CASE REPORT

Lymphoplasmacytic Sclerosing Pancreato-cholangitis: A Case Report and Review of the Literature

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Autoimmune pancreatitis is a rare but important cause of pancreatitis that is becoming increasingly recognized in the West. Lymphoplasmacytic sclerosing pancreatitis (LPSP) is a benign form of chronic pancreatitis characterized clinically by infrequent attacks of abdominal pain, jaundice, and weight loss, and pathologically by focal or diffuse chronic or lymphoplasmacytic inflammatory infiltrates centered around pancreatic ducts and ductules, accompanied by obliterative phlebitis, acinar atrophy, and interstitial fibrosis. It has been described alone or as a part of the spectrum of autoimmune gallbladder and biliary tract disease, with clinical, radiological, and pathological overlap reported with primary sclerosing cholangitis. It has been described as “primary sclerosing pancreatitis,” “sclerosing cholangitis,” “non-alcoholic duct destructive chronic pancreatitis,” and “autoimmune pancreatitis.” We report a case of LPSP that mimicked pancreatic adenocarcinoma and was subsequently treated with a pylorus-preserving Whipple procedure. This may point towards a primary biliary autoimmune process involving the pancreatic duct, causing a benign form of chronic pancreatitis that may be difficult to characterize pre-operatively to avoid surgery. This case typifies the growing awareness of this relatively recently characterized clinical entity, its similar presentation to pancreatic carcinoma, and the importance for LPSP to be included in the differential diagnosis of pancreaticobiliary disease. Finally, we review the literature.

INTRODUCTION

Lymphoplasmacytic sclerosing pancreatitis (LPSP) is a benign form of chronic pancreatitis characterized clinically by infrequent attacks of abdominal pain, jaundice and weight loss, and pathologically by focal or diffuse chronic or lymphoplasmacytic inflammatory infiltrates centered around pancreatic ducts and ductules, accompanied by obliterative phlebitis, acinar atrophy, and interstitial fibrosis.
phlebitis, acinar atrophy, and interstitial fibrosis [1-12]. It has been described alone or as a part of the spectrum of autoimmune gallbladder and biliary tract disease, with clinical, radiological, and pathological overlap reported with primary sclerosing cholangitis (PSC) [1-9]. LPSP has been described in the literature as “primary sclerosing pancreatitis,” “sclerosing cholangitis,” “non-alcoholic duct destructive chronic pancreatitis,” and “autoimmune pancreatitis” [16]. Lymphoplasmacytic sclerosing pancreatitis mimics pancreatic adenocarcinoma in clinical presentation with many reported cases in the literature having undergone pancreaticoduodenectomy leading to durable relief of symptoms and improved quality of life [5-7, 9-10]. Strict criteria for non-operative diagnosis of LPSP are currently lacking, although radiological, serological, and pathological clues have been suggested [4-9, 11-13], and a good response to steroid treatment has been reported to obviate the need for surgery [14-15]. We report a case of lymphoplasmacytic sclerosing pancreato-cholangitis, which presented with a dominant distal common bile duct stricture and a suspicion for pancreatic adenocarcinoma, with a negative work-up for malignancy on imaging and histopathology after endoscopy.

CASE REPORT

A 77-year-old retired male with a past medical history significant for diabetes mellitus well controlled on glipizide, initially presented to his primary care physician with intermittent periumbilical pain, heartburn and a one-year history of 30-pound weight loss. There was no association with food or bowel movements; however, his symptoms coincided with commencing fluconazole for a fungal infection of his foot. He denied alcohol use. Initial evaluation revealed no other etiology to explain the patient’s symptoms. Ten months later the patient presented with painless jaundice and weight loss. Physical examination at the time revealed icterus only. On presentation, initial laboratory results revealed a total bilirubin of 11, aspartate transaminase of 246, alanine transaminase of 422, alkaline phosphatase of 606, amylase of 309, and lipase of 2,667. The white cell count, hemoglobin, hematocrit, and electrolytes were normal. Computerized tomography (CT) scan of the abdomen revealed slight intrahepatic ductal dilatation but no masses within the pancreas. A subsequent abdominal ultrasound excluded cholelithiasis. Endoscopic retrograde cholangio-pancreatography (ERCP) demonstrated a 2.5 cm distal common bile duct (CBD) stricture in the suprapapillary segment which was stented. Brushings of the CBD stricture were benign. The patient was then transferred to our institution for further management including endoscopic ultrasound (EUS), which demonstrated mild narrowing in the suprapapillary segment of CBD with CBD wall thickening measuring 2.1 mm and an irregular outer border. No pancreatic masses or signs of chronic pancreatitis were seen. Additionally, no peripancreatic or celiac axis lymph nodes were seen. Fine-needle aspiration of bile duct wall and pancreatic head revealed a few cohesive groups of ductal epithelium with mild atypia admixed with clusters of benign glandular epithelium, but no features suggestive of malignancy. A repeat ERCP showed a tight suprapapillary CBD stricture approximately 1.5 cm in length, without significant proximal CBD and intrahepatic ductal dilatation. A large biliary sphincterotomy along with brushings and biopsies of the intrapancreatic portion of the common bile duct was performed, followed by placement of a biliary stent. Repeat CBD brushing and biopsies were once again negative for malignant cells. At this point, a long discussion with the patient and his family took place, explain-
ing the overwhelming concern regarding a possible malignancy despite negative histopathology and cytology so far.

The patient agreed to undergo surgery and a successful pylorus-preserving Whipple procedure was performed (Figure 1). The common bile duct, as well as the pancreatic duct, revealed areas of periductal chronic inflammatory infiltrate, reactive epithelial changes, and periductal fibrosis (Figures 2a, 2b, and 2c). The fibrosis involved not only the main pancreatic duct but its branches as well. The periductal concentric nature of the fibrosis

Figure 1. Gross pathology, showing a mildly dilated pancreatic duct without obvious mass or gross atrophy.

Figure 2a. Low magnification (x40), showing marked periductal fibrosis (Trichrome stain) and very mild interstitial fibrosis in the pancreatic parenchyma. Figure 2b. Higher magnification (x200), showing a cross section of a duct with periductal fibrosis and lymphoplasmacytic inflammatory infiltration. Figure 2c. Higher magnification (x200): showing a duct with lymphoplasmacytic infiltrate around the duct and infiltrating into the epithelium. Figure 2d. Higher magnification (x200), showing a duct displaying squamous metaplasia.
was easily evident even on low magnification. In many areas, the pancreatic duct also appeared focally dilated with injury to the lining epithelium. Squamous metaplasia (Figure 2d), mucinous metaplasia, and papillary hyperplasia in the pancreatic ductal system were also identified. The adjacent acini showed evidence of atrophy, interstitial fibrosis and relative islet cell hyperplasia. Calcifications, fat necrosis or marked interstitial fibrosis with atrophy typical of chronic pancreatitis of other etiologies (e.g., alcoholic or gall stone pancreatitis) were not seen. The histopathologic nature of obstruction to the common bile duct and pancreatic duct strongly suggested “sclerosing pancreato-cholangitis.”

At follow-up, one month after surgery, the patient was able to tolerate a regular diet, and had no further episodes of jaundice or abdominal pain.

DISCUSSION

Sarles and colleagues first described LPSP in 1961 and suggested the possibility of immune abnormality in chronic pancreatitis as a “phenomenon of self-immunization” [1]. Kawaguchi and colleagues, in 1991, reported two cases of LPSP with cholangitis and considered them to be a variant of PSC extensively involving pancreas, which could clinically mimic pancreatic carcinoma [2]. In 1995, Yoshida and colleagues described a patient with chronic pancreatitis who had hyperglobulinemia with positive autoantibodies and responded to steroid therapy — leading to the notion of chronic pancreatitis caused by an autoimmune abnormality. More recently, Nakazawa and colleagues reported a group of PSC cases with pancreatitis, demonstrating a better clinical course and response to steroids than typical cases of PSC [4]. The authors concluded that similar etiologic agents might impact on both the pancreas and biliary tract, either simultaneously or in sequence. LPSP has been also reported to be associated with Sjogren syndrome, primary biliary cirrhosis, Crohn’s disease, and ulcerative colitis [5, 6].

The histopathologic hallmark of LPSP is lymphoplasmacytic infiltrates centered around pancreatic ducts and ductules, accompanied by obliterative phlebitis, acinar atrophy, and interstitial fibrosis [1-12]. These lesions typically cause diffuse or focal swelling with narrowing of main pancreatic duct and/or common bile duct. LPSP lacks the parenchymal calcifications, pseudocysts, and/or fat necrosis commonly found in other forms of chronic pancreatitis, and a diagnosis of LPSP can only be made when the distinctive histologic features are present in a patient lacking a history of gall-stone pancreatitis, pancreas divisum, excess alcohol ingestion, or other environmental etiology for pancreatic atrophy, including previous pancreatic radiation [9]. Pancreata with LPSP often are diffusely enlarged and firm, containing irregular strictures of the main pancreatic duct apparent on ERCP [8].

The pathogenesis of LPSP remains unclear. The inflammatory infiltrates are largely made up of CD4+ T lymphocytes with fewer B lymphocytes. It has been proposed that the T lymphocytes release cytokines, which in turn up-regulate the aberrant expression of HLA class II molecules by the duct epithelial cells. Additionally, antibodies to lactoferrin (present on ductal acinar cells) and carbonic anhydrase II antigens (present on ductal epithelial cells) may initiate the formation of the lymphocytic infiltrate as a consequence of the immune reaction mediated by type 2 helper cells and antibodies [16].

The diagnosis of LPSP is typically made post-operatively as it mimics pancreatic adenocarcinoma, and the majority of patients often undergo pancreaticodu-
denectomy, given the very high clinical suspicion of malignancy. There are no pre-operative clinical signs of LPSP that help differentiate it from pancreatic adenocarcinoma, particularly since both conditions present with jaundice, weight loss, and/or nonspecific abdominal pain. The Johns Hopkins group report [6] no difference in pre-operative carcinoembryonic antigen and CA 19.9 (carbohydrate antigen 19.9) levels between patients with LPSP and those with pancreatic adenocarcinoma [7]. Although strict criteria for non-operative diagnosis of LPSP are currently lacking, some radiologic, serologic and pathologic clues have been suggested [4-9, 11-13]. Cross-sectional imaging with enhanced CT or magnetic resonance imaging (MRI) scans may show diffusely enlarged pancreas without a mass [6, 7]. The diffuse enlargement can also be seen on abdominal ultrasound, and more accurately by EUS [7]. A preoperative diagnosis of LPSP could further be corroborated by finding of diffuse, irregular narrowing of the main pancreatic duct on ERCP or magnetic resonance cholangio-pancreatography [6, 7].

Of interest from both a diagnostic viewpoint and also with regards to medical management is the association of LPSP with high serum levels of immunoglobulin G4 (IgG4) [11, 12] and its response to treatment with steroids. Hamano and colleagues reported that the elevation in the level of the IgG4 correlates with the activity of the disease, and that glucocorticoid (a daily dose of 0.5 to 1 mg of prednisolone per kilogram of body weight, tapered to a maintenance dose of 5 to 10 mg per day for six months) therapy induced clinical remissions and significantly decreased serum IgG4 concentrations [11-12, 14-15]. Other laboratory abnormalities include the presence of antinuclear antibody, anti-lactoferrin antibody, rheumatoid factor and antibodies to carbonic anhydrase II and smooth muscle [16]. In patients with radiologic and serologic suspicion of LPSP, a negative fine needle aspiration or biopsy for malignancy might be further evidence for the benign nature of the process. However, an adequate sample of tissue is required to evaluate tissue for all pathological features of LPSP — in most cases a core biopsy will not provide enough tissue to evaluate these features [7].

Patients may be medically managed by carefully monitoring response to steroid therapy in a subset of patients, obviating the need for surgery. Nevertheless, the majority of patients with LPSP will likely continue to be managed by pancreaticoduodenectomy, based on an inability to exclude the possibility of pancreatic neoplasia, and patients undergoing this surgery have reported durable relief of symptoms and improved quality of life [6, 10]. However, progressive disease after surgery has been reported in up to one-third of patients, with 25 percent developing recurrent jaundice and one developing recurrent pancreatitis in the series of 31 patients reported by the Memorial-Sloan Kettering group (median length of follow up was 38 months) [7]. Interestingly, the Johns Hopkins group reported no patients with recurrent post-operative jaundice and only one patient with recurrent pancreatitis in their series of 37 patients (median length of follow up was 33 months) [6]. In light of the limited clinical experience with LPSP and variation in post-operative course, close follow-up is mandatory in all patients [7].

The clinical, radiologic and pathologic overlap between LPSP and PSC is of interest in the case we have presented, since histologic involvement of the common bile duct by fibrosis, inflammation, and edema has been demonstrated in 73 percent of patients with LPSP [8]. Hirano and colleagues also point out that extrapancreatic bile duct changes are frequently associated with autoimmune pancreati-
tis [17]. The case we present, with a dominant distal common bile duct stricture, revealed areas of peri ductal chronic inflammatory infiltrate, reactive epithelial changes, and peri ductal fibrosis of the common bile duct, as well as the pancreat ic duct. This may point towards a primary biliary autoimmune process involving the pancreatic duct, causing a benign form of chronic pancreatitis which may be difficult to characterize pre-operatively to avoid surgery. Furthermore, this case typifies the growing awareness of this relatively recently characterized clinical entity, its similar presentation to pancreatic carcinoma, and the importance for LPSP to be included in the differential diagnosis of pancreaticobiliary disease.

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