical broad-spectrum antibiotics were prescribed for 10 days before excluding septic arthritis (cefazolin: 2 g qid [four times a day] for 4 days, followed by piperacillin/tazobactam; 2.25 g qid and vancomycin; 1 g qid for 6 days), the right knee swelling and pain did not improve. However, with steroid treat-
ment (prednisolone, 20 mg once daily) there was an improvement in the right knee arthritis and the subcutaneous nodules of the lower extremities.

On the eighth day of hospitalization, the patient complained of epigastric pain. An abdominal radiograph showed mild fecal stasis; however, abdominopelvic computed tomography revealed a 14-cm circumscribed well-marginated heterogenous solid mass in left upper quadrant (Figure 3). This mass showed grossly internal hypervascular texture with irregular necrosis and external gastric invasion with tumor vascular continuity to gastric intramural vessels, with abutting to pancreas body and tail with partial invasion. Histological examination of the pancreatic mass was performed and pancreatic NET was confirmed (Figure 4). The patient was advised to undergo pancreatic mass resection and chemotherapy; however, he refused treatment for the pancreatic NET. On the 28th day of hospitalization, he was referred to another hospital for supportive treatment.

**DISCUSSION**

Panniculitis is defined as inflammation of the subcutaneous fat layer underlying the epidermis of the skin. It is often diagnosed through a skin biopsy and is classified by four histological subtypes—septal panniculitis or lobular panniculitis, each one with or without vasculitis—depending on the site of intense microscopic inflammation. Several conditions are associated with panniculitis; inflammatory disease (Crohn’s disease, ulcerative colitis), infections (bacterial infection, tuberculosis), trauma, deposition (hypercalcemia, hyperuricemia), enzymatic destruction (lipasemia, alpha-1 antitrypsin deficiency), and malignancy [3].

Pancreatic disease is one of the causes of panniculitis (pancreatic panniculitis), which is usually identified as lobular panniculitis upon pathologic examination. The pathogenesis of pancreatic panniculitis is not clear; however, it is suggested that the liberated pancreatic enzymes (lipase, amylase, trypsin, and phospholipase) from the destructed pancreas enter into the systemic circulation via the thoracic duct, portal vein, or lymphatic channels,
resulting in the saponification or necrosis of subcutaneous fat, causing panniculitis [4,5]. The most common pancreatic disorders associated with pancreatic panniculitis are acute or chronic pancreatitis, which usually result from alcohol abuse, trauma, or cholelithiasis. Pancreatic panniculitis has also been reported to be an extra-pancreatic manifestation of pancreatic cancer; usually acinar cell carcinoma and less frequently pancreatic NET [6].

In the current literature, four cases of pancreatic NET accompanied by subcutaneous fat necrosis have been published [7-10]. Two cases were insulinoma [7,8] and the other two were identified as nonfunctional NET [9,10]. Like in our patient, cases from previous reports visited the hospital presenting panniculitis with constitutional symptom such as weight loss, anorexia or fatigue. However, no one in previous cases suffered from any musculoskeletal symptoms. Pancreatic NET is known to originate from the islet cells, which produce the endocrine hormones insulin and glucagon and not pancreatic enzymes. Therefore, it is suggested that there are mechanisms other than pancreatic carcinoma that cause pancreatic panniculitis. In previous reports, Schwartz and Fleishman [8], Preiss et al. [9], and Berkovic and Hallermann [10] described a relatively large mass; 12 cm, 11×13-cm and 5-cm sized NET, respectively. One possible mechanism of pancreatic panniculitis associated with pancreatic NET is that the large mass may cause obstruction of the pancreatic ducts and thus temporarily increase the exocrine enzyme levels, resulting in pancreatic panniculitis. Similar to previous reports, the patient in our case also had a large mass (14×11 cm); however, pancreatic enzyme levels were within the normal range. Another possible explanation is that the panniculitis may be related to paraneoplastic syndrome, which is either a direct effect of the toxins released from tumor cells or is mediated by a hypersensitive reaction due to the presence of tumoral antigens [11].

Arthritis is also an extra-pancreatic manifestation of pancreatic cancer. The ankle joints are most commonly affected (71%), followed by the small joints of the hand (62%), and knee joints (61%). However, any joints can be affected, which can mimic rheumatoid arthritis, gout, or septic arthritis. In arthritis that is associated with pancreatic cancer, the synovial fluid is often yellow and either turbid or creamy, with fat droplets and particles in the supernatant [12]. Dahl et al. [5] reported that the levels of free fatty acids are elevated in the synovial fluid, suggesting increased lipolytic activity in the periarticular adipose tissue. In addition, van Klaveren et al. [13] described elevated lipase in analysis of the synovial fluid. In our case, the synovial fluid was yellowish and turbid with an elevated white blood cell count. However, we did not measure the fatty acid or lipase concentrations because we were not aware that knee arthritis was associated with pancreatic NET at the time of joint aspiration.

The main treatment strategy for panniculitis and arthritis related to pancreatic disease is to control the underlying disease [14]. In the case of pancreatic cancer, surgery was recommended and endoscopic procedures such as pancreatic stenting have also been described. Steroids, non-steroidal anti-inflammatory drugs and immunosuppressants for skin lesions or arthritis have been found to be ineffective [15]. In the case presented in this report, the patient refused the mass resection and chemotherapy for treatment of pancreatic NET. However, the arthritis and panniculitis improved after steroid treatment.

SUMMARY

Clinicians should be reminded that panniculitis and arthritis are extra-pancreatic manifestations of pancreatic cancer, including pancreatic NET, and can precede the pancreatic manifestations such as obstructive jaundice or palpable abdominal mass. Awareness of these associations is important as early recognition and treatment of pancreatic cancer appears to be the most significant factor in determining the prognosis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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