Autoimmune Pancreatitis: A Multiorgan Disease Presenting a Conundrum for Clinicians in the West

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Abstract: Autoimmune pancreatitis (AIP), a clinical entity originally described in East Asia and more recently recognized in the United States and Europe, poses a diagnostic conundrum for clinicians in the West due to immunoglobulin G4 seronegativity. Although expert panels classify this disease into 2 types, it remains difficult to stratify the disease given that both types share most clinical, biochemical, and imaging characteristics. The classic presentation of AIP can mimic that of pancreatic carcinoma, which increases the urgency of evaluation, diagnosis, and treatment. In this article, we elucidate the differences between the 2 types of AIP, highlight the shortcomings of the current classification system, and propose a more inclusive view of the disorder.

Autoimmune pancreatitis (AIP), a clinical entity originally described in East Asia[1-3] and more recently recognized in the United States and Europe,[4-6] poses a diagnostic conundrum for clinicians in the West due to the prevalence of immunoglobulin G4 (IgG4) seronegativity and extrapancreatic manifestations. Although expert panels classify this disease into 2 types, it remains difficult to stratify the disease given that both types share most clinical, biochemical, and imaging characteristics. Type 1 AIP is distinguished by the presence of IgG4 antibodies and is more common in patients of East Asian ethnicity. Type 2 is the seronegative form of AIP and is more common in patients of Western ethnicity. AIP is associated with disorders of other organs, including inflammatory bowel disease (IBD), sclerosing cholangitis, sclerosing sialadenitis, tubulointerstitial nephritis, and retroperitoneal fibrosis. The presentation of AIP can mimic that of a pancreatic neoplasm, increasing the urgency of evaluation and diagnosis.[3,7,8] In this article, we elucidate the differences between the 2 types of AIP. We also highlight the shortcomings of the current classification system and propose a more inclusive view of this disorder without subclassifying these entities, with the intention of alerting physicians to this confusing situation. Finally, we emphasize the importance of early evaluation to distinguish this relatively benign, corticosteroid-responsive disease from pancreatic carcinoma.

Table. Characteristics of the Types of Autoimmune Pancreatitis as Defined by the International Consensus Diagnostic Criteria

Characteristics	Type 1 Autoimmune Pancreatitis	Type 2 Autoimmune Pancreatitis
Epidemiology	Asia > United States, Europe	Europe > United States > Asia
Age	60 years or older	Younger (~40 years)
Sex	Men > women	Men ≈ women
Serology	High serum IgG4, autoAb+	Normal serum IgG4, autoAb–
Histopathology	Marked lymphocyte and plasmacyte infiltration and fibrosis Infiltration of IgG4+ plasma cells	Granulocytic epithelial lesion often with destruction and obliteration of the pancreatic duct
Symptoms (overall)	Painless/obstructive jaundice Pancreatic exocrine insufficiency New-onset diabetes	
Abdominal pain	Rare	Common
Radiologic findings	Pancreatic swelling ("sausage-shaped")	
Other organ involvement	Salivary/submandibular/lacrimal glands Bile ducts (sclerosing cholangitis) Kidneys (renal mass, tubulointerstitial nephritis) Retroperitoneal fibrosis	Rare
Association with IBD	Rare	Common
Response to corticosteroids	Responsive	
Relapse rate	High	Low

AutoAb, autoantibody; IBD, inflammatory bowel disease; IgG4, immunoglobulin G4.

Classification

AIP is a form of chronic pancreatitis that is clinically characterized by the presentation of cholestasis, obstructive jaundice, and/or a pancreatic mass; histologically characterized by fibrosis and a lymphoplasmacytic infiltrate; and therapeutically characterized by a dramatic response to corticosteroid treatment. In 2011, AIP was formally classified by the International Consensus Diagnostic Criteria into 2 categories: type 1 and type 2 (Table).[9,10]

Type 1 AIP is characterized by the histologic description of lymphoplasmacytic sclerosing pancreatitis. It is associated with IgG4-positive serology and other organ involvement (sclerosing cholangitis, sclerosing sialadenitis, tubulointerstitial nephritis, and retroperitoneal fibrosis). This type of AIP is more common in older men and people of East Asian ethnicity, and it has a high relapse rate.

Type 2 AIP is characterized by the histopathologic pattern of chronic pancreatitis called idiopathic duct–centric pancreatitis or by the presence of granulocyte epithelial lesions. It is associated with IBD but has no known serologic biomarker. This type is more common in younger people of Western (European and American) ethnicity, does not show a sex predilection, and rarely recurs.

Clinical Presentation

Classically, AIP presents with obstructive jaundice and/or a pancreatic mass.[9] There may be an insidious prodrome of feeling unwell, with complaints of a gnawing midline discomfort sometimes associated with ingestion of food, medications, or alcohol. Mild weight loss is not uncommon. A minority of patients present with a more acute, painful pancreatitis. An international, multicenter survey of 731 AIP patients found obstructive jaundice to be a more frequent presentation in type 1 vs type 2 AIP (75% vs 47%; $P<.001$), whereas abdominal pain (41% vs 68%; $P<.001$) and acute pancreatitis (5% vs 34%; $P<.001$) were more frequent in type 2 AIP.[10] Patients with type 1 AIP have a high relapse rate, and patients with type 2 AIP rarely experience relapse.[11]

Imaging

The characteristic findings seen on computed tomography (CT), magnetic resonance imaging (MRI), pancreatography, and endoscopic ultrasound (EUS) are common for both types of AIP.[12-15] CT/MRI in AIP shows an enlarged pancreas with featureless borders often described as "sausage-shaped" (Figure 1). Imaging scans frequently demonstrate pancreatic swelling and occasionally show a

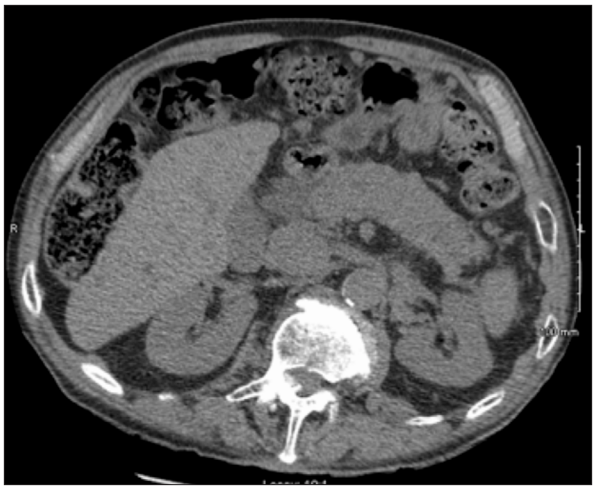

Figure 1. A "sausage-shaped" pancreas.

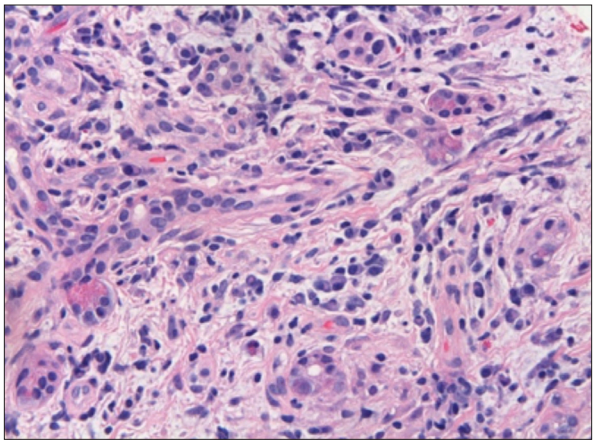

Figure 3. A photomicrograph of a pancreatic biopsy showing pancreatic acini and ducts surrounded by dense inflammation comprised of clusters of plasma cells, lymphocytes, and an occasional eosinophil (hematoxylin and eosin stain, 400× magnification).

mass, both of which affect biliary obstruction and cholestasis (Figure 2).[16] In such cases, the bile duct morphology can be attenuated (stricturing) or dilated, obfuscating the clinical picture because these findings are also present in sclerosing cholangitis and cholangiocarcinoma, which are entities associated with IBD.[17] Pancreatographic features include segmental or diffuse irregular narrowing of the main duct.[18]

CT/MRI can be used to differentiate neoplasms from AIP, which demonstrates clear anatomic surgical planes. Vascular structures are unaffected in most AIP patients, with the exception of venous thrombosis and the development of collateral vessels secondary to the inflammatory process. However, inflammatory changes may extend to peripancreatic lymph nodes, in which case a biopsy is required to rule out neoplasia. In positron emission tomography studies, uptake of fluorodeoxyglucose in organs known to be affected by IgG4-related disease other than the pancreas suggests AIP.[19] The classic EUS finding in AIP is hyperechoic parenchyma of a pancreatic mass with clear margins. However, with EUS, a definitive diagnosis must be established histologically via multiple fine-needle aspirations or a core biopsy of the lesion.[20-22]

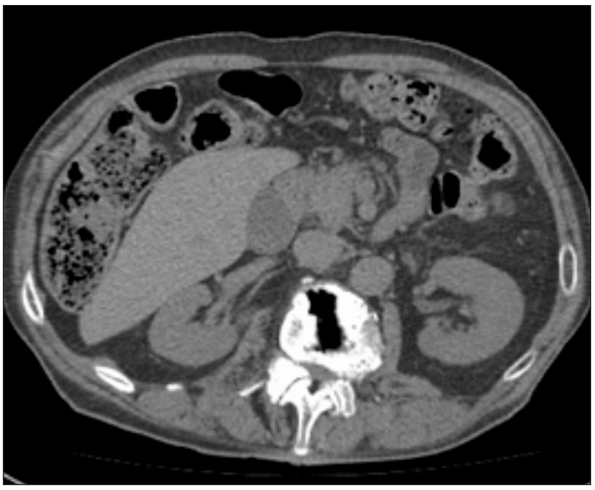

Figure 2. A mass in the head of the pancreas, which can produce biliary obstruction and cholestasis.

Other Organ Involvement

Both types of AIP can be associated with extrapancreatic disease. Type 1 commonly has other organ involvement related to IgG4 infiltration. Although previously regarded as isolated single-organ diseases without any known underlying systemic condition, IgG4-related diseases were recently recognized as a unified entity.[19,23,24] These diseases can manifest as sclerosing cholangitis, sclerosing sialadenitis, tubulointerstitial nephritis, and/or retroperitoneal fibrosis.[6,25] Other affected areas include the lung, prostate, aorta, pericardium, pituitary gland, and lymph nodes. This involvement can present at any time before or after the diagnosis of AIP.[26]

Both types of AIP are associated with IBD, although much less commonly in type 1.[7,8,27-29] This association is predominantly with ulcerative colitis; however, there are reports of AIP associated with Crohn's disease. The incidence is much greater in type 2 AIP (seronegative patients in the West) compared with type 1 AIP (seropositive Asian patients).

Histopathology

Given the clinical and radiologic similarities between AIP and pancreatic carcinoma, a tissue sample is essential for establishing a definitive diagnosis. This requires EUS, CT guidance, or surgical intervention. The find-

ing of lymphoplasmacytic infiltration is diagnostic for AIP (Figure 3), and tissue samples often stain positive for IgG4, confirming the diagnosis.[30,31] The Japanese Pancreas Society introduced the first diagnostic criteria, which were expanded by the Mayo Clinic and named the HISORt criteria (histology, imaging, serology, other organ involvement, and response to corticosteroid therapy).[32] These criteria allow for the noninvasive diagnosis of type 1 AIP; however, obtaining tissue for histologic confirmation remains essential to diagnose type 2 AIP and rule out carcinoma.[31,33,34]

Treatment

Corticosteroids are generally considered to be very effective in the treatment of AIP. A clinical and radiologic response to corticosteroids is usually seen in 2 to 4 weeks, which, per the HISORt criteria, corroborates the diagnosis of AIP in patients without a biopsy.[35] Patients usually receive prednisone at 40 to 50 mg daily (weight adjusted, 0.6-1.0 mg/kg daily) for 4 weeks; this dose is slowly reduced by 5 mg per week for up to 11 or 12 weeks.[36,37] Relapse is common in type 1 AIP and most often affects the proximal biliary tree and/or pancreas. Another course of corticosteroid treatment should be initiated, and long-term corticosteroid maintenance therapy for up to 3 years may benefit patients with continuous relapses. If patients do not tolerate corticosteroids or if the risks and complications associated with long-term therapy are unacceptable, corticosteroid-sparing immunomodulators such as azathioprine or rituximab (Rituxan, Genentech/Biogen Idec) have been utilized with long-term success.[38,39]

Neoplasms Associated With Autoimmune Pancreatitis

Patients with IgG4-related disease are suspected to have an increased risk of malignancies.[36,40,41] A report from Japan revealed that, over a 3-year period of observation, 11 of 106 patients with IgG4-related disease were diagnosed with cancer, including colon cancer, lung cancer, and lymphoma.[41] This is 3.5 times more frequent than in the general population. Another report from Japan similarly demonstrated that 15% of their cohort of 108 patients developed cancer within the first year of diagnosis.[26] An issue of whether to distinguish AIP from cancer on initial presentation remains a dilemma. This dilemma is especially imposing in patients who present with seronegative studies, as most patients do in the West. When other imaging studies and core biopsies are completed, and the results are negative, most experts recommend a short course of corticosteroids. The follow-up imaging studies and the patient's response should verify the diagnosis.

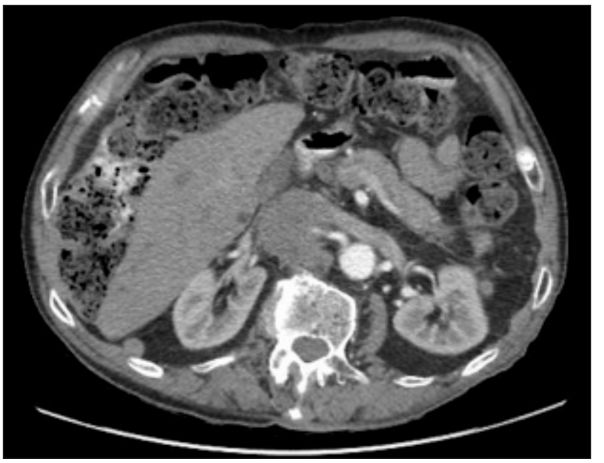

Figure 4. Resolution of a pancreatic mass on a repeat computed tomography scan.

If the results are equivocal and the lesion is resectable, surgery is recommended. However, in our institution, where we have experienced pancreatic surgeons, surgery is performed very infrequently.

Analysis

The original diagnosis of AIP was one of exclusion until the 1960s when hypergammaglobulinemia was determined to be a more objective marker for diagnosis.[42] Decades later, investigators noted 2 distinct patterns of the disease.[5,6] It was not until the early 2000s that a more definitive set of guidelines and classifications were established. The guidelines defined 2 types of AIP, classifying them by their serologic and histologic characteristics, and discussing other distinguishing features of each type (Table). Our intention is to alter the strict classifications accepted today and demystify these associations. The 2 types of AIP are interrelated, but we feel that classification into 2 simple but tightly defined groups is misguided.

AIP was originally described in East Asia using criteria for what is now defined as type 1 AIP. IBD is much less common in East Asians compared with whites; thus, a concurrent diagnosis of AIP and IBD in East Asia was considered an outlier and not part of the AIP manifestation. As AIP was recognized more in the West and type 2 AIP was described, the association with IBD gained more attention. Interestingly, both AIP and IBD are associated with other organ involvement, many types of which they share in common. This commonality causes us to question whether AIP is a separate entity or part of the complex of extracolonic manifestations of IBD.

Figures 1 through 3 are from a patient who has the potential to manifest characteristics from both types 1 and 2 AIP (an elderly white man with a history of Crohn's disease, nonsarcoid hilar adenopathy, and recurrent AIP).

Initial and repeat biopsies confirmed the presence of IgG4-negative type 1 AIP. The patient's response to corticosteroid treatment was confirmed with repeat CT imaging (Figure 4). However, several months later, the patient seroconverted positive for IgG4 with markedly elevated serum levels. Cases such as this one suggest that AIP (both types 1 and 2) is not an isolated disease, but rather part of a syndrome with a unifying autoimmune component.

The conclusive diagnosis of seronegative AIP has been challenging until recently. Historically, AIP was a diagnosis of exclusion. After other causes of pancreatitis were evaluated more easily (gallstones, alcohol, viruses, or medications), these seronegative patients were left with the ambiguous diagnosis of idiopathic pancreatitis. With this vague diagnosis and suspicion for AIP, clinicians were sometimes reluctant to commit patients to a course of corticosteroid treatment, especially when the possibility of a neoplasm had not been completely eliminated.

The precision of AIP diagnosis has greatly improved in recent years, secondary to the concomitant evolution of diagnostic technologies. CT can distinguish autoimmune from other types of pancreatitis, and the use of EUS with fine-needle aspirations and core biopsies has further defined the diagnosis. These techniques are significantly less invasive modes of obtaining definitive histology, thus ruling out carcinoma and confirming a diagnosis of AIP that is otherwise difficult to make, especially in IgG4-negative patients in the West.

Of concern to many clinicians is when the pancreatic histopathology is inconclusive or when tissue biopsy is not possible. In this not-uncommon scenario, one is tempted to refer patients for immediate surgical consultation for a definitive operation for cancer or palliative bypass decompression. However, it is recommended that a short trial of corticosteroid treatment be given first. Such a trial can elucidate the difference between AIP and carcinoma because AIP has a dramatic and lasting response to this therapy. Pancreatic carcinoma may show temporary clinical improvement with corticosteroid treatment; however, rapid recurrence of symptoms and/or radiologic findings is highly suggestive of neoplasm and warrants aggressive surgical intervention.

A correct and timely recognition of AIP prevents unnecessary surgery and reduces patient anxiety, whereas a misdiagnosis of AIP can be very problematic, especially if patients are misdiagnosed with pancreatic cancer. We suspect that the number of AIP patients who mistakenly have undergone surgical resection for suspected carcinoma has altered the epidemiologic data on pancreatic cancer survivorship. We emphasize, however, that early pancreatic cancer detection is paramount to patient survival. We conclude that early, accurate differentiation between AIP and pancreatic carcinoma can reduce patient morbidity.

Conclusion

AIP is ubiquitous, presents in several ways, and is associated with other intercurrent medical problems, including IBD and other autoimmune disorders. The classic presentation of AIP can mimic that of pancreatic carcinoma. This presents a conundrum for clinicians in the West because a majority of white patients are IgG4-seronegative, making the definitive diagnosis of AIP nearly impossible without tissue biopsy. In this scenario, rather than immediate invasive surgical intervention, we recommend obtaining tissue for diagnosis via EUS- or CT-guided biopsy and beginning treatment with corticosteroids. The clinical response to corticosteroids is rapid and dramatic in both types of AIP, reassuring the clinician that the decision to start this medication was appropriate. Serial follow-up imaging studies will ultimately justify this decision.

The authors have no relevant conflicts of interest to disclose.

References

1. 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(7):1561-1568.
2. Nishimori I, Tamakoshi A, Otsuki M; Research Committee on Intractable Diseases of the Pancreas, Ministry of Health, Labour, and Welfare of Japan. Prevalence of autoimmune pancreatitis in Japan from a nationwide survey in 2002. *J Gastroenterol*. 2007;42(suppl 18):6-8.
3. Kamisawa T, Egawa N, Nakajima H. Autoimmune pancreatitis is a systemic autoimmune disease. *Am J Gastroenterol*. 2003;98(12):2811-2812.
4. Kasmin FE, Cooperman A, Cohen SA, Wayne M, Brown WH, Siegel JH. Seronegative autoimmune pancreatitis—a commonly missed diagnosis in U.S. patients? *Gastroenterology*. 2008;134(4):A-227.
5. Sutton R. Autoimmune pancreatitis—also a Western disease. *Gut*. 2005;54(5):581-583.
6. Raina A, Yadav D, Krasinskas AM, et al. Evaluation and management of autoimmune pancreatitis: experience at a large US center. *Am J Gastroenterol*. 2009;104(9):2295-2306.
7. Ravi K, Chari ST, Vege SS, Sandborn WJ, Smyrk TC, Loftus EV Jr. Inflammatory bowel disease in the setting of autoimmune pancreatitis. *Inflamm Bowel Dis*. 2009;15(9):1326-1330.
8. Pitchumoni CS, Chari S. Ulcerative colitis and autoimmune pancreatitis. *J Clin Gastroenterol*. 2013;47(6):469.
9. Shimosegawa T, Chari ST, Frulloni L, et al; International Association of Pancreatology. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas*. 2011;40(3):352-358.
10. Kamisawa T, Chari ST, Giday SA, et al. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. *Pancreas*. 2011;40(6):809-814.
11. Sah RP, Chari ST, Pannala R, et al. Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis. *Gastroenterology*. 2010;139(1):140-148.
12. Proctor RD, Rofe CJ, Bryant TJ, Hacking CN, Stedman B. Autoimmune pancreatitis: an illustrated guide to diagnosis. *Clin Radiol*. 2013;68(4):422-432.
13. Park SH, Kim MH, Kim SY, et al. Magnetic resonance cholangiopancreatography for the diagnostic evaluation of autoimmune pancreatitis. *Pancreas*. 2010;39(8):1191-1198.
14. Hoki N, Mizuno N, Sawaki A, et al. Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography. *J Gastroenterol*. 2009;44(2):154-159.
15. Sugumar A, Levy MJ, Kamisawa T, et al. Endoscopic retrograde pancreatography criteria to diagnose autoimmune pancreatitis: an international multicentre study. *Gut*. 2011;60(5):666-670.

16. Kamisawa T, Tu Y, Egawa N, Nakajima H, Tsuruta K, Okamoto A. Involvement of pancreatic and bile ducts in autoimmune pancreatitis. *World J Gastroenterol*. 2006;12(4):612-614.
17. Nakazawa T, Ohara H, Sano H, et al. Cholangiography can discriminate sclerosing cholangitis with autoimmune pancreatitis from primary sclerosing cholangitis. *Gastrointest Endosc*. 2004;60(6):937-944.
18. Horiuchi A, Kawa S, Hamano H, Hayama M, Ota H, Kiyosawa K. ERCP features in 27 patients with autoimmune pancreatitis. *Gastrointest Endosc*. 2002;55(4):494-499.
19. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. *Lancet*. 2015;385(9976):1460-1471.
20. Moon SH, Kim MH. The role of endoscopy in the diagnosis of autoimmune pancreatitis. *Gastrointest Endosc*. 2012;76(3):645-656.
21. Levy MJ. Endoscopic ultrasound-guided trucut biopsy of the pancreas: prospects and problems. *Pancreatology*. 2007;7(2-3):163-166.
22. Mizuno N, Bhatia V, Hosoda W, et al. Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy: a comparison study with EUS-FNA. *J Gastroenterol*. 2009;44(7):742-750.
23. Stone JH, Brito-Zerón P, Bosch X, Ramos-Casals M. Diagnostic approach to the complexity of IgG4-related disease. *Mayo Clin Proc*. 2015;90(7):927-939.
24. Islam AD, Selmi C, Datta-Mitra A, et al. The changing faces of IgG4-related disease: clinical manifestations and pathogenesis [published online June 23, 2015]. *Autoimmun Rev*. doi:10.1016/j.autrev.2015.06.003.
25. Ghazale A, Chari ST, Smyrk TC, et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. *Am J Gastroenterol*. 2007;102(8):1646-1653.
26. Shiokawa M, Kodama Y, Yoshimura K, et al. Risk of cancer in patients with autoimmune pancreatitis. *Am J Gastroenterol*. 2013;108(4):610-617.
27. Danese S, Semeraro S, Papa A, et al. Extraintestinal manifestations in inflammatory bowel disease. *World J Gastroenterol*. 2005;11(46):7227-7236.
28. Kawa S, Okazaki K, Notohara K, et al. Autoimmune pancreatitis complicated with inflammatory bowel disease and comparative study of type 1 and type 2 autoimmune pancreatitis. *J Gastroenterol*. 2015;50(7):805-815.
29. Park SH, Kim D, Ye BD, et al. The characteristics of ulcerative colitis associated with autoimmune pancreatitis. *J Clin Gastroenterol*. 2013;47(6):520-525.
30. 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(8):1119-1127.
31. Kawaguchi K, Koike M, Tsuruta K, Okamoto A, Tabata I, Fujita N. Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. *Hum Pathol*. 1991;22(4):387-395.
32. Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. *Clin Gastroenterol Hepatol*. 2006;4(8):1010-1016.
33. Sah RP, Chari ST. Autoimmune pancreatitis: an update on classification, diagnosis, natural history and management. *Curr Gastroenterol Rep*. 2012;14(2):95-105.
34. Chari ST, Takahashi N, Levy MJ, et al. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. *Clin Gastroenterol Hepatol*. 2009;7(10):1097-1103.
35. Moon SH, Kim MH, Park DH, et al. Is a 2-week steroid trial after initial negative investigation for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? A prospective outcome study. *Gut*. 2008;57(12):1704-1712.
36. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. *Gut*. 2009;58(11):1504-1507.
37. Pannala R, Chari ST. Corticosteroid treatment for autoimmune pancreatitis. *Gut*. 2009;58(11):1438-1439.
38. Sandanayake NS, Church NI, Chapman MH, et al. Presentation and management of post-treatment relapse in autoimmune pancreatitis/immunoglobulin G4-associated cholangitis. *Clin Gastroenterol Hepatol*. 2009;7(10):1089-1096.
39. Topazian M, Witzig TE, Smyrk TC, et al. Rituximab therapy for refractory biliary strictures in immunoglobulin G4-associated cholangitis. *Clin Gastroenterol Hepatol*. 2008;6(3):364-366.
40. Hart PA, Kamisawa T, Brugge WR, et al. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. *Gut*. 2013;62(12):1771-1776.
41. Yamamoto M, Takahashi H, Tabeya T, et al. Risk of malignancies in IgG4-related disease. *Mod Rheumatol*. 2012;22(3):414-418.
42. Sarles H, Sarles JC, Muratore R, Guien C. Chronic inflammatory sclerosis of the pancreas—an autonomous pancreatic disease? *Am J Dig Dis*. 1961;6:688-698.