A Case of Eosinophilic Pleural Effusion Induced by Pancreatothoracic Fistula

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ABSTRACT

A 49-year-old man was admitted for evaluation of a left pleural effusion. Thoracenthesis yielded a hemorrhagic pleural effusion with a high percentage of eosinophils (15.9%). Although there were no significant abdominal signs, serological examinations demonstrated a marked increase of pancreatic enzyme activity. Moreover, abdominal CT demonstrated cystic changes between the tail of the pancreas and the spleen. Accordingly ERP was performed under pressure, and contrast medium draining from the pancreas was observed. Pancreatic pleural effusion in this patient consisted of pancreatic juice retained in the thoracic cavity, which resulted from intrapancreatic fistulation connecting to the thoracic cavity due to a pancreatic cyst caused by chronic pancreatitis. The present report indicates that we should investigate the retention of eosinophilic pleural effusion considering not only the possibility of thoracic disease, but also the possibility of a pleural effusion derived from abdominal diseases.

Key words: Eosinophilic pleural effusion, Pancreatothoracic fistula, Chronic pancreatitis

Eosinophilic pleural effusion has been reported as a complication of several disorders. However, it unusually indicates that the patient has had pancreatitis. In the present report, we describe a case of hemorrhagic pleural effusion with eosinophilia in a patient who had a history of asbestos exposure and chronic pancreatitis. The results of endoscopic retrograde pancreateography (ERP) and thoracoabdominal CT demonstrated that the eosinophilic pleural effusion in this patient was caused by an intrapancreatic fistula resulting from chronic pancreatitis. Here, we report the clinical course of this patient with a review of the literature.

CASE REPORT

A 49-year-old man was admitted to our hospital complaining of left chest pain. He had a previous history of a gastric ulcer and acute pancreatitis several months ago. His occupation was a plumber (the patient had a history of asbestos exposure), and he drank approximately 900 ml/day of Japanese Sake and smoked 20 cigarettes every day.

On November 6, 1998, the patient consulted a local orthopedic surgeon due to left chest pain. He had a previous history of a gastric ulcer and acute pancreatitis several months ago. His occupation was a plumber (the patient had a history of asbestos exposure), and he drank approximately 900 ml/day of Japanese Sake and smoked 20 cigarettes every day.

On November 6, 1998, the patient consulted a local orthopedic surgeon due to left chest pain. Since his chest X-ray examination demonstrated left pleural effusion, the patient was referred to our hospital. Left pleural effusion retention was detected on a chest X-ray film (Fig. 1), and hematological examinations demonstrated severe inflammatory findings. Therefore, bacterial pleurisy was suspected, and the patient was admitted to our hospital.

Respiratory sound was slightly decreased in the left inferior lung field. The result of hematological and serological examination were as follows: white blood cell count (WBC) 14,120/mm³ (eosinophil; 3.5%), C-reactive protein (CRP) 10.0 mg/dl, and serum amylase (s-amylase) 783 IU/liter (Table 1). A chest CT scan demonstrated left pleural effusion; however, apparent tumor shadows were not detected (Fig. 2). Thoracocentesis was performed, and 500 ml of slightly hemorrhagic pleural effusion was drained. Although the cytology of the pleural effusion did not demonstrate any significant bacteria or malignant cells, markedly numerous eosinophils (15.9%) were observed in the pleural effusion. Based on the diagnosis of pleuritis, drip infusion of an antibiotic (Cefotiam hydrochloride) was started, and the course of this patient was followed thereafter. Although 7 days after administration, subjective symptoms such as chest pain were eliminated, hematological and serological examinations demonstrated marked eosinophilia and increased pancreatic enzyme activity.

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Table 1. Laboratory Data on Admission

<table>
<thead>
<tr>
<th>Urinalysis: n.p.</th>
<th>Biochemistry:</th>
<th>T. Chol</th>
<th>139 mg/dl</th>
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<tbody>
<tr>
<td>Hematology:</td>
<td>T. Bil</td>
<td>0.5 mg/dl</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>GOT</td>
<td>21 IU/liter</td>
<td></td>
</tr>
<tr>
<td>Neu</td>
<td>GPT</td>
<td>26 IU/liter</td>
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</tr>
<tr>
<td>Lym</td>
<td>LDH</td>
<td>319 IU/liter</td>
<td></td>
</tr>
<tr>
<td>Eo</td>
<td>TP</td>
<td>6.8 g/dl</td>
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</tr>
<tr>
<td>RBC</td>
<td>Alb</td>
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<td>Hgb</td>
<td>BUN</td>
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<tr>
<td>Hct</td>
<td>Cr</td>
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<tr>
<td>Pht</td>
<td>Tumor marker:</td>
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<td></td>
</tr>
<tr>
<td>Setology:</td>
<td>CRP</td>
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</table>

Hematological examinations 13 days after administration demonstrated further exacerbated eosinophilia and markedly increased pancreatic enzyme activity as follows: WBC 8,910/mm³ (eosinophils; 20.5%), CRP 1.3 mg/dl, s-amylase: 1,593 IU/liter, and lipase: 811 IU/liter. Moreover, abdominal CT demonstrated cystic changes between the tail of the pancreas and the spleen (Fig. 3). Therefore, acute exacerbation of chronic pancreatitis was suspected, and 600 mg/day of gabexate mesylate was administered. Hematological examinations 13 days after administration demonstrated further exacerbated eosinophilia and markedly increased pancreatic enzyme activity as follows: WBC 10,350/mm³ (eosinophils; 25.0%), CRP 0.6 mg/dl, s-

Fig. 1. Chest X-ray on admission showing left pleural effusion.

Fig. 2. Chest CT on admission showing left lung. There was no apparent tumor in the left thorax.

Fig. 3. Abdominal CT showing cystic lesion between the tail of the pancreas and the spleen.

Fig. 4. Endoscopic retrograde pancreatography showing the contrast medium draining from the pancreas.
amylase 2,946 IU/liter, and lipase: 1,518 IU/liter.
Therefore, the medication was changed to 60 mg/day of nafamostat mesylate. Thereafter, eosinophil counts and pancreatic enzyme activity gradually decreased. One month after administration, the results of hematological examinations were as follows: WBC 7,560/mm³ (eosinophils; 11.0%), CRP 1.3 mg/dl, s-amylase 198 IU/liter, lipase 38 IU/liter. During the course of this patient, there were no apparent abdominal signs. Accordingly ERP was performed, and pancreatography in the tail of the pancreas demonstrated irregularity and small cysts in pancreatic ducts. Furthermore, when pancreatography was performed under pressure, contrast medium draining from the pancreas was observed (Fig. 4). A CT scan performed immediately after ERP between the inferior lung field and the pancreas demonstrated contrast medium draining into the thoracic cavity via the tail of the pancreas, and the dorsal side of the spleen (Fig. 5). Therefore, a definitive diagnosis of pancreatic pleural effusion was established. Pancreatic pleural effusion in this patient consisted of pancreatic juice retained in the thoracic cavity, which resulted from intra-pancreatic fistulation connecting to the thoracic cavity due to a pancreatic cyst caused by chronic pancreatitis.

After ERP, there were no complications, and the patient was discharged from the hospital. Thereafter, the course of this patient was followed at the Outpatient Department. After discharge, during a 2-month course, there was neither the development of significant subjective symptoms nor an increase in pancreatic enzyme activity.

**DISCUSSION**

When retention of hemorrhagic pleural effusion with eosinophilia is observed, thoracic diseases such as lung cancer, tuberculosis, pulmonary asbestosis and vermination should be initially considered. In particular, as in this case, when a patient with a history of asbestos exposure demonstrates eosinophil-dominant hemorrhagic pleural effusion, malignant mesothelioma is initially suspected. However, when the patient has a past history of pancreatitis, the possibility of pancreatic pleural effusion should also be suspected.

Reactive pleural effusion is temporarily observed in acute pancreatitis. However, there is only one report concerning eosinophilic pleural effusion with pancreatitis. As a possible pathogenic mechanism of eosinophilic pleural effusion, an Arthus type allergic reaction is described.

When pancreatic juice is retained in the thoracic cavity after direct fistulation between the pancreatic duct and the thoracic cavity during the course of chronic pancreatitis, such pleural effusion is called pancreatic pleural effusion. The past history of most patients with pancreatic pleural effusion includes heavy drinking, and 99% of these patients develop chronic alcoholic pancreatitis. The direct drainage of pancreatic juice into the thoracic cavity was reported to cause retention of pancreatic pleural effusion. Cameron et al. found that retention of pancreatic ascites occurs when the pancreatic duct ruptures in the anterior aspect of the pancreas, while pancreatic pleural effusion is retained when the pancreatic duct ruptures in the posterior aspect of the pancreas together with subsequent fistulation between the retroperitoneum and the thoracic cavity. Itakura et al. investigated the frequencies of pancreatic pleural effusion and ascites between 1972 and 1997 and reported that there were reported 153 cases of pancreatic pleural effusion and 64 cases of pancreatic ascites in Japan. The frequency of pancreatic pleural effusion was higher than that of pancreatic ascites due to the anatomical characteristics of the pancreas. That is, the pancreas is an organ located in the retroperitoneal cavity, and there is no peritoneum in the posterior aspect of the pancreas. Therefore, the pancreatic duct is more easily ruptured in the posterior aspect of the pancreas than in the anterior aspect covered by the peritoneum.

Uchiyama et al. investigated 113 cases of pancreatic pleural effusion in Japan and reported that respiratory signs such as dyspnea, coughing and chest pain were initially noted as subjective symp-
toms in 68% of patients with pancreatic pleural effusion, while the frequency of abdominal signs was lower and noted only in 24% of these patients. On admission of this patient, although pancreatic enzyme activity was markedly increased, and findings on diagnostic imaging demonstrated cystic changes in the abdominal region, there were no subjective symptoms observed in the abdominal region. This was because irritating peritoneal signs did not appear due to formation of a pancreatothoracic fistula in the dorsal side of the retroperitoneum, the pancreatic duct was decompressed by internal fistulation, fibrosis developed in the tail of the pancreas due to chronic pancreatitis, or the enterokinases contained in duodenal juice did not act on the pancreatic juice.

Definitive diagnosis of this disease requires proof that pancreatic juice was the source of the pleural effusion as well as proof of the existence of a pancreatothoracic fistula. The pleural pancreatic amylase in the pleural effusion was predominant in the amylase fraction. Among various diagnostic imagings, although ERP is the most reliable procedure, there have been few reports of ERP visualization of the thoracic cavity. Kamiya et al. reported that satisfactory ERP findings were obtained when a balloon-tip catheter was used. In our patient, a catheter was inserted near the periphery of the pancreatic duct, and a fistula was visualized by acinar filling under pressure. Sufficient pressure during ERP is considered to reopen chronic pancreatitis-induced pancreatic duct stenosis or obstruction of the fistula, resulting in confirmation of a fistula by ERP. However, since ERP under pressure may have a risk of inducing further pancreatic disorder, it should be performed with care.

When a definitive diagnosis is established, pancreatic enzyme inhibitor administration is initially indicated for pancreatic pleural effusion. However, when there is no sign of improvement within 2 to 3 weeks after starting the treatment, surgery is required.

In our patient, since administration of gabexate mesylate did not decrease the pancreatic enzyme activity, the medication was changed to nafamostat mesylate. However, there was a report revealing that when nafamostat mesylate was administered to patients during the acute exacerbation of chronic pancreatitis, amylase activity decreased, and after the medication was changed to gabexate mesylate, increases in serum amylase levels were observed again. In addition, recurrence of subjective symptoms was noted in these patients when the medication was changed to gabexate mesylate, which improved after the medication was changed again to nafamostat mesylate. In our patient, the period when gabexate mesylate was administered unexpectedly corresponded with the period when the pancreatic cysts were absorbed. Therefore, pancreatic enzymes contained in the cyst were transferred to the blood, resulting in hyperamylasemia. Moreover, it was considered that the pancreatic enzyme activity started to decrease from the time when the medication was changed to nafamostat mesylate along with the subsidence of the pancreatic cysts. Furthermore, Onodera et al. reported that the concomitant use of ulinastatin and CDP-choline satisfactorily improved the clinical picture. Therefore, it was considered that the characteristics and indication of various pancreatic enzyme inhibitors should be evaluated in conservative treatment in the future.

The present report indicates that we should investigate retention of eosinophilic pleural effusion considering not only the possibility of thoracic disease, but also the possibility of pleural effusion derived from abdominal diseases, although there were no significant abdominal signs.

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