Current challenges in the diagnosis of autoimmune pancreatitis

Rajib Gupta
Vikram Deshpande

Abstract

Autoimmune pancreatitis (AIP), an inflammatory disease of the pancreas first described in Japan, is characterized by a tumefactive lesion in the pancreas, thus clinically resembling pancreatic cancer. Currently, it is classified into two variants – type 1 AIP and type 2 AIP, each with distinct clinico-pathologic and epidemiologic features. Type 1 AIP is a part of IgG4 related disease, a generalized multi-systemic disease, and recapitulates its clinical and pathologic features. Type 2 AIP is an isolated pancreas-centric disease, and is not associated with elevated tissue or serum IgG4. Histologically, type 1 AIP is characterized by storiform-type fibrosis and obliterative phlebitis, while type 2 disease shows granulocytic epithelial lesions. Even when AIP is suspected, a diagnosis should seldom be made in isolation, but should be rendered only after collating clinical and radiologic data. Steroids remain the mainstay of treatment for both variants of AIP, although other immunosuppressive drugs like rituximab have proven successful. In this review, we summarize the current knowledge of this entity and discuss diagnostic challenges, with particular emphasis on the interpretation of needle biopsies. Recognition of AIP as a mimic of pancreatic cancer is imperative to reduce unnecessary morbidity and mortality associated with pancreatic surgery.

Keywords autoimmune pancreatitis; IgG4; IgG4 related disease

Introduction

While autoimmune pancreatitis was initially recognized in the 1960s, it was only in the 1990s that this inflammatory disease received substantial attention. The earliest comprehensive histologic description of this disease was from a group in Japan.[1] However, it was the association of IgG4 with autoimmune pancreatitis, then referred to as sclerosing pancreatitis, that spurred new developments in this field.[2] With increasing experience, the majority of patients with autoimmune pancreatitis are treated conservatively. Notably, pancreatic resections were the norm in the 20th century. In a fairly dramatic shift over the last decade, the diagnosis is frequently based on the presence of classic presenting symptoms, characteristic radiologic appearance, elevated serum IgG4 levels, as well as a swift response to immunosuppressive therapy.[3–5] Nevertheless, in some cases the disease shows overlapping features with pancreatic cancer, and it is in these cases that histopathology plays a critical role. Additionally, the lack of a specific biomarker for type 2 autoimmune pancreatitis (see below) has meant that these patients are frequently subjected to a biopsy, and occasionally, a pancreatic resection.

Rajib Gupta *M.D. Post-doctoral Clinical Fellow, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Conflicts of interest: none declared.*

Vikram Deshpande *M.D. Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. Conflicts of interest: none declared.*

Variants of autoimmune pancreatitis

Two distinct variants of autoimmune pancreatitis are recognized, labeled type 1 and type 2.[5–10] The two variants are clinically, serologically, as well as histologically distinctive, although both forms of the disease respond to immunosuppressive therapy. In fact, based on these differences, it has been suggested that the two "variants" represent distinct diseases, a position that we endorse.

The concept of type 1 autoimmune pancreatitis was originally proposed in Japan, while type 2 autoimmune pancreatitis was championed in Europe, the latter primarily on the basis of histopathologic findings. Notably, type 2 autoimmune pancreatitis is uncommon in the Asian population.

Type 1 autoimmune pancreatitis

This is the pancreatic manifestation of IgG4 related disease. IgG4 related disease is a multi-systemic disease characterized by the presence of multifocal fibroinflammatory mass lesion(s) that are responsive to immunosuppressive therapy.[11,12] Type 1 autoimmune pancreatitis bears all the clinical, serologic, and histologic hallmarks of IgG4 related disease. This is a disease of elderly men and the majority of these patients (60–75%) present with painless obstructive jaundice. A small proportion present with acute pancreatitis. Rarely the patient is entirely asymptomatic, the disease detected on cross-sectional imaging.

Histopathology

Virtually all pancreatic resections from individuals with type 1 autoimmune pancreatitis reveal a dense lymphoplasmacytic infiltrate, storiform-type fibrosis and obliterative phlebitis (Table 1).[8,9,13,14] In the authors' experience, only patients pre-treated with immunosuppressive therapy lack a brisk inflammatory infiltrate. The infiltrate is generally diffusely distributed throughout the pancreas, although accentuation in the periductal region is often appreciable (Figures 1–3). Interestingly, although significant inflammation surrounds pancreatic ducts, the ductal epithelium is well preserved. An increased number of eosinophils are invariably found, and in rare instances eosinophils may dominate the histologic picture, and in numbers sufficient to raise the possibility of an allergic or an unrelated connective tissue disease.

The disease is characterized by dense fibrosis, generally laid down in a storiform pattern (Figure 1). This is a pattern familiar to pathologists, most notably seen in dermatofibrosarcoma protuberans. The pattern is likely fashioned by the deposition of fibroblasts or myofibroblasts, the latter representing a consistent finding in autoimmune pancreatitis. Hyalinizing or keloidal type fibrosis is uncommon in this variant of autoimmune pancreatitis.

Perhaps the most unique feature of autoimmune pancreatitis is obliterative phlebitis. Partial obliteration (>obliteration of 50%

Histopathologic features to differentiate between type 1 and type 2 autoimmune pancreatitis

Histologic features	Type 1 AIP	Type 2 AIP
I. Around ducts:		
a. Lymphoplasmacytic collar around the pancreatic ducts	Usually mild	Usually moderate to marked
b. Ductal infiltration by neutrophils (granulocytic epithelial lesions), which may include duct-ulcer and/or duct-abscess	Rare to absent	Present
II. In the stroma:		
a. Storiform or cartwheel fibrosis	Present	Absent
b. Eosinophils	Common	Rare
c. Lymphoid follicles	Sometimes seen	Rare to absent
d. Obliterative Phlebitis and/or arteritis	Present	Absent
III. Neutrophils within pancreatic acini	Rare	Common
IV. Immunohistochemistry:		
a. IgG4 in the stroma	Elevated, biopsy >10 per HPF, resection >50 per HPF	Rare
b. IgG4:IgG ratio	>40%	<40%

Table 1

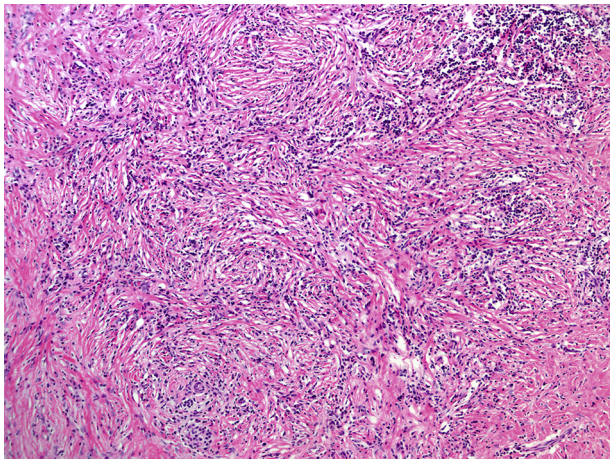

Figure 1 Type 1 autoimmune pancreatitis with prominent storiform-type fibrosis.

of the lumen) is viewed synonymously with total obliteration of the vein (Figures 4 and 5). It is important to emphasize that the pattern of obliteration differs significantly from organized thrombosis of a pancreatic vein, a finding seen in other forms of pancreatitis and malignancy. Unlike thrombosed veins, the obliterated veins in autoimmune pancreatitis show a

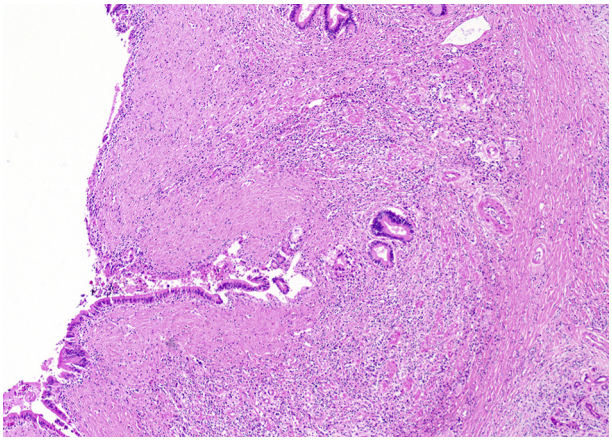

Figure 2 Type 1 autoimmune pancreatitis involving the intrapancreatic portion of the bile duct. The biliary epithelium is eroded, likely a consequence of an indwelling stent. The full thickness involvement of the bile duct is a characteristic feature of this disease.

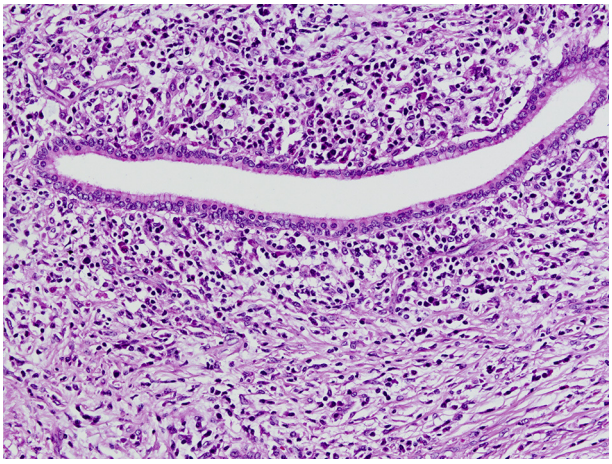

Figure 3 Type 1 autoimmune pancreatitis. Note the periductal accentuation. Nevertheless, the ductal epithelium appears well preserved.

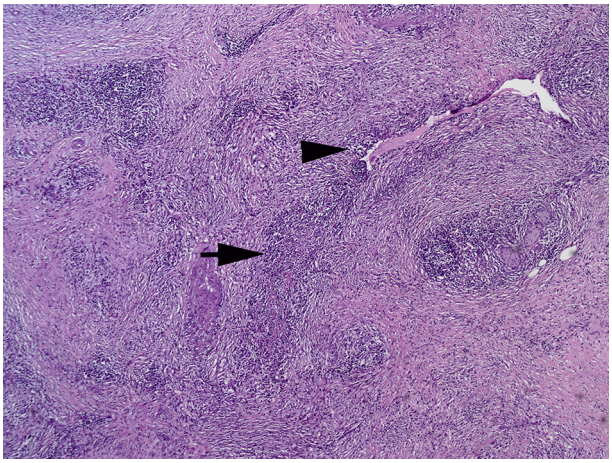

Figure 4 Type 1 autoimmune pancreatitis with obliterative phlebitis. A portion of this vein is completely obliterated (arrow), and the other segment is partially obliterated (arrow head).