



Case study

Synchronous autoimmune pancreatitis and infiltrating pancreatic ductal adenocarcinoma: case report and review of the literature

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Summary An 80-year-old white man underwent pylorus-preserving pancreaticoduodenectomy after presenting with obstructive jaundice and a dilated biliary tree on cholangiopancreatography. Histologic evaluation of the specimen revealed synchronous autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis) and infiltrating ductal adenocarcinoma of the pancreas. The mixed inflammatory infiltrate centered on the pancreatic ducts was associated with acinar loss, parenchymal fibrosis, and obliterative venulitis. Immunohistochemical labeling with an antibody to IgG4 revealed greater than 50 IgG4-positive plasma cells per high power field. Although not appreciated grossly, pancreatic intraepithelial neoplasia-3 and a neurotropic infiltrating poorly differentiated adenocarcinoma of the pancreas were also present. This case highlights the importance of carefully evaluating patients with autoimmune pancreatitis to rule out an underlying neoplasm and the importance of following those who were treated nonsurgically until the disease fully resolves.

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1. Introduction

Autoimmune pancreatitis (AIP), also known as lymphoplasmacytic sclerosing pancreatitis, is a rare form of chronic pancreatitis characterized by a mixed inflammatory infiltrate centered around the pancreatic ducts accompanied by an obliterative venulitis, acinar atrophy, and interstitial fibrosis [1]. Originally described by Sarles et al [2] in 1961 as “primary inflammatory sclerosis of the pancreas,” the term

autoimmune pancreatitis was introduced by Yoshida et al [3] in 1995. AIP typically affects middle-aged patients who lack the risk factors associated with chronic pancreatitis [4]. AIP can occur in isolation or in association with other autoimmune diseases including rheumatoid arthritis, Sjögren’s syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, and inflammatory bowel disease [4].

The clinical presentation of AIP can vary widely. Most patients present with jaundice or abdominal pain [5]. Radiographically, the classic appearance of AIP on computed tomography (CT) scan consists of diffuse enlargement of the pancreas with effacement of the usual lobular appearance of the pancreas and a low attenuation capsule-like rim [6].

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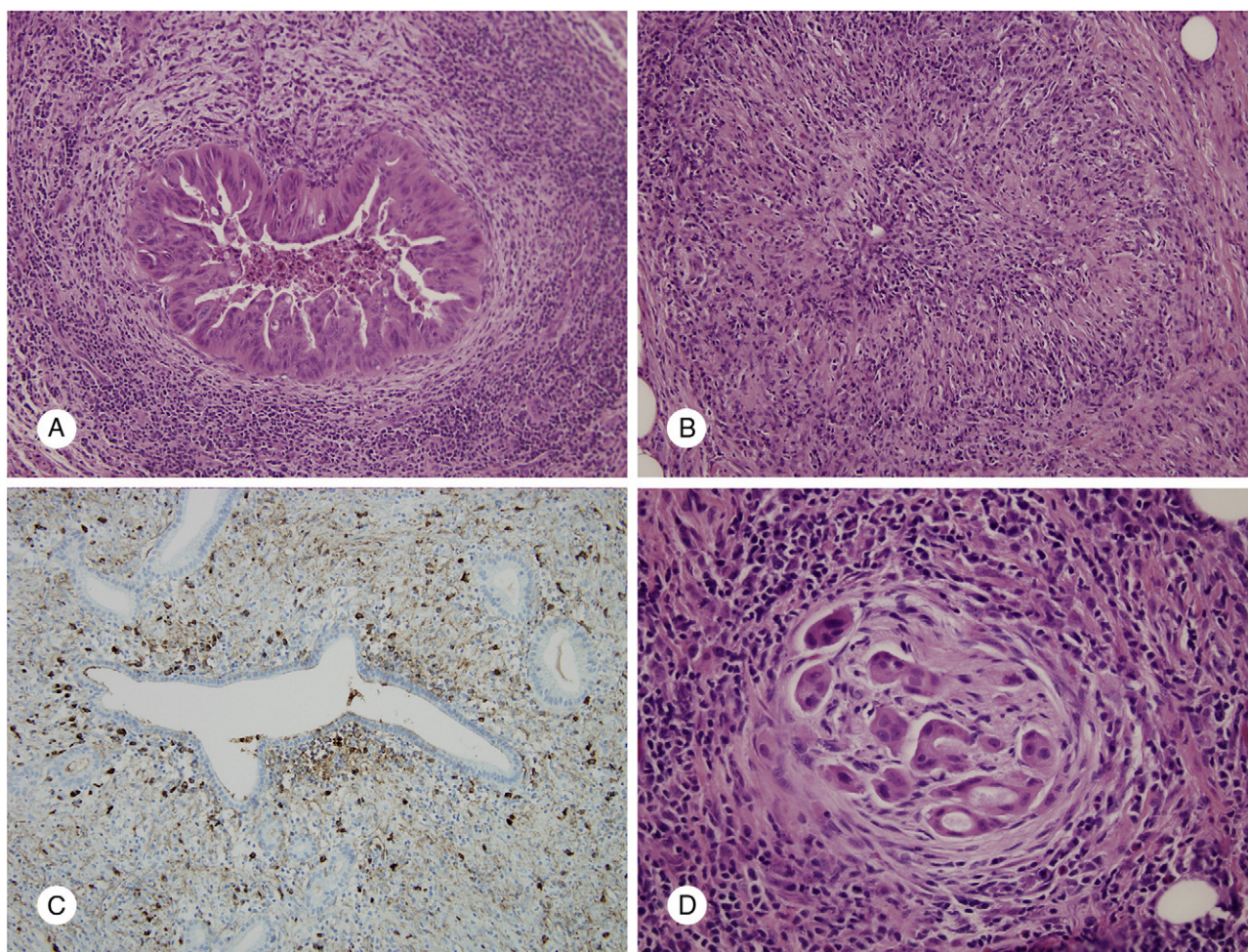


Fig. 1 A, Lymphoplasmacytic infiltrate centered on a large intralobar duct with PanIN3 (H&E, $\times 200$). B, Obliterative venulitis (H&E, $\times 400$). C, Immunohistochemical labeling with an antibody to IgG4 highlights numerous IgG4-expressing plasma cells present in the inflammatory infiltrate (IgG4, $\times 100$). D, Poorly differentiated pancreatic adenocarcinoma infiltrating nerve (H&E, $\times 400$).

Endoscopic retrograde cholangiopancreatography classically reveals diffuse irregular narrowing of the main pancreatic duct [6]. The hallmark of this disease process is a periductal lymphoplasmacytic infiltrate found on histologic examination of the specimen. Many of the inflammatory cells are plasma cells that express IgG4, and patients with AIP often have elevated serum IgG4 levels (>135 mg/dL) [7].

The clinical presentation and radiographic appearance of AIP can mimic infiltrating pancreatic ductal adenocarcinoma [1,4]. Traditionally, differentiation from a neoplasm has been made by examination of pathologic specimens after surgical resection [8]. Recently, there have been a growing number of reports of AIP treated with systemic steroids as definitive therapy [9–11]. These patients were identified through a combination of imaging studies, biopsy specimens, and laboratory abnormalities (elevated serum IgG4 levels). Some investigators have argued that all patients with a pancreatic lesion should undergo serum IgG4 testing and that those with an elevated serum IgG4 level should be initially treated with steroids [9,11]. These authors argue that patients who

respond to steroids can potentially be spared the morbidity associated with pancreatic resection, typically pancreaticoduodenectomy. Here, we report the rare case of a patient with histologically proven synchronous AIP and infiltrating pancreatic ductal adenocarcinoma. This case highlights the need for heightened vigilance when opting to manage AIP patients without surgical resection.

2. Case report

The patient was an 80-year-old white man in good health who developed obstructive jaundice. CT imaging revealed a dilated biliary tree and a strictured pancreatic duct, without evidence of discrete pancreatic mass. Endoscopic retrograde cholangiopancreatography was unsuccessful in traversing the biliary obstruction, and the patient required a percutaneous transhepatic biliary stent for palliation of his jaundice. The patient underwent a pylorus preserving pancreaticoduodenectomy with an uneventful postoperative course.

3. Pathology findings

Gross inspection of the resected pancreaticoduodenectomy specimen revealed a diffusely enlarged and firm pancreas, with effacement of the overall lobular architecture. The intrapancreatic bile and the main pancreatic ducts were diffusely narrowed. Histologically, the pancreas was remarkable for an intense mixed inflammatory cell infiltrate centered on the pancreatic ducts (Fig. 1A). The inflammatory infiltrate was predominantly composed of lymphocytes and plasma cells, with occasional eosinophils. Scattered lymphoid follicles were also present. The inflammation was associated with significant acinar drop-out and parenchymal fibrosis. Some ducts contained intraluminal neutrophils and there was infiltration of the duct epithelium by neutrophils, forming so called “granulocytic epithelial lesions”. An active venulitis with lymphocytic endothelialitis and fibrous obliteration of veins (obliterative venulitis) was noted at the leading edges of the inflammatory cell infiltrate (Fig. 1B). Immunohistochemical labeling with an antibody to IgG4 revealed large numbers of IgG4 expressing plasma cells, with greater than 50 cells labeled per high power field (Fig. 1C).

Although not appreciated grossly, an infiltrating poorly differentiated adenocarcinoma of the pancreas was also present. This adenocarcinoma showed marked neurotropism with individual neoplastic cells tracked along many of the

intrapancreatic nerves (Fig. 1D). There were no metastases in 16 resected lymph nodes, and all resection margins were negative for tumor. Additionally, many of the duct profiles contained pancreatic intraepithelial neoplasia-3 (PanIN-3) lesions (Fig. 1A).

4. Discussion

Because AIP can mimic pancreatic ductal adenocarcinoma and is increasingly diagnosed it can present a diagnostic and management dilemma. Clinicians must try to balance the potential risk of missing the diagnosis of a life-threatening disease against symptom control and the desire to avoid unnecessary surgery. These risks are all the more important in the face of effective treatment of AIP with corticosteroids in many cases.

Several groups have proposed criteria to distinguish AIP from pancreatic adenocarcinoma. The criteria include imaging results, laboratory data, and histopathologic findings (Table 1) [1,5,12,13]. However, these criteria are not definitive, and would not have insured an accurate diagnosis in our patient.

Before this report, Inoue [14] reported one case of pancreatic adenocarcinoma with AIP. The diagnosis of pancreatic carcinoma in that case was made on pancreatic duct brushings, without surgical resection, in a patient with

Table 1 Proposed diagnostic criteria for diagnosing AIP

	Zamboni et al [1]	Japan Pancreas Society [12]	Kim et al [5]	Mayo Clinic (HISORT) Criteria [13]
1. Imaging	Not included	Narrowing of more than 1/3 of the length of the pancreatic duct and diffuse enlargement of the pancreas	Diffuse enlargement of the pancreas (CT) with diffuse or segmental narrowing of the main pancreatic duct	Diffuse enlargement of the pancreas (CT)
2. Histopathologic criteria	Lymphoplasmacytic infiltration around large and medium size ducts Periductal fibrosis Venulitis Granulocytic epithelial lesion	Lymphoplasmacytic infiltration and fibrosis	Lymphoplasmacytic infiltration and fibrosis	Narrowing of the pancreatic duct Maybe nonspecific Lymphoplasmacytic infiltration and fibrosis Obliterative venulitis Abundant IgG4-positive plasma cells
3. Laboratory findings	Not included	Elevated serum gammaglobulins and/or IgG or presence of autoantibodies	Elevated IgG or IgG4 or presence of autoantibodies	Elevated IgG4
4. Response to steroid therapy	Not included	Not included	Response to steroid therapy	Response to steroid therapy
Criteria required for a definite diagnosis	Histologic findings	Imaging together with laboratory findings and/or histology	Criterion 1 with any 2-4 criteria	Criterion 1, 2 and 3 or 3 and 4

lung and bone metastasis. The diagnosis of AIP was without histologic confirmation and based on diffuse enlargement of the pancreas with elevated serum IgG4.

Kamisawa et al [10] have reported a 74-year-old patient with markedly elevated serum IgG4 levels who underwent a pancreaticoduodenectomy and was found to have a pancreatic ductal adenocarcinoma with a lymphoplasmacytic infiltrate in the biliary tree and duodenum [15]. Although this patient's IgG4-related inflammatory disease did not involve the pancreas, this case highlights the issue raised by our case, that is, the presence of IgG4-related inflammatory disease does not rule out the possibility of a synchronous pancreatic cancer.

In contrast to previously reported cases, our patient met full pathologic diagnostic criteria for both pancreatic ductal adenocarcinoma and AIP. The carcinoma was unusually neurotropic with most of the infiltrating carcinoma present within nerves. Very little of the carcinoma was intraparenchymal, and the carcinoma did not form a significant mass. A key concern in our case is that the presenting symptoms may have been related to the inflammatory process (AIP) and not the malignant process. Hence, treatment with steroids might have resulted in temporary improvement but allowed the cancer to grow unchecked.

This case may be best viewed as a cautionary tale about the treatment of patients suspected to have AIP. For patients that fully meet one of the established sets of criteria for a diagnosis of AIP, a trial of steroid therapy may be reasonable. However, if a patient only partially meets these criteria or if the imaging abnormalities fail to resolve quickly during treatment, then a resection must be carefully considered.

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