A Case of Leukemoid Reaction in Pancreatic Ductal Adenocarcinoma

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Leukemoid reaction is defined as leukocytosis exceeding 50,000 cells/mm³. When it occurs in a patient with a malignancy, secondary causes such as infections, drugs, hematologic diseases and hemorrhage need to be ruled out. After excluding such causes, paraneoplastic leukemoid reaction can be considered as a diagnosis of exclusion. Paraneoplastic leukemoid reactions have been described in association with lung, gastrointestinal, genitourinary and head and neck cancers. However, pancreatic cancer with leukemoid reaction has been rarely reported. We diagnosed a case of a 55-year-old Korean woman with extreme leukocytosis associated with advanced pancreatic cancer. (Korean J Gastroenterol 2015;66:116-121)

Key Words: Leukemoid reaction; Paraneoplastic syndromes; Pancreatic neoplasms

INTRODUCTION

Pancreatic cancer is the eighth most commonly diagnosed cancer and the fifth leading cause of cancer related deaths in Korea. The most common presenting symptoms with pancreatic cancer are pain, jaundice and weight loss. More unusual are paraneoplastic syndromes such as Cushing’s syndrome, panniculitis, dermatomyositis, arthritis, and recurrent Trousseau’s syndrome.

Leukocytosis is reported in most solid tumor types, and is associated with poor prognosis. When extreme leukocytosis occurs, secondary causes such as infections, use of corticosteroids or hematopoietic growth factors, newly developed hematologic disease, metastases to bone and massive hemorrhage need to be ruled out. Paraneoplastic leukocytosis can be diagnosed after excluding such causes. It is mainly associated with lung, breast, brain, renal, gastrointestinal and gynecological cancer.

Pancreatic cancer with paraneoplastic leukemoid reaction is rarely reported. We present a case of extreme leukocytosis with pancreatic cancer, which showed mucinous cystic component. To the best of our knowledge, this is the first case to be reported in Korea.

CASE REPORT

A 55-year-old woman presented with a six month history of left flank pain. She was referred for further evaluation of a mass in the tail of pancreas found in kidney CT at a nephrology outpatient clinic eight days prior. Comorbid conditions in-
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Fig. 1. A 5.5 cm-sized lobulating contour mass with inner cystic area in pancreatic tail with renal and splenic involvement was noted in pancreas dynamic MRI (A) and in whole body PET-CT (maximum standardized uptake value=6.0) (B).

Fig. 2. Product of distal pancreatectomy, splenectomy, and left nephrectomy. A large irregular solid mass (6.0×4.2×4.0 cm) was found at distal pancreas.

cluded hypertension and diabetes. On physical examination, there were no abnormalities. Laboratory findings revealed a platelet level of 118×10^3/μL (reference range, 140-400×10^3/μL), an amylase level of 106 U/L (reference range, 28-100 U/L) and a lipase level of 131 U/L (reference range, 13-60 U/L). Total leukocyte count, hemoglobin, urea, creatinine, electrolytes and liver function tests were within normal range. Her serum CA 19-9 level was elevated at 184.4 U/mL (reference range, 0-27.00 U/mL). Pancreas dynamic magnetic resonance imaging revealed a 5.5 cm-sized mass in the pancreatic tail with renal and splenic involvement (Fig. 1A). Whole body PET-CT was consistent with large invasive malignancy in the same area (maximum standardized uptake value=6.0) (Fig. 1B). Distal pancreatectomy, splenectomy, and left nephrectomy were performed (Fig. 2). Histologic examination revealed poorly differentiated adenocarcinoma with signet ring cell feature and mucinous cystic component (Fig. 3).

According to the American Joint Committee on Cancer (7th edition), the stage of the cancer was IIA (T3N0M0). For one month following the surgery, she was treated with concurrent chemoradiotherapy with gemcitabine and external irradiation (50.4 GY). Two months after the completion of chemoradiotherapy, she presented with complaints of epigastric pain of a week’s duration. Abdomen CT revealed multiple metastases to the liver (Fig. 4). An ultrasound-guided biopsy from the largest liver lesion was performed, and a metastatic poorly differentiated adenocarcinoma of pancreatic origin was found. She had elevated white blood cell (WBC) counts (23,730 cells/mm³; reference range, 4,000-10,000 cells/mm³) on admission without other evidence of infection. She started pal-

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Fig. 3. On histologic examination, poorly differentiated adenocarcinoma (A) with signet ring cell feature (H&E, ×100; inset: ×400) and mucinous cystic component (B) was noticed (H&E, ×100; inset: ×400).

Fig. 4. Pancreas CT shows multiple hyperechoic lesions with hypoechoic rim (arrows) in both lobes of the liver suggesting multiple metastases to the liver.

Adjuvant chemotherapy with gemcitabine and erlotinib for metastatic pancreatic cancer. Her WBC counts steadily increased, and a peripheral blood smear (PBS) was performed when WBC counts reached at 51,200 cells/mm³. WBC differential count showed 98.1% of neutrophils, 1.1% of lymphocytes, 0.7% of monocytes and 0.1% of eosinophils. PBS revealed marked granulocytosis without bands, myelocytes or metamyelocytes (Fig. 5). Among multiple blood cultures, gram-positive cocci were positive for three times, so catheter-related infection was suspected during early admission period. A central venous catheter was removed and appropriate intravenous antibiotics were given. However, her WBC counts increased despite ongoing antibiotics treatment. Her leukocyte alkaline phosphatase score was 374 (reference range, 13-130) suggesting non-malignant proliferative process. Bone marrow examination revealed reactive bone marrow with granulocyte hyperplasia without evidence of neoplastic cell infiltration (Fig. 6). Additional multiple blood cultures were negative. Other workups for infective etiology including urine cultures and chest X-ray were negative. She was taking olmetec, glimepine, and various types of gastrointestinal motility modulating and protective drugs, which are typically not associated with leukocytosis. Antibiotics including meropenem, tigecycline, cefpiran, vancomycin and teicoplanin were administered during her inpatient stay. WBC counts steadily increased regardless of the use of antibiotic or...
Fig. 5. Peripheral blood smear reveals marked granulocytosis without bands, myelocytes or metamyelocytes (H&E; A, ×200; B, ×1,000).

Fig. 6. Bone marrow examination reveals reactive bone marrow with granulocyte hyperplasia without evidence of neoplastic cell infiltration (Wright & Giemsa stain; A, ×400; B, ×1,000).

the type of antibiotic used. Chemotherapy was discontinued due to worsening liver function. The maximum WBC count during the course was 173,000 cells/mm³. She died shortly after, and her total WBC prior to expiring was 117,840 cells/mm³ (Fig. 7).

DISCUSSION

Paraneoplastic leukemoid reaction is rare in patients with primary pancreatic cancer. In literature review, we found only five previous cases of a leukemoid reaction in patients with pancreatic cancer. In 1971, Akoun et al. described the first
case of myeloid leukemoid reaction in a pancreatic cancer patient. Since then, four cases with leukemoid reaction associated with pancreatic cancer have been reported.6-9 This case, to the best of our knowledge, is the first case reporting the paraneoplastic leukemoid reaction with pancreatic cancer in Korea.

Paraneoplastic leukemoid reaction is diagnosed by excluding other secondary causes.4 In our patient, catheter-related infection was suspected during the early admission period but leukocytosis worsened after proper treatment for the infection. Multiple follow up blood cultures were negative, and further workups for infectious etiology were negative as well. Leukemoid reactions in advanced malignancy are mostly myelocytic. On the PBS, circulating neutrophils are usually mature forms, and blasts or nucleated red cells are not seen. Our patient’s peripheral smear revealed progressive granulocyte maturation without blasts or nucleated red cells. In addition, an increased alkaline phosphatase level suggested true leukemoid reaction. We performed bone marrow biopsy to evaluate for marrow irritation or metastatic tumor cell infiltration. Neither were identified. Drugs such as corticosteroids, vasopressors, lithium, heparin, and granulocyte stimulating factor are associated with leukocytosis.4,10 Our patient’s medication list did not include any of the common causes of leukocytosis. Some types of antibiotics that our patient used were associated with leukocytosis,10 but we concluded that the antibiotics were not related with leukemoid reaction, as WBC counts steadily increased regardless of the use of antibiotic or the type of antibiotic used. In addition, her leukocytosis was accompanied by neutrophilia. Although variable, drug induced leukocytosis typically do not cause neutrophilic leukocytosis. Other possible non-paraneoplastic causes, such as massive hemorrhage, were not identified in our patient.

The mechanisms of cancer-associated leukemoid reactions are poorly understood. The proposed mechanism is that inflammatory cytokine response may cause leukocytosis. These elevated cytokines can include granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and interleukin-6.8,9,11-14 Detection of multiple types of cytokine production has also been reported.13 Unfortunately, we did not check cytokine levels.

In literature review, we found unusual possible etiological factors of leukemoid reaction. Two cases of leukemoid reaction associated with mucin have been reported, including systemic mucormycosis and metastatic mucinous adenocarcinoma of lung origin.15 The suggested mechanism was that mucin produced by cancer cells attracts and activates the macrophages through the macrophage scavenger receptor.15,16 In addition, the mucin may increase expression of cyclooxygenase enzyme (COX-2) in these macrophages.15 COX-2 converts the arachidonic acid into different prostaglandins.15 Prostaglandin E2 (PGE2) secreted from the macrophages promotes the PGE2 production from macrophages itself as well as from nearby cells. In other words, mucin activates macrophages that secrete prostaglandins and tumor necrosis factor, increasing vascular permeability, pooling the leukocytes to the site of mucin production and in the bloodstream.15 As a result, the literature described the mucinous component as the agent that had attracted neutrophils to the blood circulation.15 Likewise our patient had a mucinous component on histologic examination and the mucinous component may have contributed to the leukemoid reaction.

Patients with malignant solid tumors can develop paraneoplastic syndromes including leukocytosis. Paraneoplastic leukemoid reaction may be a poor prognostic factor unless effective antineoplastic treatment is conducted.4 Further understanding of the mechanisms of these conditions and identification of such conditions may contribute to the development of new therapeutic strategies in cancer patients, and would be beneficial in the assessment of disease prognosis.
REFERENCES