Autoimmune Pancreatitis

Unveiling a Hidden Entity

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Hypothesis: After alcohol-induced and hereditary disease, idiopathic chronic pancreatitis is the most common cause of calcifying pancreatitis. This designation is used when no associated cause of chronic pancreatitis is found. We present 6 cases of idiopathic pancreatitis in which the postoperative pathological examination results demonstrated lymphoplasmacytic sclerosing pancreatitis or autoimmune pancreatitis.

Design: Retrospective case series. The medical records of 6 patients referred and treated for autoimmune pancreatitis were reviewed. The duration of follow-up varies, the longest being 5 years. The disease and a literature review are reported.

Setting: A 200-bed community hospital located in a large city. The patients were referred after being treated elsewhere for recurrent pancreatitis.

Patients and Methods: Six patients with chronic recurrent pancreatitis were evaluated. They were selected because pathological review indicated that they all had autoimmune pancreatitis.

Results: Six cases of lymphoplasmacytic sclerosing pancreatitis are presented and suggest that lymphoplasmacytic sclerosing pancreatitis should be thought of more often in chronic autoimmune pancreatitis.

Conclusion: Lymphoplasmacytic sclerosing pancreatitis is an increasingly recognized cause of chronic pancreatitis and should be considered in the evaluation of patients with chronic pancreatitis and no discernible cause.

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CHRONIC RELAPSING PANCREATITIS is most commonly associated with alcoholism, although other causes are recognized.1 Recently, an entity identified as chronic autoimmune pancreatitis or lymphoplasmacytic sclerosing pancreatitis (LPSP) has been reviewed in the literature.2 To date, the literature identifies fewer than 100 cases of chronic autoimmune pancreatitis, all of which were diagnosed at pathological review of resected specimens. Associated autoimmune disorders such as Sjögren syndrome and scleroderma, as well as sclerosing cholangitis, have been reported, particularly in elderly men. Most patients have no associated illnesses, and LPSP is rarely suspected or diagnosed preoperatively. We report our experience with 6 patients referred for surgical management of chronic pancreatitis or a suspected malignancy in which the pathological examination results helped to confirm the diagnosis. Only 1 patient had LPSP diagnosed preoperatively. The remaining 5 had the diagnosis confirmed postoperatively.

REPORT OF CASES

CASE 1

A 30-year-old woman with recurrent pancreatitis and a stricture of the pancreatic duct was referred to us. She had persistent and intractable pain. She had received celiac plexus injections for pain management for more than a year without amelioration of her symptoms. In March 1998, she underwent limited distal pancreatectomy for mild disease in the distal gland and longitudinal incision of the proximal pancreatic duct with Roux-en-Y pancreaticojunostomy. Pathological examination results demonstrated a lymphoplasmacytic infiltrate. In August 1998, she returned with recurrent symptoms after only 2 months of pain relief, and she refused treatment with steroids. Because of the persistent symptoms, fur-
ther surgical management of the distal pancreas was offered. She underwent exploration with resection of the distal pancreas. Pathological examination results from this specimen demonstrated further LPSP. She is well and pain free 5 years later. She does not require any pancreatic enzymes, and her glucose tolerance is normal.

CASE 2
A 72-year-old male dentist presented with new-onset jaundice. He reported pruritis and mild weight loss without other significant complaints. Evaluation demonstrated a dilated pancreatic ductal system but no focal masses at body imaging, and he had a mildly dilated common bile duct proximal to the pancreas. Abnormal liver function test results included a bilirubin level of 2 mg/dL (34.2 µmol/L) and an alkaline phosphatase level of 253 U/L. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated a stricture in the distal common bile duct. Because of concern that this stricture was malignant, the patient underwent exploration and a pancreaticoduodenectomy for significant focal disease in the head of the pancreas. Pathological examination results showed severe chronic pancreatitis. After a brief period, he returned with increasing jaundice. Percutaneous cholangiography revealed sclerosing cholangitis not demonstrated preoperatively, and review of his surgical specimen revealed LPSP as the histologic subtype in the resected pancreas. He was treated with steroids and a percutaneous biliary stent for several months. The stent was removed after the duct pattern improved and liver function became normal. He has remained well for 4 years. He does not require any pancreatic enzymes, and his glucose tolerance is normal.

CASE 3
A 28-year-old woman presented with severe, intractable, left-sided abdominal pain and chronic relapsing pancreatitis that had been diagnosed with computed tomography and because of elevated pancreatic enzymes during hospitalization for similar recurrent attacks. She had persistent enzyme abnormalities, and her pain persisted despite medical management. A reconstructed pancreatic computed tomographic scan demonstrated a nonperfused pancreatic tail containing a cystic lesion. She subsequently underwent uncomplicated distal pancreatectomy and splenectomy for focal distal pancreatitis. Surgical findings demonstrated a normal gland in the head, neck, and uncinate process but a markedly fibrotic, diseased distal body and tail, with a cystic mass. Pathological examination results demonstrated LPSP. She is well with complete resolution of her symptoms 5 years later. Her pancreas is functioning normally. She does not require any pancreatic enzymes, and her glucose tolerance is normal.

CASE 4
A 25-year-old woman presented with recurrent pancreatitis and a pancreatic duct stricture. Her initial symptoms began post partum and were treated with laparoscopic cholecystectomy, followed by ERCP and stone extraction. She was then hospitalized 10 times in 1 year for recurrent pancreatitis. Pancreatic stent placement had been successful technically but did not relieve her symptoms. She reported daily attacks of mild abdominal pain, usually meal related. She was receiving narcotics and antiemetics on a long-term basis with minimal benefit. Despite a conservative approach using narcotics and dietary management, symptoms persisted. She underwent distal pancreatectomy and splenectomy in June 2001 for severe distal pancreatic inflammation and fibrosis. Pathological evaluation demonstrated LPSP. She is well, with marked improvement in symptoms. She has been weaned from narcotic use and is eating a regular diet. She does not require any pancreatic enzymes, and her glucose tolerance is normal.

CASE 5
A 31-year-old woman was referred to us for the management of intractable pain secondary to chronic pancreatitis. Open cholecystectomy performed 10 years previously for cholelithiasis did not prevent attacks. Since then, she had been hospitalized for recurrent pancreatitis multiple times. She had undergone ERCP on multiple occasions, with at least 3 biliary and pancreatic stents. The last endoscopic examination had been 4 months before her referral. She complained of daily nausea and vomiting, with intermittent diarrhea and severe, if not intractable, midepigastric pain, which was not relieved with long-term narcotic pain medication. At surgery, she had a diffusely diseased pancreas with a markedly fibrotic and dense head. She underwent pancreaticoduodenectomy and recovered uneventfully. Pathological evaluation demonstrated LPSP of the resected specimen. She has had a marked improvement in her symptoms since surgery. She does not require any pancreatic enzymes, and her glucose tolerance is normal.

CASE 6
A 39-year-old woman presented with abdominal pain and recurrence of pancreatitis. She had a long history of chronic pancreatitis. In 1996, she underwent a Puestow procedure for recurrent pancreatitis and an obstructed pancreatic duct in the head of the gland. In 1997, she presented with severe pain and recurrent attacks of pancreatitis. At surgery, the most severe findings were focal in the head of the gland. A pancreaticoduodenal resection was performed. Pathological examination results demonstrated chronic fibrosing and sclerosing pancreatitis. She remained pain free until January 2004, when she presented with severe epigastric pain and worsening of pre-existing diabetes mellitus. She noted that the pain had been intermittent for 18 months but had become severe and intolerable in the last few weeks. Blood test results suggested autoimmune pancreatitis. A course of steroids did not provide relief. Pancreatic computed tomographic scan showed diffuse calcific disease in the remnant pancreas. She underwent total pancreatectomy for severe distal disease. Pathological evaluation demonstrated LPSP. She is convalescing and notes marked improvement in pain, although pain management is not com-
The clinical presentation for most patients is that of chronic pancreatitis. The clinical presentation for most patients is that of chronic pancreatitis. The clinical presentation for most patients is that of chronic pancreatitis. The clinical presentation for most patients is that of chronic pancreatitis. The clinical presentation for most patients is that of chronic pancreatitis. The clinical presentation for most patients is that of chronic pancreatitis. The clinical presentation for most patients is that of chronic pancreatitis. The clinical presentation for most patients is that of chronic pancreatitis.

In the United States, chronic pancreatitis has long been associated with alcohol, since most patients with chronic pancreatitis consume significant quantities of alcohol. A direct causal mechanism between alcohol and chronic pancreatitis is less clear. A significant number of patients with chronic pancreatitis deny any association with alcohol, or other causes, so the disease has been considered idiopathic. The prevalence of this entity is variable but ranges from 15% to 30%.

During the past decade, we have become aware that chronic pancreatitis is a heterogeneous disease. There are different mechanisms of pancreatic injury causing chronic pancreatitis, including hereditary pancreatitis, pancreatitis associated with mutations of the cystic fibrosis gene, and pancreatitis associated with cystic dystrophy of the duodenal wall. Another concept holds that acute pancreatitis may evolve into chronic pancreatitis and suggests that inflammatory disease of the pancreas more accurately describes the spectrum of pancreatitides and should replace the terms acute and chronic pancreatitis. Instillation of trinitrobenzene sulfonic acid into the pancreatic duct of rats induced changes similar to those seen in chronic pancreatitis in humans. Trinitrobenzene sulfonic acid acts as a hapten, changing the cell membrane and antigenic profile of the pancreatic duct. The new antigen stimulates an immune T-cell response, followed by an inflammatory cell infiltration of the pancreatic duct, which leads to fibrosis and acinar atrophy. Of interest are changes in the bile duct similar to those of sclerosing cholangitis after injection of trinitrobenzene sulfonic acid into the bile duct. This finding demonstrates that a nonobstructive autoimmune mechanism might be involved in chronic pancreatitis.

Although an autoimmune mechanism has been suggested for chronic pancreatitis for 50 years, the association and its proof have been less clear. In some patients with chronic pancreatitis, antibodies against carbonic anhydrase have been reported. Pathological findings in autoimmune pancreatitis show a lymphoplasmacytic infiltrate involving the pancreatic duct, lobules, acini, common duct, and peripancreatic blood vessels, particularly the walls of veins. The pancreatic ducts have an increased production of histocompatible type III antigens. A second histologic pattern was characterized by neutrophil infiltrate.

Autoimmune pancreatitis has been identified by many terms, including primary chronic pancreatitis, nonalcoholic duct destructive pancreatitis, LPSP, autoimmune pancreatitis, granulomatous pancreatitis, and sclerosing pancreatic cholangiitis. All these terms reflect a descriptive nomenclature associated with some cases of autoimmune pancreatitis.

The clinical presentation for most patients is that of chronic pancreatitis or carcinoma, in which a mass associated with jaundice is identified in the head of the pancreas or distal bile ducts. Most reports about this entity are reviews of pathological findings in resected pancreatic specimens. In a review of 254 pancreatic resections for chronic pancreatitis, the prevalence of LPSP was 15%.

Patient demographics are variable. The age of the patients in our study ranged from 25 to 72 years. With the exception of 1 elderly man, the other patients were young women without associated autoimmune diseases. In the literature, at least 20 men (70%) and 8 women (30%) are described. None of the women had an associated autoimmune disease or sclerosing cholangitis; in contrast, 15 (75%) of the men had at least 1 of these conditions. Finally, 16 of the 20 men were older than 40 years, and only 2 of the 8 women were. Our experience is similar. None of the patients in our study consumed alcohol regularly, and none of them were binge drinkers. None of the patients in our study took any substances or medications that are toxic to the pancreas.

Autoimmune pancreatitis is underidentified, but the course may be modified with steroids if the diagnosis is made preoperatively. Although only a few reports describe a response to steroid therapy, it is reasonable to offer it as a specific therapy. In the 1 patient with disease diagnosed before surgery, we used steroid therapy, albeit ineffectively.

The diagnostic criteria are mainly histologic, with the presence of a dense lymphocytic infiltration around the main and/or secondary pancreatic ducts, with focal or diffuse duct destruction and the prevalence of T lymphocytes. However, histologic specimens are provided after surgery and justify preoperative therapy. Immunohistochemical staining of cells shows the cells to be CD3 positive; CD8 positive; and, occasionally, TIA-1 positive. Some cases also contained CD20- and CD68-positive cells.

Other criteria that may assist in the diagnosis of autoimmune pancreatitis include a high titer of nonorgan-specific autoantibodies, cytologic specimens obtained at ultrasonography- or computed tomography-guided fine-needle biopsy, clinical response to steroids, suggestive morphologic changes at computed tomography in different contrast phases or ductal alterations at magnetic resonance cholangiopancreatography, and ductal alterations observed at ERCP.

We suspect that the diagnosis of autoimmune pancreatitis will become easier and more common with time. Mild or moderate pancreatitis may be overlooked more easily in the absence of histologic findings. Pancreatic resection may be performed mistakenly for moderate autoimmune pancreatitis, or pancreatic cancer may be erroneously treated with steroids.

We suspect that autoimmune pancreatitis is related to idiopathic chronic pancreatitis; the prevalence is unknown. The diagnosis is difficult and should be suspected in all patients with autoimmune pancreatitis. Surgical specimens establish the diagnosis. Fine-needle biopsy has diagnostic potential, but it is invasive and its role is undefined. We hope with more attention focused on idiopathic pancreatitis, and specifically on autoimmune pancreatitis, that more definitive diagnostic criteria and treatment regimens will be developed and applied. Until then, it is necessary to remain aware of
autoimmune pancreatitis in the nonalcoholic patient with chronic pancreatitis.

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