



EDUCATIONAL OBJECTIVE: Readers will recognize the signs and symptoms of autoimmune pancreatitis

RYAN LAW, DO

Department of General Internal
Medicine, Cleveland Clinic

MARY BRONNER, MD

Section Head, Morphologic
Molecular Pathology, Pathology
and Laboratory Medicine Institute,
Cleveland Clinic

DAVID VOGT, MD

Departments of Hepato-pancreato-
biliary and Transplant Surgery, Gen-
eral Surgery, and Transplantation
Center, Digestive Disease Institute,
Cleveland Clinic

TYLER STEVENS, MD

Digestive Disease Institute,
Cleveland Clinic

Autoimmune pancreatitis: A mimic of pancreatic cancer

ABSTRACT

Autoimmune pancreatitis is an idiopathic inflammatory disease that produces pancreatic masses and ductal strictures. This benign disease resembles pancreatic carcinoma both clinically and radiographically. The diagnosis of autoimmune pancreatitis is challenging to make. However, accurate and timely diagnosis may preempt the misdiagnosis of cancer and decrease the number of unnecessary pancreatic resections.

KEY POINTS

Hallmark features of autoimmune pancreatitis include an elevated serum immunoglobulin G4 level, focal or diffuse pancreatic enlargement on imaging, and dense lymphoplasmacytic infiltrates on histologic study.

The disease can be associated with extrapancreatic manifestations, including sclerosing cholangitis, sialadenitis and retroperitoneal fibrosis.

Autoimmune pancreatitis responds dramatically to corticosteroid treatment.

A 66-YEAR-OLD KOREAN MAN presented with a 2-week history of progressive jaundice, mild epigastric discomfort, and a weight loss of 12 lb. His serum bilirubin level was 5.8 mg/dL (reference range 0.0–1.5), and his alkaline phosphatase level was 325 U/L (20–120). Computed tomography (CT) revealed a 3-cm mass in the head of the pancreas.

Endoscopic retrograde cholangiopancreatography (ERCP) revealed a tight stricture in the intrapancreatic portion of the common bile duct. Brush cytology was negative for malignant cells. A plastic stent was placed to help palliate the jaundice. Endoscopic ultrasonography done at the same time revealed a hypoechoic mass in the head of the pancreas abutting the portal vein. Endoscopic ultrasonography-guided fine-needle aspiration biopsy was negative for malignant cells (FIGURE 1).

Exploratory laparotomy revealed a fibrotic pancreas with a palpable mass in the pancreatic head. The mass was unresectable, as it was adhering to the portal vein. A choledochoduodenostomy (anastomosis of the common bile duct to the duodenum) was created for palliation of jaundice. Intraoperative core biopsy revealed destruction of the pancreatic acinar architecture by marked lymphoplasmacytic inflammation and lymphocytic and obliterative venulitis, consistent with autoimmune pancreatitis.

Immediately after surgery, his serum immunoglobulin G4 (IgG4) level was 380 mg/dL (reference range 1–112). His bilirubin and alkaline phosphatase values came down into the normal range in the immediate postoperative period, and his jaundice resolved after a few days.



FIGURE 1. Endoscopic ultrasonographic image showing fine-needle aspiration of a hypoechoic mass (arrow) in the head of the pancreas.

■ **A CHRONIC INFLAMMATORY CONDITION**

Autoimmune pancreatitis is a chronic inflammatory condition with distinct clinical, radiographic, and histologic features.

Sarles et al,¹ in 1961, were first to propose that autoimmunity may be a factor in chronic pancreatitis. Three decades later, autoimmune pancreatitis was codified as a separate disease on the basis of a case report of a patient with serum elevations of IgG and gamma globulin, pancreatic duct narrowing, lymphocytic infiltration, fibrosis, and a marked response to steroid therapy.² Yet its pathogenesis remains poorly understood.

Extrapancreatic manifestations include sclerosing sialadenitis, sclerosing cholangitis, and retroperitoneal fibrosis.

Of note, autoimmune pancreatitis can mimic pancreatic adenocarcinoma clinically and radiographically. One must differentiate between the two disorders to prevent unnecessary surgery or delay in corticosteroid therapy.

■ **RATES ARE POORLY DEFINED**

The exact prevalence and incidence of autoimmune pancreatitis remain poorly defined. Most of the initial epidemiologic data have come from Japan and Korea. The prevalence was 0.7 per 100,000 patients in a survey of the Japanese population.³ Further studies are needed to ascertain its incidence and prevalence in the United States.

In patients with chronic pancreatitis, the estimated prevalence is between 4.6% and 6%, and 11% in patients undergoing pancreatic resection for suspected pancreatic cancer.^{4,5}

Autoimmune pancreatitis appears to be a disease of the elderly, as most patients are more than 50 years old at diagnosis. Twice as many men as women are affected.⁵ Many patients have no history of alcohol abuse or other traditional risk factors for chronic pancreatitis.

■ **CLINICAL PRESENTATION: PAINLESS JAUNDICE, WEIGHT LOSS**

TABLE 1 lists the typical clinical features of autoimmune pancreatitis.

The most common clinical presentation is obstructive jaundice with little or no abdominal pain. In one series,⁴ 65% of patients presented with painless jaundice secondary to biliary obstruction. Obstructive acute pancreatitis can occur, due to inflammatory strictures of the main pancreatic duct.

Weight loss results from impaired digestion and decreased appetite. Autoimmune pancreatitis is complicated by pancreatic exocrine insufficiency in 88% of cases⁶ and by endocrine dysfunction in 67%.³

Many patients have extrapancreatic lesions such as sclerosing sialadenitis, retroperitoneal fibrosis, and autoimmune sclerosing cholangitis.⁷ The cholangiographic appearance of autoimmune sclerosing cholangitis may resemble that of primary sclerosing cholangitis or cholangiocarcinoma. Less common extrapancreatic findings include interstitial nephritis and mediastinal adenopathy. These extrapancreatic findings do not always coincide with pancreatic inflammation. The histopathologic findings in extrapancreatic lesions parallel those in the pancreas.⁸

The patient described at the beginning of this article had several of these features, including painless jaundice, weight loss, elevated alkaline phosphatase, and an inflammatory pancreatic mass.

■ **DIAGNOSIS IS IMPROVING**

The diagnosis of autoimmune pancreatitis has improved, thanks to a growing awareness of the condition. The most widely accepted diagnostic

One must differentiate between autoimmune pancreatitis and cancer to prevent unnecessary surgery

criteria come from Korea, Japan, and the United States (TABLE 2).⁹⁻¹³ Efforts to establish international diagnostic criteria are under way.^{9,14}

Laboratory findings

Serum amylase and lipase are neither sensitive nor specific for autoimmune pancreatitis. Usually, their values are within normal limits or only mildly elevated.

A **cholestatic pattern of elevation** (elevated alkaline phosphatase and bilirubin, with normal or only slightly elevated alanine and aspartate aminotransferases) is found in patients with an inflammatory mass in the pancreatic head and in those with autoimmune sclerosing cholangitis. In one series,⁴ pancreatic enzymes were elevated in only 3 (13%) of 17 cases, while cholestasis was present in 16 (94%).

Gamma globulin, total IgG, and IgG4 are commonly elevated in autoimmune pancreatitis. Serum IgG4 is considered the most sensitive and specific marker and is elevated in 63% to 94% of patients with autoimmune pancreatitis.^{4,15-17} Several studies found the diagnostic accuracy, sensitivity, and specificity to be highest (> 90%) when a cut point of 135 mg/dL was used.^{17,18} A subsequent study¹⁵ revealed a sensitivity of 76% and a specificity of 93% using the same cut point. Recall that the IgG4 level in our patient was 380 mg/dL.

Autoantibodies that are elevated in autoimmune pancreatitis include antilactoferrin antibodies and anticarbonic anhydrase II antibodies.¹⁹ Both are “organ-specific”: the former are found in pancreatic acinar cells, and the latter are found in ductal cells. The sensitivity of both antibodies is greater than 50% in patients with autoimmune pancreatitis. However, they are not often measured, since testing for them is not widely available.^{20,21}

Antinuclear antibody and rheumatoid factor are also associated with autoimmune pancreatitis but are not very specific.

Radiographic findings

The most common radiographic feature is diffuse enlargement of the entire pancreas. The appearance of the gland is often described as “sausage-like,” a feature best seen with CT and magnetic resonance imaging (MRI).

TABLE 1

Characteristic findings of autoimmune pancreatitis

Clinical presentation

Predisposition for elderly men
Common presenting symptoms:
vague abdominal pain, weight loss, jaundice
Rarely seen with acute recurrent pancreatitis
Evidence of diabetes mellitus is frequently observed

Laboratory data

Increased levels of serum gamma globulin, total immunoglobulin G (IgG,) or IgG4
Hepatobiliary enzymes are frequently increased, pancreatic enzymes may be normal
Presence of autoantibodies

Pancreatobiliary imaging

Enlargement of the pancreas, diffuse or focal
Irregular narrowing of main pancreatic duct on endoscopic retrograde cholangiopancreatography
Calcifications and cysts are rare
Stenosis of the distal common bile duct
Sclerosing cholangitis is often mistaken for primary sclerosing cholangitis

Histopathologic findings

Intense lymphoplasmacytic infiltrate with notable IgG4 positivity
Storiform fibrosis of the pancreatic parenchyma
Obliterative phlebitis/venulitis on Movat histochemical vascular staining

Extrapancreatic associations

Sclerosing cholangitis similar to primary sclerosing cholangitis
Retroperitoneal fibrosis
Sclerosing sialadenitis
Mediastinal adenopathy
Interstitial nephritis
Occasional association with other autoimmune diseases

Treatment

Dramatic response to steroids

However, sometimes the pancreas is focally enlarged (ie, with an “inflammatory mass”) as in our patient (FIGURE 2). Delayed pancreatic enhancement on CT and MRI is due to inflammation, edema, and fibrosis.²²

A well-defined capsule-like rim surrounding the pancreas is another common feature.²³ This rim-enhancement is hypointense on T2 MRI, suggesting the presence of peripheral in-

TABLE 2

Diagnostic criteria for autoimmune pancreatitis worldwide

	MAYO CLINIC CRITERIA ^{10,11}	KOREAN CRITERIA ¹²	JAPANESE CRITERIA ¹³
I. Imaging criteria	Not essential Narrowing of main pancreatic duct on ERCP (typical) Pancreatic enlargement on CT, MRI, or ultrasonography (typical) Atrophy, calcification, or pancreatitis (atypical)	Essential Narrowing of main pancreatic duct on ERCP Pancreatic enlargement on CT, MRI, or ultrasonography	Essential Narrowing of main pancreatic duct on ERCP Pancreatic enlargement on CT, MRI, or ultrasonography
II. Laboratory criteria	IgG4	IgG or IgG4 Autoantibodies	Gamma globulin, IgG, or IgG4 Autoantibodies
III. Histologic criteria	Lymphoplasmacytic sclerosing pancreatitis IgG4+ cells	Lymphoplasmacytic sclerosing pancreatitis IgG4+ cells	Lymphoplasmacytic sclerosing pancreatitis
IV. Extrapancreatic involvement	IgG4+ cells Steroid response	IgG4+ cells Steroid response	Not included
V. Steroid response	Pancreatic lesion Extrapancreatic lesion	Pancreatic lesion Extrapancreatic lesion	Not included
Definite diagnosis	I (typical) + II I (atypical) + II + V II and/or IV (IgG4+ cells) + V	I + II I + III I + IV I + V	I + II I + III

ERCP = endoscopic retrograde cholangiopancreatography, CT = computed tomography, MRI = magnetic resonance imaging, IgG = immunoglobulin G

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flammation and fibrosis.

Calcifications and pseudocysts are rarely seen in autoimmune pancreatitis.

On ultrasonography, the involved pancreatic parenchyma appears hypoechoic, consistent with edema.

Endoscopic retrograde cholangiopancreatography

ERCP or magnetic resonance cholangiopancreatography may reveal segmental or diffuse narrowing of the main pancreatic duct.^{24,25} Bile-duct strictures may occur throughout the biliary tree.²³

Autoimmune pancreatitis with biliary involvement must be distinguished from primary sclerosing cholangitis because the former responds to corticosteroid treatment. Cholangiographic features in primary sclerosing cholangitis include band-like strictures and a beaded or “pruned-tree” appearance, while autoimmune pancreatitis more commonly produces long strictures with prestenotic dilatation.²⁶

ERCP allows temporary stents to be placed in obstructed segments of the biliary tree to open them up in the setting of acute cholangitis.



FIGURE 2. Dual-phase helical computed tomography shows focal enlargement of the pancreatic tail (arrow) in a patient with autoimmune pancreatitis.

Biopsy guided by endoscopic ultrasonography

Some have proposed using endoscopic ultrasonography to guide biopsy in cases of suspected autoimmune pancreatitis.^{27,28}

Fine-needle aspiration biopsy, guided by endoscopic ultrasonography, is frequently used to rule out adenocarcinoma. However, its yield for cancer is not perfect (about 70%–90%), so a negative biopsy does not rule out cancer. Further, autoimmune pancreatitis is rare, so a patient with a negative finding on fine-needle aspiration biopsy is still more likely to have cancer than autoimmune pancreatitis. In this case, the negative study should be combined with other information (eg, IgG4) to decide whether empiric treatment should be given.

Core biopsy, also guided by endoscopic ultrasonography, collects a greater amount of tissue for analysis and may allow the histologic diagnosis of autoimmune pancreatitis, but it carries a greater risk of bleeding. Also, its yield may be lower than initially thought. In one series, only 26% of ultrasonographically guided core samples from patients with confirmed autoimmune pancreatitis had diagnostic histologic features.²⁹

New immunohistologic techniques are being developed to increase the yield from cytologic and tissue specimens.

Histopathologic findings

On gross examination, the pancreas is firm and enlarged with gray-yellow discoloration.^{1,23,30}

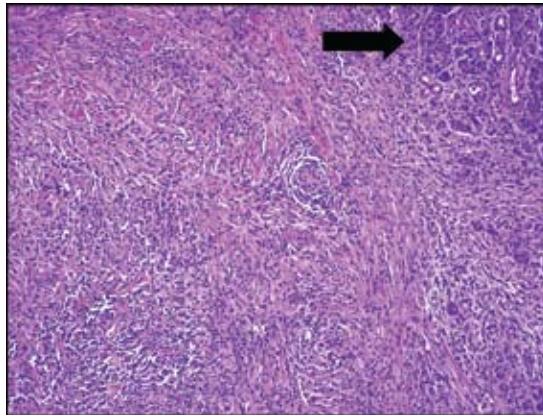


FIGURE 3. Autoimmune pancreatitis with intense and destructive fibroinflammatory replacement of normal pancreatic parenchyma. A focal atrophic lobule of residual acinar tissue can be seen in the upper right-hand corner (arrow).

The typical lobular architecture is disturbed by diffuse fibrosis (**FIGURE 3**). In localized disease, the inflammatory mass is most often in the head of the pancreas. Our patient had features of fibrosis on gross examination during surgery, but he also had a focal inflammatory mass in the pancreatic head.

Histologic evaluation remains the gold standard for diagnosis. The histologic diagnosis can be made in patients who have any or all of the following three most common histologic features of autoimmune pancreatitis^{10,23,31–33}:

- Parenchymal and often periductal lymphoplasmacytic infiltration, which is typically florid in intensity
- Storiform fibrosis
- Obliterative phlebitis.

The histologic findings in our patient included lymphoplasmacytic infiltration and obliterative phlebitis, which were essential to establishing the diagnosis. In a series of 53 patients, parenchymal inflammation with periductal lymphoplasmacytic accentuation was found in all of them.³³

Infiltration. The lymphocytic response is dominated by CD4⁺ and CD8⁺ T lymphocytes. Plasma cells are abundant (> 10 per high-power field) and are positive for IgG4 on immunostaining (**FIGURE 4**).^{31,34,35} In one cohort,¹¹ 15 (94%) of 16 patients with autoimmune pancreatitis had abundant IgG4-positive cells in tissue obtained by pancreatic core biopsy. IgG4-positive plasmacytes can also be seen in

About 11% of patients undergoing surgery for suspected pancreatic cancer have autoimmune pancreatitis

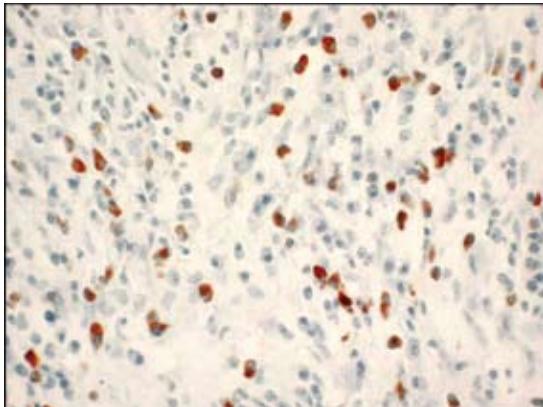


FIGURE 4. IgG4 immunohistochemistry in autoimmune pancreatitis showing more than 30 stained plasma cells (brown cells) per 400X high-power field (dimethylaminoazobenzene chromagen and hematoxylin counterstain).

involved extrapancreatic sites, such as the biliary tree, retroperitoneum, lymph nodes, and salivary glands.⁸

Biopsy of extrapancreatic sites, including the bile ducts and major duodenal papilla, may also facilitate the diagnosis.^{34,35} In a recent study,³⁴ 80% of autoimmune pancreatitis patients with pancreatic head involvement had significant numbers of IgG4-positive cells on biopsy of the major duodenal papilla. Biopsy of the periampullary duodenum may be a safer alternative to guided fine-needle aspiration or core biopsy.

In addition to lymphocytes, the inflammatory infiltrates in autoimmune pancreatitis may contain macrophages, mast cells, neutrophils, and eosinophils. Nonnecrotizing granulomas are occasionally seen, including periductal granulomas.

Fibrosis. Ductal luminal destruction can be seen in conjunction with fibrosis that thickens the duct wall and forms interlobular septa.³³ Fibrosis may also affect the acinar tissue and produce profound lobular atrophy. In severe cases, the fibrotic changes can encompass large areas, with myofibroblasts arranged in a storiform pattern resembling an inflammatory pseudotumor.³⁶

Phlebitis. The vascular changes in autoimmune pancreatitis have been underemphasized relative to the pancreatic parenchymal fibroinflammatory changes. Venulitis is seen mainly in small and medium-size pancreatic

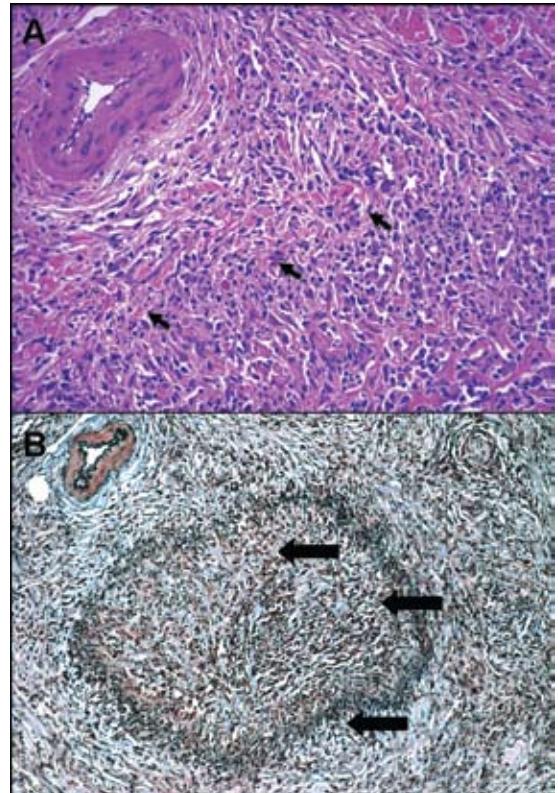


FIGURE 5. Obliterative venulitis. Panel A shows a hematoxylin and eosin stain, which poorly visualizes obliterative venulitis. The artery is easily found (arrows); however, the paired venule is poorly seen. The lack of visualization of the venule suggests that it is obliterated by the inflammatory process. Panel B shows a Movat pentachrome stain of the same area. This confirms the highly specific obliterative and lymphocytic venulitis of autoimmune pancreatitis (arrows). Fibrosis and lymphoplasmacytic infiltration destroy the vein wall and disrupt its elastin fibers, resulting in narrowing and even occlusion.

and peripancreatic veins. The inflammatory response and fibrosis disrupt the venous endothelium and often result in obliterative phlebitis.

The venous lesions can be notoriously difficult to see on hematoxylin and eosin staining alone, whereas the prominent elastin fiber disruption of vein walls in autoimmune pancreatitis is highlighted and made obvious on Movat staining (FIGURE 5).³¹ In a recent study,³¹ a Movat histochemical vascular stain had 100% sensitivity (in 15 cases of autoim-

Serum amylase and lipase are neither sensitive nor specific for autoimmune pancreatitis

immune pancreatitis) and 99% specificity (falsely identifying only 1 of 103 usual chronic pancreatitis, pancreatic cancer, and normal pancreatic controls) for lymphocytic and obliterative venulitis. Sixty-five percent to 100% of patients show obliterative phlebitis on histology enhanced with a Movat vascular stain.^{31,37} Movat vascular staining should be performed in conjunction with IgG4 immunohistochemistry for all suspected cases of autoimmune pancreatitis.³¹

However, Movat staining may not be available if an operative frozen section is being analyzed. In these cases, the venous lesions can be found by localizing the paired arteries, which are usually entirely normal and readily evident. If paired veins are not seen in this manner, a high level of suspicion should be raised for autoimmune pancreatitis with lymphocytic vein destruction.

■ CORTICOSTEROIDS ARE EFFECTIVE

Our patient's jaundice temporarily resolved after his biliary bypass operation. If the diagnosis had been made earlier, he could have been treated with corticosteroids.

Corticosteroids have been used to treat autoimmune pancreatitis, with great success. (However, autoimmune pancreatitis occasionally resolves spontaneously and stays in remission without corticosteroids.) A common regimen is oral prednisone 40 mg/day for 4 weeks and then tapered by 5 mg every 1 to 2 weeks. Patients who have a delayed response may receive long-term maintenance corticosteroid therapy (2.5–5 mg of oral prednisone).^{38–40}

The radiographic and laboratory abnormalities typically resolve promptly with steroid therapy. A radiographic response is seen as early as 2 to 3 weeks, with normalization occurring in 4 to 6 weeks.⁴⁰ Serum IgG4 levels decrease concurrently.³⁸

Between 36% and 60% of patients with diabetes and autoimmune pancreatitis have better insulin secretion and glycemic control once corticosteroid therapy is started.^{3,6,38,40} Fifty percent of patients with exocrine insufficiency have functional improvement after corticosteroid therapy.⁶

Extrapancreatic lesions also improve with therapy.^{40,41} Obstructive jaundice may require

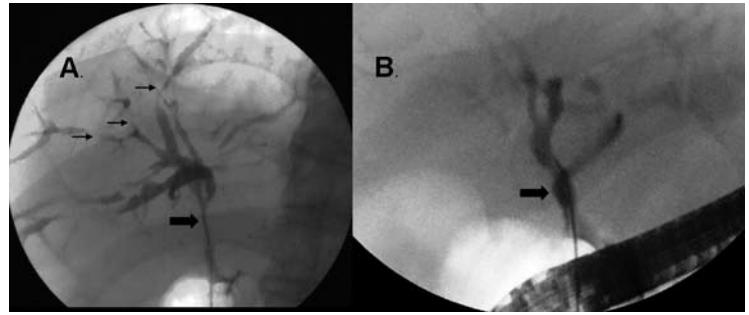


FIGURE 6. In panel A, endoscopic retrograde cholangiopancreatography (ERCP) prior to corticosteroid therapy shows a high-grade hilar stricture (large arrow) and intrahepatic strictures (small arrows). In panel B, ERCP 6 weeks after corticosteroid therapy shows resolution of the hilar stricture (arrows) and marked improvement in the intrahepatic strictures.

endoscopic placement of a temporary biliary stent, but after a few weeks of steroid therapy the stent can usually be removed.

The decision to treat with corticosteroids is usually based on symptoms, imaging features (stricture or mass), a low suspicion of cancer (eg, negative biopsy), and an elevated IgG4. A histologic diagnosis of autoimmune pancreatitis is usually not available or required but may be sought through endoscopic ultrasonography-guided core biopsy or laparoscopic biopsy if the diagnosis is in doubt.

Another reasonable approach is an empiric trial of corticosteroids, reassessing the symptoms and repeating the imaging tests after 1 to 2 months. In fact, a response to corticosteroids is a component of most diagnostic criteria (TABLE 2).

Recurrence rates range from 6% to 32%.^{4,33,39,42,43} Patients who relapse after initial corticosteroid therapy may be treated again with prednisone in high doses (40 mg/day).^{38,41} Immunomodulatory therapy has been used successfully to treat relapsed disease in a single reported series: seven patients received either azathioprine (Imuran) 2 mg/kg daily or mycophenolate mofetil (CellCept) 750 mg twice daily, and all remained in complete remission at a median follow-up of 6 months with no adverse events.⁴⁴

In cases that fail to respond to corticosteroids, the diagnosis of autoimmune pancreatitis should be re-evaluated and surgery should be considered to look for cancer.

A negative fine-needle aspiration biopsy does not rule out cancer

■ CASE CONTINUED

Our patient felt well at his 2-month follow-up visit. However, his serum alkaline phosphatase had increased to 649 U/L, and his serum IgG4 had increased to 980 mg/dL.

ERCP repeated via the biliary-enteric anastomosis revealed a high-grade hilar stricture and diffuse intrahepatic strictures (FIGURE 6). Brush cytology from the hilar stricture was negative for malignant cells. Prednisone 40 mg once daily was started to treat presumed biliary involvement of autoim-

mune pancreatitis.

ERCP repeated 6 weeks later showed that the hilar stricture had completely resolved, and the intrahepatic strictures had markedly improved (FIGURE 6). His serum alkaline phosphatase level was now 73 U/L, and his serum IgG4 was 231 mg/dL.

Almost 2 years after starting corticosteroid therapy, the patient has remained in good control and the prednisone has been tapered off completely. His latest laboratory values are alkaline phosphatase 70 U/L and IgG4 46 mg/dL. ■

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An empiric trial of steroids is reasonable

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ADDRESS: Tyler Stevens, MD, Digestive Disease Institute, A31, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail stevens@ccf.org.



CME CALENDAR

2009

NOVEMBER

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 Cleveland Clinic
 Cleveland, OH

9TH ANNUAL MULTIDISCIPLINARY GENITOURINARY ONCOLOGY COURSE
 November 18
 Cleveland Clinic
 Cleveland, OH

UPDATE ON TREATMENT DECISIONS FOR GASTROINTESTINAL DISEASES, FEATURING:

- 30TH TURNBULL SYMPOSIUM
- 45TH GASTROENTEROLOGY UPDATE
- HEPATIC-PANCREATIC-BILIARY COURSE

November 19–20
 Cleveland Clinic
 Cleveland, OH

PULMONARY HYPERTENSION SUMMIT
 November 20–21
 Cleveland Clinic
 Cleveland, OH

DECEMBER

8TH ANNUAL LIVER UPDATE
 December 5
 Cleveland Clinic
 Administrative Campus
 Beachwood, OH

2010

FEBRUARY

21ST ANNUAL INTERNATIONAL COLORECTAL DISEASE SYMPOSIUM
 February 11–13
 Harbor Beach Marriott
 Fort Lauderdale, FL

DIASTOLOGY AND NEW ECHO TECHNOLOGIES SUMMIT
 February 24–27
 Hyatt Regency Bonaventure
 Conference Center & Spa
 Fort Lauderdale, FL

MARCH

12TH ANNUAL PAIN MANAGEMENT SYMPOSIUM
 March 6–10
 Loews Coronado Bay Resort & Spa
 Coronado Bay, CA

MAY

BONE SUMMIT 2010
 (Date, location to be announced)

SEPTEMBER

21ST CENTURY TREATMENT OF HEART FAILURE
 (Date, location to be announced)

OBESITY SUMMIT 2010
 (Date to be announced)
 Cleveland Clinic
 Cleveland, OH

OCTOBER

NEPHROLOGY UPDATE 2010
 October 7–9
 Renaissance Cleveland Hotel
 Cleveland, OH

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