Autopsy of a Patient with Primary Pancreatic Lymphoma with Findings Resembling Severe Acute Pancreatitis

Yoshinori Harada¹, Yoshio Sogame², Ryuta Nakao¹, Takehiro Ogata¹, Hiroaki Yasuda², Junichi Sakagami¹,², Yoshito Itoh² and Hideo Tanaka¹

Abstract:
Primary pancreatic lymphoma is a rare pancreatic malignancy, reportedly accounting for only 0.2-0.7% of all primary pancreatic tumors. Primary pancreatic lymphoma is often difficult to distinguish from other diseases, such as acute pancreatitis. We herein report the autopsy of a patient with primary pancreatic lymphoma with imaging findings resembling those of severe acute pancreatitis, with a focus on the gross and histological features.

Key words: primary pancreatic lymphoma, severe acute pancreatitis, autopsy


Introduction
Primary pancreatic lymphoma (PPL) is a rare pancreatic malignancy, reportedly accounting for 0.2-0.7% of all primary pancreatic tumors and 1% of extranodal lymphomas (1-4). According to the World Health Organization, the majority of PPL lesions are localized to the pancreas with pancreatic clinical manifestations, although PPL often involves invasion of the adjacent lymph nodes or distant metastases (5).

The clinical manifestations of PPL are non-specific and include abdominal pain (58%), jaundice (47%), abdominal mass, and decreased body weight (6). PPL is associated with typical lymphoma, symptoms such as chills, a fever, and nocturnal sweating in a small percentage of patients (2%) (7). Diffuse large B-cell lymphoma is the most common histological type of PPL, accounting for 77% of all PPLs (8-10). PPL has fewer characteristic imaging findings and is often difficult to distinguish from other diseases, such as acute pancreatitis.

We herein report the clinical course and autopsy of a patient with PPL, who presented with symptoms and imaging and blood test findings similar to those of patients with severe acute pancreatitis.

Case Report
A man in his late 70s reported symptoms of anorexia and lower abdominal pain 2 months before admission. One month before admission, the pain worsened and began to spread over the entire abdomen; therefore, he was admitted to a local hospital. Laboratory tests showed a high degree of inflammatory reaction, as evidenced by a white blood count of 8,060 cells/μL and C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels of 20.18 mg/dL and 544 U/L, respectively. Abdominal computed tomography (CT) revealed pancreatic swelling and right pleural effusion, and the patient was diagnosed with severe acute pancreatitis. Although he received treatment for severe acute pancreatitis, his condition did not improve, so he was transferred to our hospital.

Contrast-enhanced CT of the abdomen at the time of transfer revealed an enlarged pancreatic tail with poor contrast and a low-density soft shadow extending into the right perirenal area and retroperitoneal space around the splenic and celiac arteries (Fig. 1). A 10-mm area with indistinct borders and a weak contrast effect was observed in the pan-

---

¹Department of Pathology and Cell Regulation, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Japan, ²Department of Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Japan and ³Department of Gastroenterology and Hepatology, Fukuchiyama City Hospital, Japan

Received: July 30, 2022; Accepted: September 1, 2022; Advance Publication by J-STAGE: October 5, 2022
Correspondence to Dr. Yoshinori Harada, yoharada@koto.kpu-m.ac.jp
Computed tomography image of the pancreas after contrast medium administration. The arterial-pancreatic phase is shown. The arrowhead, arrow, and number sign indicate the 10-mm mass in the body of the pancreas, pancreatic-duct dilatation, and necrotic lesion in the pancreatic tail, respectively.

The laboratory data obtained on transfer are summarized in Table 1. The pancreatitis-associated data were as follows: amylase, 71 U/L; trypsin, 646 ng/ml; phospholipase A2, 612 ng/dL; LDH, 599 U/L; CRP, 18.82 mg/dL. The patient continued to receive treatment based on the diagnosis of severe acute pancreatitis; he was treated with gabexamate mesylate and cefmetazole sodium, followed by nafamostat mesylate, ulinastatin, and meropenem hydrate (upper panels of Fig. 2). Serum levels of LDH and CRP increased with time (lower panel of Fig. 2). Eight days after transfer, the patient’s level of consciousness decreased rapidly, seizures and right conjugate deviation were observed, and his general condition worsened. He died 20 days after being transferred to our hospital. A pathological autopsy was performed to elucidate the etiology of his death with the consent of his family.

The autopsy revealed tumor invasion in the pancreas and peripancreas, heart (307 g), liver (897 g), left kidney (128 g), gallbladder, stomach, ileum, sigmoid colon, abdominal aorta, right diaphragm, and retroperitoneum. Lymphadenopathy of the neck, mediastinum, and mesentery was also observed. A cutout view of the pancreas and the peripancreatic tissues is depicted in Fig. 3; the tail region indicated by the arrow was excised to prepare the samples shown in Fig. 4. The whitish tumor was located mainly in the pancreatic tail (Fig. 4A), although it was also observed in the pancreatic head/body; multiple tumorous lesions were observed in the pancreas. The mass in the pancreatic body revealed by CT was also identified in the autopsied specimen (data not shown). Hematoxylin-eosin and CD20-staining images corresponding to the macroscopic image in Fig. 4A are presented in Fig. 4B and 4C, respectively. For reference, immunohistochemical staining of AE1-/AE3-positive non-neoplastic epithelial cells is depicted in Fig. 4D; the pancreatic tissue is enclosed by dotted lines (Fig. 4D). The dilated pancreatic duct was observed in the body/tail; the maximal diameter of the pancreatic duct in the tail was 4 mm in size.
**Figure 2.** Clinical course. Solid lines represent the levels of lactate dehydrogenase (LDH) (U/L), c-reactive protein (CRP) (mg/dL), and amylase (U/dL) in serum. Administered drugs are depicted in squares.

**Figure 3.** Gross appearance of formalin-fixed pancreatic and peripancreatic tissues. A cutout view is shown. The portion indicated by the arrow was cut out to prepare the specimens shown in Fig. 4. Scale bar=20 mm.

(data not shown). A scar lesion was observed in the pancreatic tail (arrowheads, Fig. 4B). In the magnified views, large atypical lymphocytes had diffusely proliferated and infiltrated the pancreatic tissue (Fig. 5A). The atypical lymphocytes were positive for CD20 (Fig. 4C and 5B), CD79a, and MUM1 and negative for CD3, CD5, CD10, CD23, CD30, CD138, and BCL6; the diagnosis was PPL (diffuse large B-cell lymphoma). AE1/AE3 immunoreactivity in the pancreatic tail showing the remaining pancreatic epithelia is depicted in a magnified view in Fig. 5C. Massive infiltration of lymphoma cells was observed in the wall of the pancreatic duct (Fig. 5D). Strong invasion of lymphoma cells was seen in the peripancreatic adipose tissue (Fig. 5E). Fat necrosis was partly observed in the peripancreatic region of the pancreatic tail (arrows, Fig. 4B and 5F).

An extensive hemorrhagic cerebral infarct was identified in the region of the left middle cerebral artery. No tumor invasion was observed in the cerebrum or cerebellum. Congestion and edema were observed in the lungs (left, 453 g; right, 378 g), with no local lesions suggestive of neoplasms or infection. No abnormalities were observed in the large intestine. The autopsy findings revealed that the progression of PPL and hemorrhagic cerebral infarction were the main cause of death.

**Discussion**

The clinical questions in this study were as follows: 1) Was the diagnosis of severe acute pancreatitis appropriate given the long disease course and relatively mild degree of abdominal pain? and 2) Was there a complication of pancreatic carcinoma in the pancreatic body? In this patient, massive lymphoma cell infiltration was evident from the pancreatic body through the pancreatic tail, with particularly strong infiltration in the tail (Fig. 4 and 5). We observed extensive infiltration of lymphoma cells in a broad zone of the peripancreatic area (Fig. 5E), although fat necrosis, a typical finding in acute pancreatitis, was observed in a small area of the pancreatic tail (arrow, Fig. 4B and 5F). Therefore, PPL (diffuse large B-cell lymphoma) was considered the chief diagnosis, although some mild acute pancreatitis was present in a limited region. Pancreatic carcinoma was not observed in the pancreatic body.

Imaging is vital in the diagnosis of pancreatic lesions. Ac-
According to previous studies, PPL appears as a homogeneous mass with less contrast enhancement than pancreatic adenocarcinoma on abdominal CT (2, 11); PPL was reported to have two distinct morphologic patterns: localized well-defined and diffuse tumor patterns (12, 13). However, the present case did not necessarily apply to such morphologic patterns. On abdominal contrast-enhanced CT, vascular invasion and pancreatic duct dilatation are rare in PPL (2). PPL is suspected when tumors are present in the pancreatic head without main pancreatic duct dilatation and lymph node swelling below the renal vein, and lymphoma can be ruled out when calcification or necrosis is observed in the pancreatic mass (13). In the present study, abdominal CT showed mild dilatation of the pancreatic duct concomitantly with necrosis of the pancreatic tail, which made it quite difficult to diagnose PPL (Fig. 1).

Although 14% of pancreatic adenocarcinomas reportedly present with acute pancreatitis, PPL is rarely complicated with acute pancreatitis (14). The mechanism underlying pancreatitis associated with PPL is reportedly “pancreatic duct obstruction, rupture of the pancreatic duct with direct parenchymal invasion of the tumor, and ischemia secondary to vascular occlusion by the tumor (15, 16).” In the present case, we observed massive infiltration of lymphoma cells into the wall of the pancreatic duct (Fig. 5D). Therefore, we considered the mild acute pancreatitis in the tail to have been induced by the obstructed pancreatic duct.

A blood analysis revealed an elevated serum LDH level in this patient, which influenced the diagnosis of the severity of the acute pancreatitis. According to the literature, an elevated serum LDH concentration is observed in 43% of patients with PPL (17). Soluble interleukin-2 receptors are used in the diagnosis of malignant lymphoma, although they were not evaluated in this patient because we suspected carcinoma in the pancreatic body.

An endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) is reportedly valuable in the diagnosis of PPL (18), but it was not performed because the patient had a hemorrhagic cerebral infarction early on, and his general condition deteriorated. The tumor-bearing condition may have affected the patient’s blood coagulability. Furthermore, because we suspected severe acute pancreatitis, invasive biopsy tests could not be performed. When PPL is suspected, an EUS-FNAB should be performed at an early stage to make a definitive diagnosis.

In this study, we performed an autopsy on a patient with PPL that could not be diagnosed before death due to atypical imaging findings. To our knowledge, this is only the
Figure 5. Microscopic findings of the pancreas (A to D) and the peripancreatic tissue (E and F). (A) Hematoxylin and Eosin staining image (high-power view). (B) CD20 immunostaining (high-power view). (C) AE1/AE3 immunostaining (high-power view). (D) CD20 immunostaining (medium-power view) of the pancreatic duct. The lumen of the pancreatic duct is indicated by a number sign. (E) A peripancreatic tissue image (medium-power view) shows lymphoma cells strongly infiltrating the peripancreatic area. (F) Medium magnified image of the region indicated by the arrow in Fig. 4B; fat necrosis is seen in the peripancreatic area.

Table 2. A Summary of 3 Patients with Primary Pancreatic Lymphoma Presenting as Severe Acute Pancreatitis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Pancreatic enzyme</th>
<th>Lactate dehydrogenase</th>
<th>CT findings</th>
<th>Pathological diagnosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74/F</td>
<td>amylase 268 U/L (RR, 30-110 U/L) lipase 3,000 U/L (RR, 73-393 U/L)</td>
<td>729 U/L (RR, 84-246 U/L)</td>
<td>severe pancreatitis without a focal lesion, developing pseudocysts and nonspecific upper abdominal and right retrocrural lymphadenopathy.</td>
<td>DLBCL</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>39/F</td>
<td>amylase 642 U/L (RR, 60-108 U/L) lipase 988 U/L (RR, 7-58 U/L)</td>
<td>ND</td>
<td>bulky heterogeneously enhancing pancreas with extensive mesenteric inflammation, with mild peri-hepatic and peri-pancreatic fluid; peritoneal nodules and necrotic sub diaphragmatic lymph nodes</td>
<td>ALCL</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>late 70s/M</td>
<td>p-amylase 50 U/L (RR, 8-49 U/L) trypsin 646 ng/mL (RR, 100-550 ng/mL) PLA2 612 ng/dL (RR, 130-400 ng/dL)</td>
<td>599 U/L (RR, 114-243 U/L)</td>
<td>an enlarged pancreatic tail and a low-density soft shadow extending into the right perirenal area and retroperitoneal space; A 10-mm area in the pancreatic body and mildly dilated pancreatic duct; enlarged lymph nodes near the aorta to the right of the common iliac artery, ascites, and bilateral pleural effusion.</td>
<td>Present case DLBCL</td>
<td>determined by an autopsy sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19</td>
</tr>
</tbody>
</table>

third report in a patient with PPL with findings similar to those of patients with severe acute pancreatitis (16, 19). The clinical and pathological findings of the three cases with PPL presenting as severe acute pancreatitis are summarized in Table 2 (16, 19). In all of the cases, a histopathological diagnosis could not be performed early in the disease, so the patients could not be treated for lymphoma. Although PPL is very rare, its antemortem diagnosis is reportedly possible using histological examinations, such as an EUS-FNAB (18). Early and invasive histopathological examinations are required for the accurate diagnosis of PPL, even if the findings resemble those of severe acute pancreatitis.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
The authors thank Mr. T. Kawamura and Mr. T. Okuda of Kyoto Prefectural University of Medicine for histological staining.

References

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).