A Case of Concomitant Pancreatic Ductal Adenocarcinoma and Type 1 Autoimmune Pancreatitis: A Potential Issue in the Diagnosis of Carcinoma by Endoscopic Ultrasound-guided Fine-needle Biopsy

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Abstract:
We herein report a 64-year-old man with concomitant pancreatic ductal adenocarcinoma (PDAC) and type 1 autoimmune pancreatitis (AIP). An endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) from the pancreatic head mass revealed level 2 histology of AIP and atypical glands. We diagnosed definitive focal AIP using the clinical diagnostic criteria. Computed tomography revealed that the pancreatic mass had not been reduced by steroid therapy. Surgery was performed after a histological PDAC diagnosis was made via a transpapillary biliary biopsy. The resected specimen revealed PDAC associated with AIP. It is important to consider the cooccurrence of PDAC and AIP even if the histological diagnosis via an EUS-FNB is AIP.

Key words: autoimmune pancreatitis, endoscopic ultrasound-guided fine-needle biopsy, pancreatic ductal adenocarcinoma, steroid pulse therapy


Introduction

Type 1 autoimmune pancreatitis (AIP) is a distinct form of pancreatitis of unknown etiology associated with IgG4-related disease. AIP is clinically diagnosed using the International Consensus Diagnostic Criteria (ICDC) (1) and 2018 Japanese Clinical Diagnostic Criteria for AIP (JPS2018) (2) in Japan. Endoscopic ultrasound (EUS)-guided fine-needle aspiration (EUS-FNA) is commonly used to diagnose solid pancreatic tumors, with a sensitivity exceeding 90% (3). However, a histological diagnosis of definitive AIP via EUS-FNA is difficult if inadequate tissue is obtained (1). Recently, the use of EUS-guided fine-needle biopsy (FNB) needles has improved the quality and quantity of histological specimens (4-7). A systematic review comparing the diagnostic yields of EUS-FNA and an EUS-FNB according to the histological criteria of AIP revealed that FNB needles were better than FNA needles (8). An EUS-FNB is commonly used for the histological diagnosis of AIP (9, 10).

Pancreatic ductal adenocarcinoma (PDAC) is an important mimicker of AIP; the clinical and imaging findings are similar. The cooccurrence of PDAC and AIP has been previously reported. In a recent large study of patients with AIP and PDAC (11), PDACs were typically metachronous and were found in the part of the pancreas affected by inflammation. However, synchronous cooccurrence of PDAC and AIP was only seen in 33% of patients subjected to detailed analyses. Therefore, cooccurrence may be rare.

We herein report a case of concomitant PDAC and AIP...
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Case Report

A 64-year-old man was admitted to a previous hospital with jaundice. His medical history included hypertension, hyperuricemia, hyperlipidemia, inguinal hernia, hepatitis C, hyperthyroidism, and scleroderma. He did not drink alcohol or smoke and had no relevant family history. The serum levels of total bilirubin, aspartate aminotransferase, alkaline phosphatase, and \( \gamma \)-glutamyl transpeptidase were elevated to 7.6 mg/dL (normal range: 0.4-1.5 mg/dL), 176 U/L (13-30 U/L), 257 U/L (10-42 U/L), 966 U/L (106-322 U/L), and 721 U/L (13-64 U/L), respectively. The serum C-reactive protein level was 0.18 mg/dL (normal range: \( \leq 0.14 \) mg/dL), and the white blood cell count was 3,600/mm\(^3\) (3,300-8,600/mm\(^3\)). The serum levels of IgG, IgG4, CEA, and CA19-9 were 1,494 mg/dL (normal range: 861-1,747 mg/dL), 270 mg/dL (11-121 mg/dL), 1.0 ng/mL (0.0-5.0 ng/dL), and 20 U/mL (0-37 U/mL), respectively.

Computed tomography (CT) revealed a 30-mm-diameter pancreatic head mass without dilation of the upstream main pancreatic duct (MPD). On contrast-enhanced CT, the pancreatic mass was hypovascular in the pancreatic phase and enhanced in the portal and delayed phases (Fig. 1). Endoscopic retrograde cholangiography (ERC) revealed a distal common bile duct stricture, and a biliary plastic stent (PS) was inserted in a transpapillary manner. Three EUS-FNBs were performed, and atypical cells were observed in one specimen. However, there were no histological findings suggestive of PDAC or AIP. Therefore, the patient could not be diagnosed with either PDAC or AIP at the previous hospital and was therefore transferred to our hospital for a further examination and treatment.

The size of the pancreatic mass on contrast-enhanced CT had not increased compared to two months prior, so we repeated an EUS-FNB. A histological evaluation revealed dense lymphoplasmacytic infiltration, fibrosis, and >10 IgG4-positive cells/high-power field (HPF) (Fig. 2A). Notably, many IgG4-positive cells were diffusely distributed in the inflamed regions (Fig. 2B), suggesting AIP. Although some atypical glands were identified (Fig. 2C, D), the cells were too blunt to confirm a histological diagnosis of PDAC; we therefore suspected that the cellular atypia reflected inflammation caused by AIP or contamination by inflamed intestinal mucosa. Endoscopic retrograde pancreatography (ERP) revealed narrowing of the MPD and duct of Santorini as well as dilation of the branch duct in the pancreatic head and uncus (Fig. 3A). As stated above, ERC revealed distal common bile duct stricture (Fig. 3B). We therefore diagnosed the patient with definitive AIP based on the ICDC criteria but could not rule out PDAC because atypical cells were evident on an EUS-FNB.

Given these findings, we prescribed steroid pulse therapy. Each course involved methylprednisolone 500 mg/day 3 days per week; we administered 2 courses according to a previous report (12). Two weeks later, the serum IgG and IgG4 levels had decreased to 834 and 132 mg/dL, respectively. While the pancreatic head mass had not shrunk, and heterogeneity of the pancreatic mass appeared on contrast-enhanced CT after steroid therapy (Fig. 4), endoscopic retrograde cholangiopancreatography (ERCP) showed that the MPD and duct of Santorini were less narrow, and the distal common bile duct stricture seemed to be improved (Fig. 5); these findings suggested that the steroid treatment was effective. Therefore, we removed the biliary PS and started oral prednisolone (PRL) 20 mg/day as steroid induction therapy.

Eleven days later, acute obstructive cholangitis developed, and the biliary PS was re-inserted. We suspected that the PSL level might be inadequate so increased the dose to 40 mg/day. Two weeks later, the serum IgG and IgG4 levels were 924 and 74.2 mg/dL, respectively. ERC showed that the distal biliary stricture had not improved. Therefore, we conducted a transpapillary bile duct biopsy for the first time, and the biopsy specimen yielded a pathological diagnosis of adenocarcinoma. We diagnosed him with resectable PDAC and planned to perform surgery after neoadjuvant chemotherapy (NAC).

The PSL was tapered and then stopped, and NAC (gemcitabine plus S-1) was started to treat PDAC. However, se-
Figure 2. A: Dense lymphoplasmacytic infiltration and fibrosis were observed [Hematoxylin and Eosin (H&E) staining, ×10 objective]. B: Numerous IgG4-positive cells were identified diffusely in the inflamed portions (IgG4 ×20 objective). C, D: Some atypical glands (arrows) were identified (H&E staining, C: ×20 objective, D: ×40 objective).

Figure 3. A: Endoscopic retrograde pancreatography showed the narrowing of the main pancreatic duct and the duct of Santorini as well as dilation of the branch duct in the head and uncus of the pancreas. B: Endoscopic retrograde cholangiography showed the distal common bile duct stricture.

A severe eruption occurred, so we changed the second course to S-1 monotherapy and performed subtotal stomach-preserving pancreaticoduodenectomy two weeks after the NAC treatment. We resected a 30-mm-diameter mass from the pancreatic head. A histological examination revealed differentiated tubular adenocarcinoma involving the distal common bile duct and duct of Wirsung in the pancreatic head (Fig. 6A). NAC had caused marked cancer cell effacement and degeneration. The cancer cells were blunt, resembling the atypical cells in the EUS-FNB sample, which we recognized as cancer cells. Although the AIP lesion had entirely regressed, obliterative phlebitis consisting of both inflammatory cells and fibrosis was identified in 10 foci of a single elastin-stained slide (Fig. 6B). The duct of Santorini, which was not involved in the PDAC, was intact in the epithelium, and mild lymphoplasmacytic infiltration was evident beneath the epithelium. There were only a few IgG4-positive cells, but foci with >10 positive cells/HPF were apparent (Fig. 6C). The histopathological findings of the resected specimen combined with those of the biopsy sample were consistent
Figure 4. The pancreatic head mass had not shrunk in size after the steroid therapy on contrast-enhanced CT (A: pancreatic phase, B: portal phase, C: delayed phase).

Figure 5. A: The narrowing of the main pancreatic duct and the duct of Santorini were slightly improved on endoscopic retrograde pancreatography. B: The distal common bile duct stricture was slightly improved on endoscopic cholangiography.

Discussion

We herein report a case of cooccurring PDAC and AIP. We preoperatively diagnosed AIP using the ICDC criteria. An EUS-FNB revealed level 2 histological findings of AIP with atypical glands. However, imaging revealed that steroid therapy was ineffective. We therefore re-evaluated the histological data and found evidence of adenocarcinoma. After surgery, we finally diagnosed the patient with synchronous PDAC and AIP.

The EUS-FNB specimen revealed dense lymphoplasmacytic infiltration, fibrosis, and >10 IgG4-positive cells/HPF, meeting the ICDC criteria for level 2 histology of AIP (1). The level 2 parenchymal imaging, level 2 ductal imaging (via ERP), and level 1 serology criteria were met. Therefore, our preoperative diagnosis was definitive AIP based on the ICDC criteria. EUS-FNBs were performed three times at the previous hospital and once at our institution; atypical glands were observed in two of the four specimens. We initially considered that these cells might reflect inflammation caused by AIP. We prescribed steroid pulse therapy because we could not exclude the possibility of PDAC given that atypical cells were evident in the EUS-FNB specimens. We obtained histological evidence of adenocarcinoma via a transpapillary bile duct biopsy after observing no response to the steroid. A retrospective histological review of the EUS-FNB specimen (performed after the histological evaluation of the surgical specimen) revealed that the atypical cells were adenocarcinoma cells.

The diagnosis of PDAC based on an EUS-FNB specimen is difficult; the number of carcinoma cells may be low, and the cells may also exhibit minimal atypia. In addition, the level 2 histology of AIP in the background was eye-catchy, and atypical cells in the setting of clinical suspicion of AIP easily gave rise to an alternative evaluation. The diagnosis of PDAC was obtained only by the bile duct bi-
Figure 6. A: Effacement and degeneration of cancer cells by neoadjuvant chemotherapy were markedly observed (Hematoxylin and Eosin staining ×10 objective). B: Substantial obliterative phlebitis consisting of both inflammatory cells and fibrosis (arrows) was noted (EVG ×4 objective). C: A few IgG4-positive cells were observed (IgG4 ×20 objective).

Figure 7. Clinical course.

opsys in the present case, although an EUS-FNB shows higher sensitivity than a bile duct biopsy in the histological diagnosis for PDAC. We should consider performing a bile duct biopsy for the histological diagnosis of PDAC in patients with biliary stricture when histological evidence of malignancy cannot be obtained by an EUS-FNB.

Two pathologies are possible when abundant IgG4-positive cells are observed in an EUS-FNB specimen. First, IgG4-positive plasma cells may be abundant around a PDAC. Second, AIP and PDAC may cooccur, as in our case. In resected PDAC specimens, abundant IgG4-positive cells tend to be confined to only a few regions (10, 13-15). In contrast, in the synchronous occurrence of AIP and PDAC, many areas may show abundant IgG4-positive plasma cells; this is also useful for distinguishing the two conditions. However, needle biopsy samples may contain PDAC regions...
with abundant IgG4-positive cells. Therefore, it is important to consider the possibility of synchronous occurrence of AIP and PDAC even when the findings indicate level 1 or 2 histology of AIP at the time of the diagnosis.

Macinga et al. (11) conducted the largest study to date on patients with AIP and PDAC. The synchronous cooccurrence rate of PDAC and AIP was 33%. Most carcinomas (70%) were found in pancreatic regions affected by AIP. There are several reasons why AIP and PDAC may develop concomitantly. First, AIP is a risk factor for PDAC, as is chronic pancreatitis. Second, AIP is a paraneoplastic syndrome. Shiokawa et al. (16) suggested that AIP might be a paraneoplastic syndrome; the cancer risk was highest within one year after the AIP diagnosis, and AIP did not relapse after successful treatment of other malignancies. Finally, a secondary PDAC histological reaction may be misdiagnosed as AIP.

In our case, the histopathological findings were characteristic of AIP in the lesions surrounding the PDAC, as in previous resected cases with concomitant AIP and PDAC (15, 17-20). In addition to the histological findings mentioned above, widening of the duct of Santorini (evident on ERP) after steroid therapy supports a diagnosis of AIP. A histological evaluation of the resected specimen revealed mild lymphoplasmacytic infiltration around the epithelium of the duct of Santorini, without any PDAC. Therefore, we speculate that an AIP lesion involving the duct of Santorini regressed after steroid therapy. Heterogeneity of the pancreatic mass was observed on CT after the steroid therapy. Steroid therapy might be effective in part of an AIP, but not for PDAC. The differing responses to steroid therapy between AIP and PDAC might therefore have caused the heterogeneity in the pancreatic mass. Another possible explanation is that the cell-rich AIP lesion inside the PDAC was replaced by edema or loose connective tissue after the steroid therapy.

We diagnosed definitive AIP on the basis of the ICDC level 2 histology of pancreas. However, atypical glands were observed in the an EUS-FNB specimen. As the steroid was not effective, we re-conducted the histological examination and obtained a transpapillary bile duct biopsy specimen when exchanging the biliary stent. The effect of steroid therapy on imaging findings must be considered, especially when atypical cells are observed, even if AIP is definitively diagnosed based on histological findings. It is important to consider synchronous PDAC and AIP even if an EUS-FNB yields histological findings suggestive only of AIP.

In summary, we encountered a case of concomitant PDAC and AIP. We preoperatively diagnosed definitive AIP based on the clinical diagnostic criteria and histological findings. It is important to consider the possibility of synchronous PDAC after a definitive diagnosis of AIP is made. A careful evaluation of imaging findings after steroid therapy is important to exclude PDAC associated with AIP.

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

References


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