

Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORt criteria

SURESH T. CHARI

Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA

Autoimmune pancreatitis (AIP) is a recently defined form of chronic pancreatitis. While numerous case reports and small case series of AIP have been reported from Japan, there have been relatively few from the West. Based on a retrospective review of our experience with resected AIP and a review of the literature, we have identified five cardinal features of AIP in histology, imaging, serology, other organ involvement, and response to steroid therapy, which are summarized in the mnemonic HISORt. A combination of the HISORt criteria can be used to definitively diagnose a wide spectrum of manifestations of AIP.

Key words: autoimmune diseases, pancreatitis, steroids

Definition

Autoimmune pancreatitis AIP may be defined as the pancreatic manifestation of a systemic fibroinflammatory disease which afflicts not only the pancreas, but also a variety of other organs, including the bile duct, salivary glands, retroperitoneum, and lymph nodes. Organs affected by AIP have a lymphoplasmacytic infiltrate rich in IgG4-positive cells. The inflammatory process responds to steroid therapy, while the intense fibrosis may lead to permanent structural and functional damage to the gland.¹

Clinical presentations

AIP has protean clinical presentations which may be classified in relation to the onset of disease as acute or late, and according to the organs affected as pancreatic

or extrapancreatic. By far the most common presentation of AIP is acute, with obstructive jaundice and pancreatic enlargement mimicking pancreatic cancer; very occasionally it may present acutely with features of acute pancreatitis. Although AIP is a form of chronic pancreatitis (CP), it differs significantly from other forms of chronic calcifying pancreatitis in that it is relatively painless. In the postacute phase it may present, or be incidentally discovered, because of persistent pancreatic mass, atrophic pancreas with or without calcification, or pancreatic steatorrhea. Thus its pancreatic manifestations can mimic pancreatic cancer, acute pancreatitis, painless chronic pancreatitis, or unexplained functional insufficiency.

The extrapancreatic manifestations are equally diverse and may be seen simultaneously with its pancreatic manifestations, may precede them, or may occur many years later when the pancreas may or may not be symptomatic. The most common extrapancreatic organ involved is the biliary tree, where distal biliary involvement mimics pancreatic cancer-related stricture. More proximal involvement may cause suspicion that it may be cholangiocarcinoma or primary sclerosing cholangitis. Other well-described manifestations include salivary gland involvement resembling Sjögren's syndrome, mediastinal adenopathy resembling sarcoidosis, retroperitoneal fibrosis, and tubulointerstitial nephritis.

The five cardinal features of AIP

In order to diagnose the diverse presentations of AIP one must have a high index of suspicion and be conversant with its manifestations. To identify the full spectrum of changes occurring in AIP, one must learn to recognize its five cardinal features in histology, imaging, serology, other organ involvement, and its response to steroid therapy (the Mayo Clinic's HISORt criteria have been described in detail by Chari et al.¹).

Histology and immunostaining

AIP has unique histological features that differentiate it from other inflammatory pancreatitides.²⁻⁷ The pathognomonic histological features of AIP [which is also known as lymphoplasmacytic sclerosing pancreatitis (LPSP)], are a periductal lymphoplasmacytic infiltrate associated with storiform fibrosis, and obliterative phlebitis wherein the lymphoplasmacytic infiltrate surrounds pancreatic venules while sparing arterioles.^{2,3,5,6} The lymphoplasmacytic infiltrate in AIP has abundant IgG4-positive cells on immunostaining.⁸⁻¹⁰ A less common variant called idiopathic duct-centric pancreatitis (IDCP)^{3,7} or nonalcoholic duct-destructive pancreatitis,⁴ has been described in some patients. There are very few IgG4-positive cells in IDCP.¹¹

Imaging

The characteristic imaging features include a diffuse “sausage-shaped” enlargement of the gland on a computerized tomography scan or magnetic resonance imaging with delayed peripheral (rim) enhancement.^{12,13} On pancreatography, a diffusely irregular, narrow pancreatic duct is highly suggestive of AIP.^{13,14} However, some patients may have focal masses or strictures,¹⁵⁻¹⁷ or show evidence of calcification¹⁸ or acute pancreatitis.^{19,20}

Serology

Serological abnormalities in AIP include elevated titers of gammaglobulins, IgG, and a variety of antibodies including antinuclear antibody, rheumatoid factor, carbonic anhydrase, and lactoferrin.^{13,21,22} However, elevated titers of gammaglobulins, IgG, antinuclear antibody, and rheumatoid factor are nonspecific, and are found in a variety of conditions, including many autoimmune disorders. Recently, Hamano et al.²³ reported that elevated serum levels of the IgG4 subset of immunoglobulin G were a sensitive and specific marker of AIP.

Other organ involvement

AIP has traditionally been reported to be “associated” with a number of other disorders such as primary sclerosing cholangitis (PSC), Sjögren’s syndrome, and retroperitoneal fibrosis. However, more recent studies suggest that the “associations” are in fact manifestations of AIP that mimic other well-described diseases. Kamisawa et al.^{8,10,24} have proposed that AIP is a sys-

temic disease which predominantly afflicts the pancreas, and have called it IgG4 disease. This concept is supported by the findings of abundant infiltration with IgG-positive cells in a number of organs in AIP.²⁴⁻²⁷ The organs most commonly involved are the biliary ductal system, where it causes PSC-like intra- and extrahepatic biliary strictures,^{26,27} the salivary glands, where it produces a Sjögren’s syndrome-like picture,²⁸ and the retroperitoneum, where it causes retroperitoneal fibrosis.⁹

Response to steroid therapy

The pancreatic,^{23,29} biliary,²⁷ and salivary gland diseases³⁰ associated with infiltration with IgG4-positive cells respond, often dramatically, to steroid therapy, whereas the diseases they mimic do not. This unique response to steroid therapy may be useful in the diagnosis of AIP.

When to suspect and how to diagnose AIP

AIP should be suspected in patients with obstructive jaundice, pancreatic mass/enlargement, or pancreatitis who have one or more HISORt criteria, i.e., suggestive histology showing lymphoplasmacytic infiltrate with storiform fibrosis, imaging showing a diffusely enlarged pancreas, serology showing elevated IgG4 levels, or evidence of other organ involvement. In such patients, the diagnosis can be confirmed if (a) a review of the histology shows a full spectrum of changes of LPSP, or immunostaining shows abundant IgG4-positive cells, (b) imaging shows a diffusely enlarged pancreas and a diffusely irregular, narrow pancreatic duct, and serology shows elevated IgG4 levels, or (c) in patients with elevated IgG4 or extrapancreatic manifestations or both, and these manifestations resolve with steroid therapy.

These criteria were developed based on our experience of more than 75 patients diagnosed at the Mayo Clinic. This has allowed us to diagnose not only a wide range of pancreatic manifestations of AIP, but also its extrapancreatic manifestations. However, as our understanding of the disease grows, these criteria will certainly need review and modification.

References

1. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. *Clin Gastroenterol Hepatol* 2006;4:1010-6.
2. Kloppel G, Luttges J, Lohr M, Zamboni G, Longnecker D. Autoimmune pancreatitis: pathological, clinical, and immunological features. *Pancreas* 2003;27:14-9.

3. Notohara K, Burgart LJ, Yadav D, Chari S, Smyrk TC. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. *Am J Surg Pathol* 2003;27:1119–27.
4. Ectors N, Maillet B, Aerts R, Geboes K, Donner A, Borchard F, et al. Non-alcoholic duct-destructive chronic pancreatitis. *Gut* 1997;41:263–8.
5. Abraham SC, Wilentz RE, Yeo CJ, Sohn TA, Cameron JL, Boitnott JK, et al. Pancreaticoduodenectomy (Whipple resections) in patients without malignancy: are they all “chronic pancreatitis”? *Am J Surg Pathol* 2003;27:110–20.
6. Weber SM, Cubukcu-Dimopulo O, Palesty JA, Suriawinata A, Klimstra D, Brennan MF, et al. Lymphoplasmacytic sclerosing pancreatitis: inflammatory mimic of pancreatic carcinoma. *J Gastrointest Surg* 2003;7:129–37.
7. Yadav D, Notohara K, Smyrk TC, Clain JE, Pearson RK, Farnell MB, et al. Idiopathic tumefactive chronic pancreatitis: clinical profile, histology, and natural history after resection. *Clin Gastroenterol Hepatol* 2003;1:129–35.
8. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, et al. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;38:982–4.
9. Kamisawa T, Funata N, Hayashi Y, Tsuruta K, Okamoto A, Amemiya K, et al. Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. *Gut* 2003;52:683–7.
10. Kamisawa T, Funata N, Hayashi Y. Lymphoplasmacytic sclerosing pancreatitis is a pancreatic lesion of IgG4-related systemic disease. *Am J Surg Pathol* 2004;28:1114.
11. Zhang L, Notohara K, Levy MJ, Chari ST, Smyrk TC. IgG4-positive plasma cell infiltration in the diagnosis of autoimmune pancreatitis. *Modern Pathology* 2007;20:23–8.
12. Irie H, Honda H, Baba S, Kuroiwa T, Yoshimitsu K, Tajima T, et al. Autoimmune pancreatitis: CT and MR characteristics. *Am J Roentgenol* 1998;170:1323–7.
13. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 1995;40:1561–8.
14. Horiuchi A, Kawa S, Hamano H, Hayama M, Ota H, Kiyosawa K. ERCP features in 27 patients with autoimmune pancreatitis. *Gastrointest Endosc* 2002;55:494–9.
15. Pearson RK, Longnecker DS, Chari ST, Smyrk TC, Okazaki K, Frulloni L, et al. Controversies in clinical pancreatology. Autoimmune pancreatitis: does it exist? *Pancreas* 2003;27:1–13.
16. Wakabayashi T, Kawaura Y, Satomura Y, Fujii T, Motoo Y, Okai T, et al. Clinical study of chronic pancreatitis with focal irregular narrowing of the main pancreatic duct and mass formation: comparison with chronic pancreatitis showing diffuse irregular narrowing of the main pancreatic duct. *Pancreas* 2002;25:283–9.
17. Wakabayashi T, Kawaura Y, Satomura Y, Watanabe H, Motoo Y, Okai T, et al. Clinical and imaging features of autoimmune pancreatitis with focal pancreatic swelling or mass formation: comparison with so-called tumor-forming pancreatitis and pancreatic carcinoma. *Am J Gastroenterol* 2003;98:2679–87.
18. Takayama M, Hamano H, Ochi Y, Saegusa H, Komatsu K, Muraki T, et al. Recurrent attacks of autoimmune pancreatitis result in pancreatic stone formation. *Am J Gastroenterol* 2004;99:932–7.
19. Nishimura T, Masaoka T, Suzuki H, Aiura K, Nagata H, Ishii H. Autoimmune pancreatitis with pseudocysts. *J Gastroenterol* 2004;39:1005–10.
20. Ichikawa T, Nakao K, Hamasaki K, Ohkubo K, Toriyama K, Eguchi K. An autopsy case of acute pancreatitis with a high serum IgG4 complicated by amyloidosis and rheumatoid arthritis. *World J Gastroenterol* 2005;11:2032–4.
21. Okazaki K, Chiba T. Autoimmune-related pancreatitis. *Gut* 2002;51:1–4.
22. Kino-Ohsaki J, Nishimori I, Morita M, Okazaki K, Yamamoto Y, Onishi S, et al. Serum antibodies to carbonic anhydrase I and II in patients with idiopathic chronic pancreatitis and Sjogren’s syndrome. *Gastroenterology* 1996;110:1579–86.
23. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344:732–8.
24. Kamisawa T, Egawa N, Nakajima H. Autoimmune pancreatitis is a systemic autoimmune disease. *Am J Gastroenterol* 2003;98:2811–2.
25. Kamisawa T. IgG4-positive plasma cells specifically infiltrate various organs in autoimmune pancreatitis. *Pancreas* 2004;29:167–8.
26. Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, et al. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? *Am J Surg Pathol* 2004;28:1193–203.
27. Nishino T, Toki F, Oyama H, Oi I, Kobayashi M, Takasaki K, et al. Biliary tract involvement in autoimmune pancreatitis. *Pancreas* 2005;30:76–82.
28. Kamisawa T, Egawa N, Inokuma S, Tsuruta K, Okamoto A, Kamata N, et al. Pancreatic endocrine and exocrine function and salivary gland function in autoimmune pancreatitis before and after steroid therapy. *Pancreas* 2003;27:235–8.
29. Kamisawa T, Yoshiike M, Egawa N, Nakajima H, Tsuruta K, Okamoto A. Treating patients with autoimmune pancreatitis: results from a long-term follow-up study. *Pancreatol* 2005;5:234–8; discussion 238–40.
30. Yamamoto M, Takahashi H, Sugai S, Imai K. Clinical and pathological characteristics of Mikulicz’s disease (IgG4-related plasmacytic exocrinopathy). *Autoimmun Rev* 2005;4:195–200.