

Editorial

Autoimmune Pancreatitis: Making Progress Step by Step

Podcast interview: www.gastro.org/cghpodcast.

Autoimmune pancreatitis (AIP) is a rare disease that initially was described more than 40 years ago,¹ but one that recently is being increasingly recognized. If one searches PubMed, 754 publications on this topic are identifiable since the year 2000, and the pace of publication is increasing. This is not likely because of an increase in incidence or prevalence, but because of more focus on and recognition of this condition. The term *autoimmune pancreatitis* was first used in 1995, and now is accepted widely. It now is clear that in many patients the disease process affects more than just the pancreas, with the kidneys, bile ducts, salivary glands, and retroperitoneum most commonly being involved.^{2,3} There is a frequent increase in serum levels of immunoglobulin (Ig)G subclass 4, and infiltration of tissues with IgG4-positive plasma cells and other chronic inflammatory cells. If it is an autoimmune disease, the immunologic trigger(s), autoantigen(s), and immunologic mechanism(s) remain obscure.⁴ Many important clinical questions also remain unanswered. What is the best method to diagnose AIP? How can it be differentiated from other pancreatic diseases, and particularly pancreatic ductal adenocarcinoma? What therapy is best? Is long-term immunosuppressive therapy needed (in the model of autoimmune hepatitis)? How should relapses be managed? In this issue of *Clinical Gastroenterology and Hepatology*, two of these important clinical questions are addressed.

The diagnosis of AIP is based on clinical and imaging features, serology, and histology. Diagnostic criteria have been proposed.^{5,6} The most commonly used criteria in the United States are the histology, imaging, serology, other organ involvement, and response to steroid treatment (HISORt) criteria proposed by the Mayo Clinic. The most common presentation across the world is obstructive jaundice, caused by compression of the intrapancreatic bile duct by the pancreatitis and/or more proximal strictures of the extrahepatic biliary system. This presentation mimics pancreatic ductal adenocarcinoma, and the ability to distinguish these 2 conditions is critical. Surgeons have long recognized that even with the most careful preoperative testing, up to 5% of pancreaticoduodenectomy resections performed for presumed pancreatic carcinoma turn out to be benign disease (both chronic pancreatitis and autoimmune pancreatitis).⁷ Treating a patient with benign disease who will respond to steroids with a pancreaticoduodenectomy is as obviously suboptimal as is delaying potentially curative surgery in a patient with malignancy for a trial of steroids. However, differentiating pancreatic cancer from AIP is not easy.

In the study by Chari et al⁸ in this issue, the computed tomography (CT) findings in 48 patients with AIP were compared with 100 patients with pancreatic carcinoma. They propose 3 different pancreatic imaging patterns that extend and modify the HISORt criteria. The first pattern is highly suggestive of AIP and was defined as a diffusely enlarged pancreas with featureless borders, with delayed enhancement (enhancement during the portal venous phase of the contrast-enhanced CT), with or without a capsule-like, low-attenuation rim. In the study, all patients with this pattern had AIP. A pattern highly suggestive of pancreatic cancer was defined as the presence of 1 or more of 4 features: a

low-density focal mass, pancreatic ductal dilation (>4 mm), pancreatic duct cut-off, and atrophy of the pancreas upstream from the mass or stricture. In the study, 92% of patients with this pattern had pancreatic carcinoma. An indeterminate pattern also was proposed, consisting of focal enlargement of the pancreas without the features highly suggestive of cancer. In the study, this pattern was seen in 3% of pancreatic cancer patients and 31% of AIP patients. The diagnostic importance of CT is not limited to the appearance of the pancreas. A number of extrapancreatic features also can be defined. These include the presence of metastatic disease in those with cancer, and a variety of characteristic findings in those with AIP. Characteristic renal lesions, biliary tract strictures, and retroperitoneal fibrosis are seen in more than 50% of patients with AIP.^{3,8} A caveat is important. The ability of CT to distinguish AIP from cancer requires not only a high-quality multidetector contrast-enhanced CT, but also a radiologist familiar with both the pancreatic and extrapancreatic findings of AIP. Imaging techniques that show more detailed pancreatic ductal anatomy, such as magnetic resonance cholangiopancreatography and even endoscopic retrograde cholangiopancreatography, also can be quite helpful. AIP usually shows diffuse narrowing and irregularity of the pancreatic duct, whereas a dominant stricture and upstream ductal dilation are characteristic of ductal adenocarcinoma. In addition to these imaging findings, the clinical features and serology can help in identifying AIP. The presence of parotid or lacrimal gland enlargement, in addition to the renal, biliary, and retroperitoneal conditions mentioned previously, suggests AIP. An increase in serum IgG4 is the most specific marker of AIP, particularly if increased more than twice the upper limit of normal. Unfortunately, only about three quarters of patients with AIP have increases in IgG4, and increases may be seen occasionally in patients with pancreatic cancer and cholangiocarcinoma. Similarly, marked increases in CA 19-9 are more compatible with cancer, although false increases can be seen in those with AIP, particularly if there is associated biliary ductal obstruction. Histology showing characteristic features of AIP is diagnostic, although this is often not available and requires core biopsy of the pancreas rather than fine-needle aspiration. On the other hand, fine-needle aspiration under endoscopic ultrasound guidance is accurate in excluding the diagnosis of pancreatic carcinoma. A final method to distinguish between AIP and pancreatic carcinoma is a trial of steroids. This is controversial, although recent studies have suggested that a 2-week trial of prednisone may be sufficient to make this distinction.⁹

Despite the refinements that Chari et al⁸ have made to the HISORt criteria, approximately 30% of patients will not fit imaging, serologic, or other organ involvement criteria. Therefore, the clinician must perform a core needle biopsy, treat the patient with steroids, or subject the patient to surgery. In these cases, a core biopsy that is diagnostic of AIP is invaluable because the options of steroid treatment or surgery are not attractive. Although short-term steroid treatment has been proposed, treatment with steroids for 8 to 12 weeks in a patient with pancreatic carcinoma likely will convert a surgical candidate to a patient with locally unresectable disease. In addition, surgery is a particularly high-risk option for AIP patients because there is no role for intraoperative biopsy and frozen-section histopathologic analysis; thus, a pancreaticoduodenectomy is performed. Limited evidence suggests that patient outcome after pancreaticoduodenectomy for AIP is satisfactory.¹⁰ Furthermore, as the authors stress, a negative evaluation for pancreatic cancer in a patient with suspected AIP is not tremendously reassuring because a majority of patients with classic

features of pancreatic cancer undergo a pancreatoduodenectomy without a definitive diagnosis, even though cytologic brushings and biopsy specimens frequently are obtained. Although the retrospective nature of the study led to a bias with a high number of AIP patients, it is noteworthy that 16% of patients in the validation set had indeterminate imaging. Thus, this conundrum will raise its head on a regular basis, and multidisciplinary evaluation and management are critical.

Although Chari et al⁸ diligently have studied and refined their diagnostic criteria for AIP, with nearly 1 in 3 patients presenting a diagnostic dilemma, we must look to other diagnostic criteria. The article by Sandanayake et al¹¹ in this issue of the journal provides a glimpse of the diagnostic utility of obtaining a cholangiogram or pancreatogram in AIP. In this study, all 28 patients underwent endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography, and, not surprisingly, 60% of patients had a stricture in the intrapancreatic portion of the bile duct, but 82% of patients also had proximal, hilar, or intrahepatic biliary strictures. Only 4 patients had a normal biliary tree. Also, focal pancreatic duct strictures were seen in 43% of patients whereas diffuse strictures of the duct were evident in 18% of patients. These findings suggest that cholangiography and pancreatography may be valuable adjuncts in the diagnosis of AIP. Obviously, where available, a high-quality, noninvasive magnetic resonance cholangiopancreatography is preferable.

Once a diagnosis of AIP is made, therapy with corticosteroids should be initiated. The optimal dose is not known, but most centers have been using a dosage of 40 mg of prednisone daily for 8 weeks, followed by a taper over 6 to 8 weeks. Relapse of both pancreatic and extrapancreatic disease can occur.¹² Relapse appears to be common, particularly in those with extrapancreatic systemic disease (called *IgG4-associated systemic disease*) and particularly in those with more proximal biliary strictures (often called *IgG4-associated cholangitis* [IAC]). Whether this is because a relapse in this area causes easily identifiable features (jaundice) or whether relapse is actually more common in the biliary tree is not known. Relapses of biliary involvement may occur in up to 50% of patients when steroids are stopped.^{12,13} The optimal definition and management of relapses is not known. In particular, when should immunosuppressive agents such as azathioprine, 6-mercaptopurine, or other agents be considered? If so, should they be started at initial presentation or reserved for the patients who relapse? Once started, is lifelong therapy required? In this issue of the journal, Sandanayake et al¹¹ report on 28 patients with AIP, 23 of whom had IAC. All patients responded to initial steroid therapy. Of those with IAC, 5 (18%) could not be weaned successfully from steroids. An additional 8 patients (29%) relapsed at a mean of 4 months after steroids were stopped. All of those who failed steroid weaning or who relapsed had IAC, and relapse occurred in the biliary tree or in other extrapancreatic locations, not in the pancreas. All responded to restarting or increasing steroids. Azathioprine was started in 10 patients, with a target dose of 2 mg/kg. With the addition of azathioprine, steroids were able to be stopped in 75%. Although other immunosuppressive agents also have been tried in AIP/IAC including mycophenolate and rituximab, an analogy with autoimmune hepatitis and the long-term safety of azathioprine suggest it should be the first-line therapy in those who fail steroid weaning or relapse. Whether life-long therapy is required remains to be determined.

Despite the 754 publications since 2000, much remains to be defined in AIP. The 2 articles in this issue of *Clinical Gastroenterology*

and *Hepatology* give us useful insights into important clinical questions and refine our understanding of this rare but important disease.

Supplementary data

Note: to access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org.

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Conflicts of interest

The authors disclose no conflicts.

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