

IgG4-related Sclerosing Disease: Autoimmune Pancreatitis and Extrapancreatic Manifestations¹

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CME FEATURE

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LEARNING OBJECTIVES FOR TEST 4

After completing this journal-based CME activity, participants will be able to:

- Identify the organs that may be involved by IgG4-related sclerosing disease.
- Describe the typical and atypical imaging findings of autoimmune pancreatitis and extrapancreatic manifestations of IgG4-related sclerosing disease.
- Discuss the importance of imaging for a timely diagnosis of IgG4-related sclerosing disease to prevent potentially unnecessary invasive procedures or complications.

TEACHING POINTS

See last page

Autoimmune pancreatitis is the pancreatic manifestation of IgG4-related sclerosing disease, which recently was recognized as a distinct disease entity. Numerous extrapancreatic organs, such as the bile ducts, gallbladder, kidneys, retroperitoneum, thyroid, salivary glands, lung, mediastinum, lymph nodes, and prostate may be involved, either synchronously or metachronously. Most cases of autoimmune pancreatitis are associated with elevated serum IgG4 levels; extensive IgG4-positive plasma cells; and infiltration of lymphocytes into various organs, which leads to fibrosis. There are several established diagnostic criteria systems that are used to diagnose autoimmune pancreatitis and that rely on a combination of imaging findings of the pancreas and other organs, serologic findings, pancreatic histologic findings, and response to corticosteroid therapy. It is important to recognize multiorgan involvement of IgG4-related sclerosing disease and be familiar with its clinical and imaging features because it demonstrates a favorable response to treatment.

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Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography, H-E = hematoxylin-eosin, MRCP = magnetic resonance cholangiopancreatography

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Introduction

Autoimmune pancreatitis is a distinct type of chronic pancreatitis and is characterized by abundant infiltration of IgG4-positive plasma cells and associated fibrosis that lead to organ dysfunction. Patients with autoimmune pancreatitis typically present with jaundice or abdominal discomfort; severe abdominal pain or acute pancreatitis is unusual. Current evidence, such as reversible improvement with corticosteroid therapy, strongly suggests an autoimmune cause for autoimmune pancreatitis; however, its exact pathophysiology remains speculative.

Kamisawa et al (1) proposed the concept of IgG4-related sclerosing disease and suggested that autoimmune pancreatitis is, in fact, a part of that disease spectrum. Laboratory values that may help in the diagnosis of this condition include elevated IgG and IgG4 serum levels and autoantibodies (eg, rheumatoid factor and antinuclear). **The extrapancreatic organs that may be involved include the bile ducts, gallbladder, kidneys, retroperitoneum, mesentery, thyroid, lacrimal glands and orbits, salivary glands, lymph nodes, lungs, gastrointestinal tract, and blood vessels (2–27).** Although autoimmune pancreatitis is present in most patients with IgG4-related sclerosing disease, the latter has been reported in patients with no pancreatic involvement (20,28).

Patients with IgG4-related sclerosing disease usually demonstrate a dramatic response to corticosteroid therapy, often within a few weeks, although spontaneous resolution may occur (3,29,30). To date, there is no consensus for the steroid therapy regimen or duration of treatment. Starting doses range from 30 to 40 mg of an oral corticosteroid (eg, prednisone) and typically are followed by a tapered dose of varying duration after 3–4 weeks. However, disease recurrence is common (occurring in 20%–40% of patients) after stopping steroid treatment or during the tapering period (31). Management of recurrent disease is controversial. Most clinicians administer a repeat course of corticosteroids with an immunomodulator such as azathioprine.

The recent increase in the number of cases of IgG4-related sclerosing disease and autoimmune pancreatitis probably represents an increase in awareness and diagnosis on the basis of serum markers and IgG4 immunostaining at biopsy rather than a rise in incidence. Imaging findings play a major role in the diagnosis of autoimmune pancreatitis, and an awareness of its extrapancreatic findings is critical for accurate diagnosis.

In this article, we discuss the diverse imaging findings of pancreatic and extrapancreatic

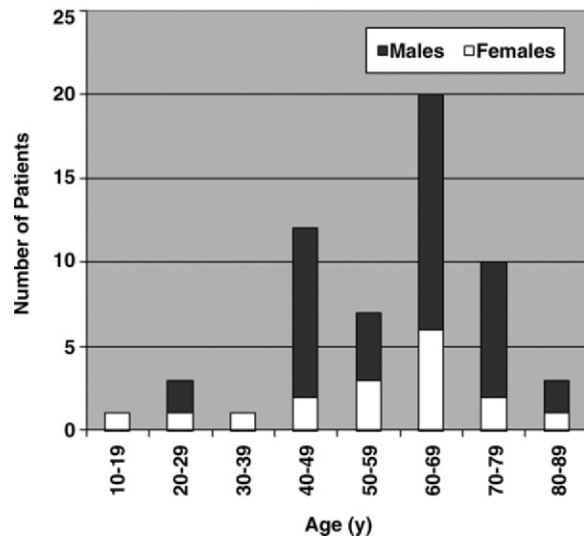


Figure 1. Graph shows the age distribution of the patients in our study with autoimmune pancreatitis.

Teaching Point

Extrapancreatic Involvement in 57 Patients with Autoimmune Pancreatitis and IgG4-related Sclerosing Disease

Involved Organ	No. of Cases	Frequency (%)
Biliary tree	44	77
Kidneys	20	35
Lymph nodes	19	33
Gallbladder	9	16
Salivary gland	8	14
Thyroid gland	7	12
Arteries	7	12
Retroperitoneum	5	9
Lungs	3	5
Mesentery	2	3
Orbits or lacrimal glands	2	3

involvement of IgG4-related sclerosing disease on the basis of our experience with 57 patients at our institutions during the past 9 years.

Patient Group

The retrospective chart review of the patients in this study was approved by our institutional research ethics board, and informed consent was waived. Between 2000 and 2009, 57 patients (mean age, 59 years; range, 18–85 years) received a diagnosis of autoimmune pancreatitis at our institutions, including 40 men (mean age, 62 years; range, 42–85 years) and 17 women (mean age, 60 years; range, 18–81 years) (Fig 1). All available images, including those from ultrasonography (US), computed tomography (CT), magnetic resonance

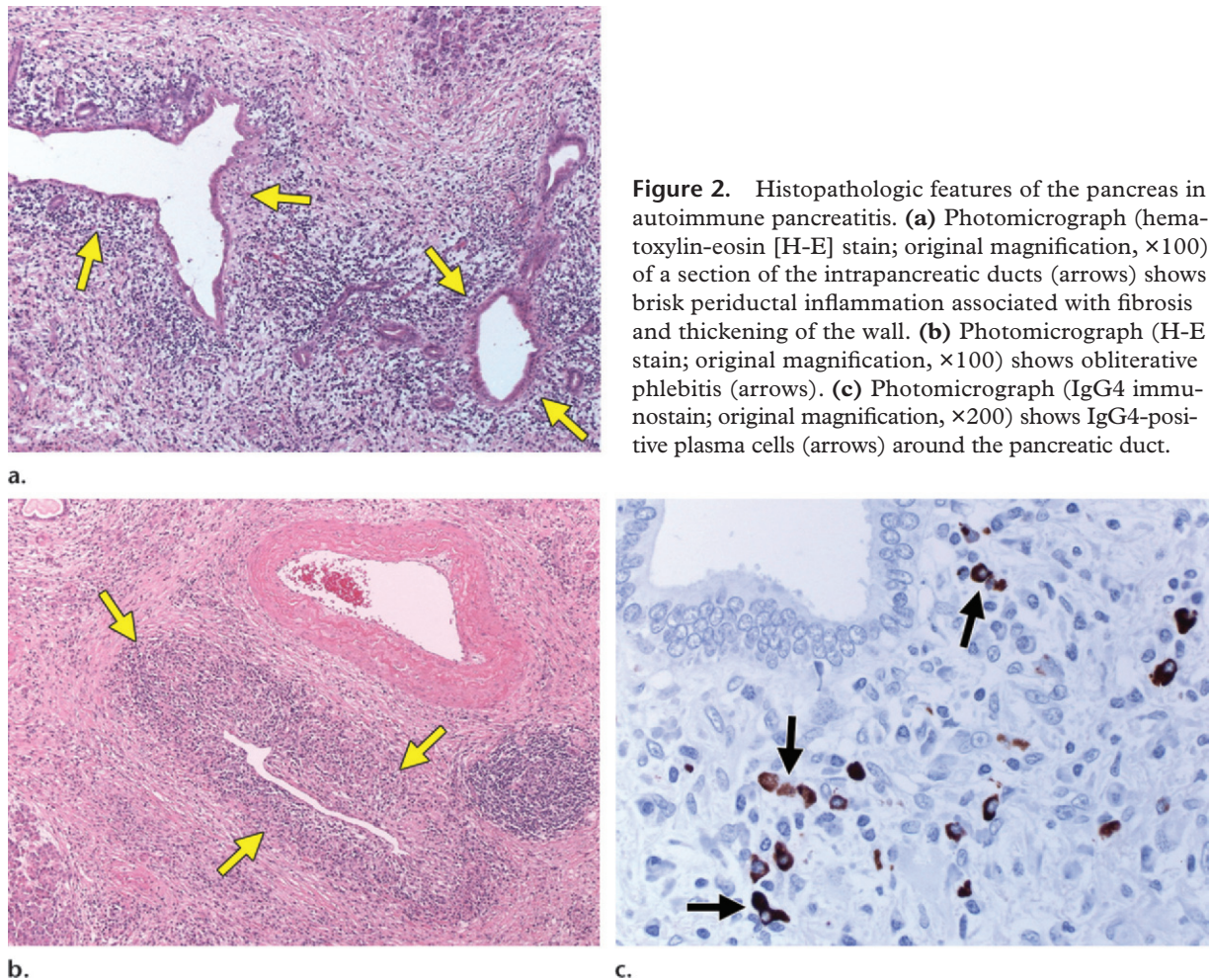


Figure 2. Histopathologic features of the pancreas in autoimmune pancreatitis. **(a)** Photomicrograph (hematoxylin-eosin [H-E] stain; original magnification, $\times 100$) of a section of the intrapancreatic ducts (arrows) shows brisk periductal inflammation associated with fibrosis and thickening of the wall. **(b)** Photomicrograph (H-E stain; original magnification, $\times 100$) shows obliterative phlebitis (arrows). **(c)** Photomicrograph (IgG4 immunostain; original magnification, $\times 200$) shows IgG4-positive plasma cells (arrows) around the pancreatic duct.

(MR) imaging, MR cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP), were retrospectively reviewed. Autoimmune pancreatitis was diagnosed on the basis of the diagnostic criteria proposed by Kim et al (32), which included a combination of the following radiologic, laboratory, clinical, and histologic findings: *(a)* enlargement of the pancreas and irregular segmental narrowing of the main pancreatic duct at imaging; *(b)* abnormally elevated serum IgG or IgG4 levels or the presence of autoantibodies; *(c)* characteristic histopathologic features; and *(d)* response to corticosteroid therapy. In all patients, finding *a* was present with at least one of the other findings.

The clinical symptoms included epigastric discomfort or pain in 33 patients (58%), jaundice in 31 patients (54%), weight loss in 29 patients (51%), and new-onset diabetes in 22 patients (38%). Only one patient had a history of excessive alcohol consumption. The most common organs involved, aside from the pancreas, were the biliary tree and kidneys (Table). The numbers of involved organs were as follows: one organ in five

patients, two organs in 18 patients, three organs in 21 patients, four organs in 10 patients, and five organs in three patients.

Autoimmune Pancreatitis

Autoimmune pancreatitis is characterized by periductal infiltration with IgG4-positive plasma cells, which leads to periductal and interlobular fibrosis (33) (Fig 2). Periductal fibrosis leads to diffuse narrowing of the pancreatic duct and acinar atrophy. Diagnostic criteria for autoimmune pancreatitis have been proposed by various research groups on the basis of several factors such as imaging, histologic and serologic findings, extrapancreatic involvement, and response to corticosteroid therapy. The criteria proposed by the Japanese Pancreas Society consist of radiologic, serologic, and histopathologic findings. According to this system, typical radiologic findings must be present with at least one serologic or histopathologic finding (34,35). In the criteria proposed by Kim et al (32), from Korea, response

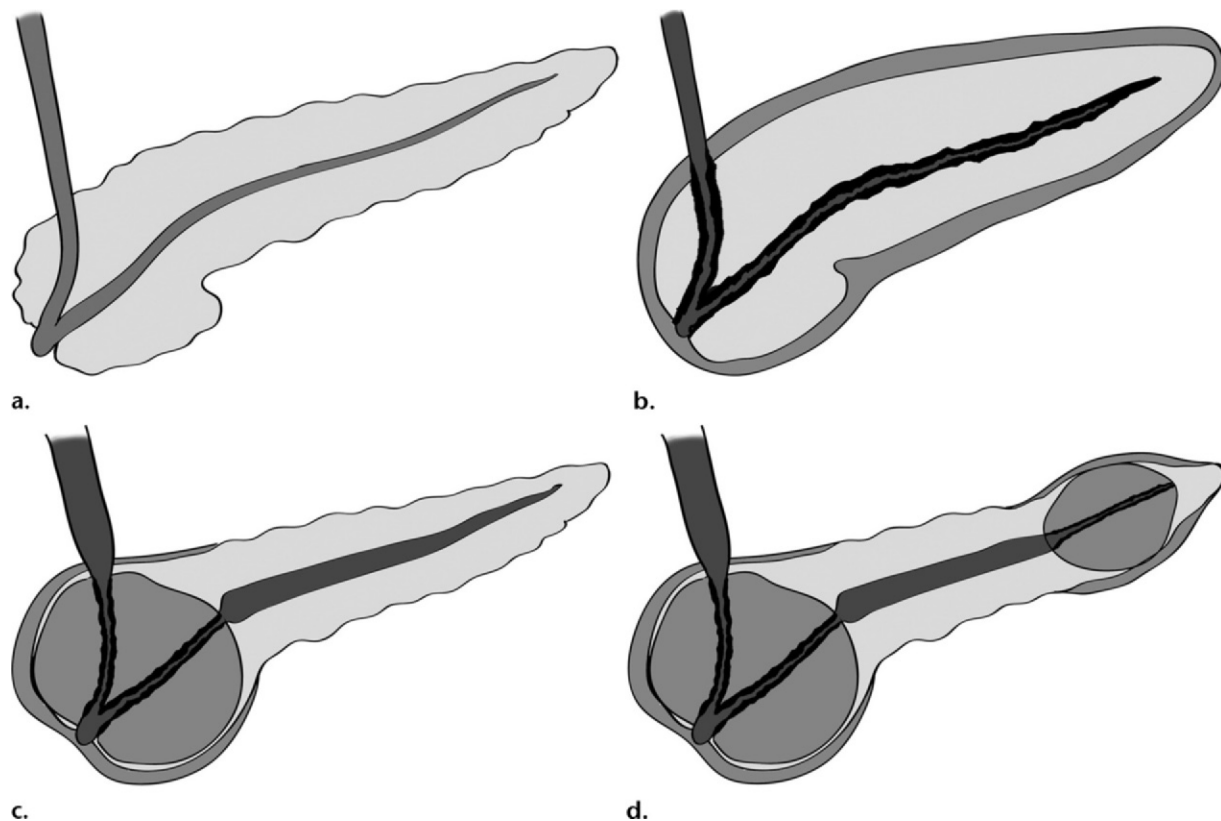


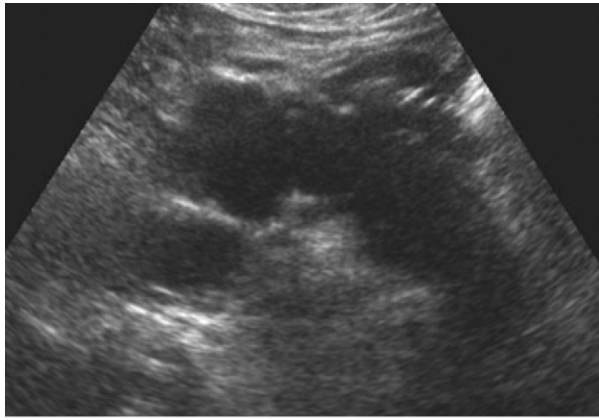
Figure 3. Different patterns of autoimmune pancreatitis. (a) Drawing shows the normal appearances of the pancreas, pancreatic duct, and distal common bile duct. (b) Drawing shows diffuse autoimmune pancreatitis, which demonstrates irregular narrowing of the entire pancreatic duct, with a halo around the gland and focal, irregular narrowing of the intrapancreatic portion of the common bile duct. (c) Drawing shows focal autoimmune pancreatitis, which affects the head of the pancreas, with localized stenosis of the pancreatic duct and intrapancreatic portion of the common bile duct and mild upstream pancreatic duct and bile duct dilatation. (d) Drawing shows multifocal autoimmune pancreatitis, which demonstrates segmental narrowing in the affected segments of the pancreatic and bile ducts.

to steroid therapy is included, in addition to the three items in the Japanese criteria, and a diagnosis of autoimmune pancreatitis is made when typical radiologic findings and any of the remaining three findings are present. In Mayo Clinic criteria, reported by Chari et al (36), a diagnosis of autoimmune pancreatitis is made in patients with one or more of the following findings: (a) histologic findings that are diagnostic for autoimmune pancreatitis, (b) characteristic CT and pancreatographic findings with elevated serum IgG4 levels, and (c) response to steroid therapy, which is indicative of a pancreatic or extrapancreatic manifestation of autoimmune pancreatitis. **Characteristic imaging findings play an important role in the diagnosis of autoimmune pancreatitis in most classification systems, although the applicability of other findings varies.**

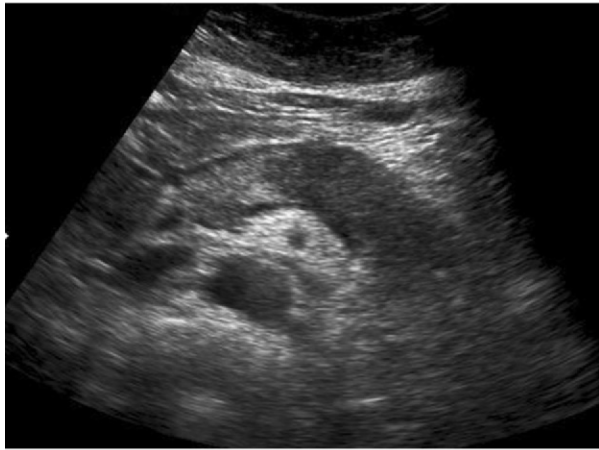
Teaching Point

Autoimmune pancreatitis accounts for 2%–11% of all cases of chronic pancreatitis (36). Men are affected at least twice as often as women, with a reported male-to-female ratio as high as 15:2 (37). The age at presentation ranges from 14 to 85 years, with the mean age over 60 years (38). Autoimmune pancreatitis typically manifests with fluctuating obstructive jaundice, vague abdominal pain, weight loss, steatorrhea, and diabetes. Diabetes (usually type II) is present in 43%–68% of patients, but it may improve with corticosteroid therapy (39). Autoimmune pancreatitis is an important mimic of pancreatic carcinoma; 3%–9% of patients who undergo resection for a presumed carcinoma have autoimmune pancreatitis (40).

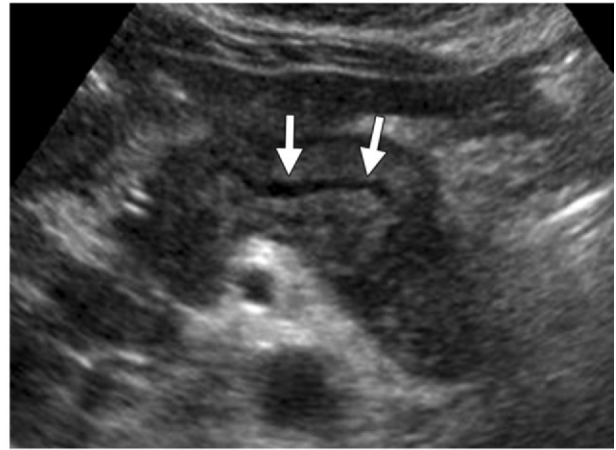
There are three recognized patterns of autoimmune pancreatitis: diffuse, focal, and multifocal (Figs 3, 4). Diffuse disease is the most common type, with a diffusely enlarged sausage-like pancreas and a sharp margin, loss of the lobular con-



a.



b.



c.



tour, and an absence of pancreatic clefts seen at imaging (5,41). Focal disease is less common than diffuse disease and manifests as a focal mass, often with involvement of the pancreatic head, an appearance that may mimic that of pancreatic malignancy. Focal disease tends to be relatively

Figure 4. US appearances of autoimmune pancreatitis in three patients. **(a)** US image shows a diffuse hypoechoic pancreas, an appearance indicative of the diffuse type of autoimmune pancreatitis. **(b)** US image shows the pancreatic body and tail, which appear hypoechoic, a finding indicative of the focal type of autoimmune pancreatitis. **(c)** US image shows multifocal hypoechoic areas in the pancreatic head and tail, a finding indicative of the multifocal type of autoimmune pancreatitis. Note the prominence of the pancreatic duct (arrows) between the two diseased segments.

Figure 5. Autoimmune pancreatitis with sparing of the ventral pancreas in a 60-year-old woman. Coronal contrast-enhanced CT image shows a diffusely hypoattenuating pancreas. The ventral pancreas (arrow) is spared, and there is no biliary dilatation.

well demarcated, and, when present, upstream dilatation of the main pancreatic duct is typically milder than in patients with pancreatic carcinoma (42). In some patients with focal autoimmune pancreatitis, only the dorsal pancreas or pancreatic tail is involved; such patients do not demonstrate obstructive jaundice (Fig 5) (43). Multifocal involvement also may be present (Fig 4c).

In patients with autoimmune pancreatitis, the affected area of the pancreas typically appears hypoechoic at US (Fig 4), hypoattenuating at CT, mildly hyperintense at T2-weighted MR imaging, and hypointense at T1-weighted MR

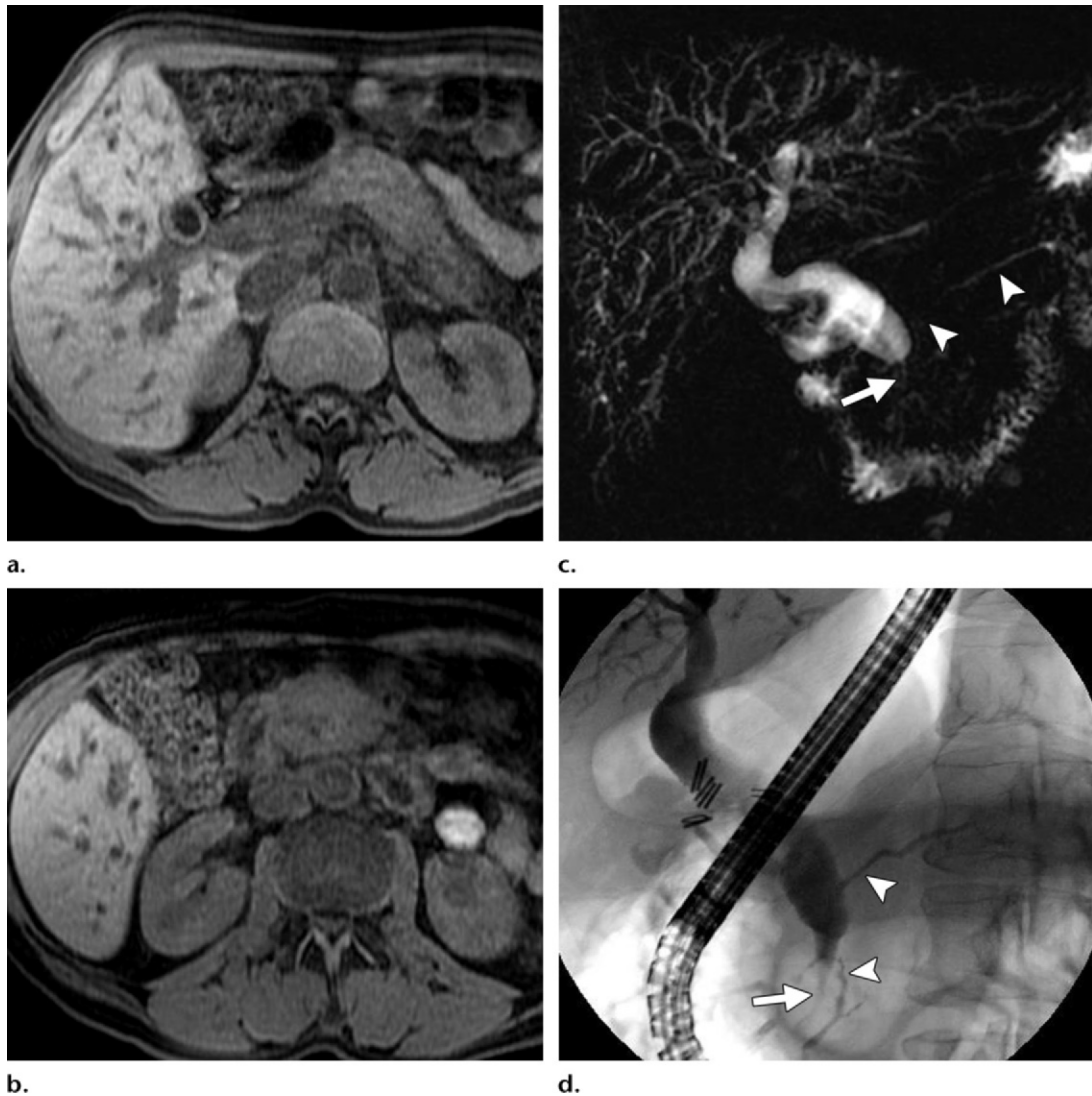
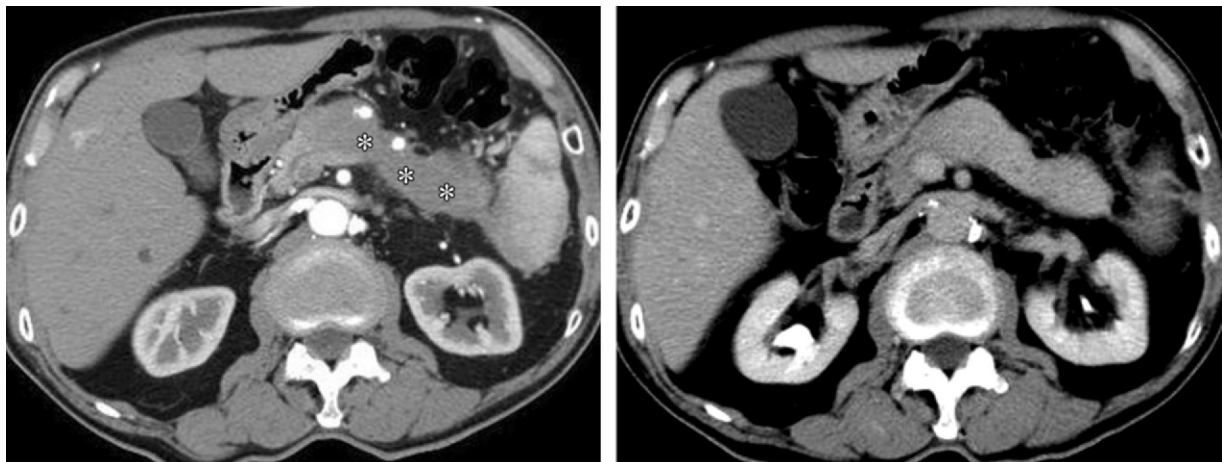


Figure 6. Diffuse autoimmune pancreatitis in a 65-year-old man. **(a, b)** T1-weighted MR images (**a** obtained at a higher level than **b**) show mild enlargement of the pancreas, which is diffusely hypointense. **(c)** MRCP image shows narrowing of the intrapancreatic segment of the common bile duct (arrow) and dilatation of the upstream bile ducts. The main pancreatic duct (arrowheads), which is located in the pancreatic head, is not clearly visualized, a result of narrowing. **(d)** ERCP image clearly shows irregular narrowing of the main pancreatic duct (arrowheads) and the intrapancreatic segment of the common bile duct (arrow).

imaging (Fig 6). At contrast-enhanced CT and MR imaging, decreased enhancement often is seen in the early phase, and moderate delayed enhancement is seen in the late phase, a finding likely due to fibrosis (Figs 7, 8) (44,45). The

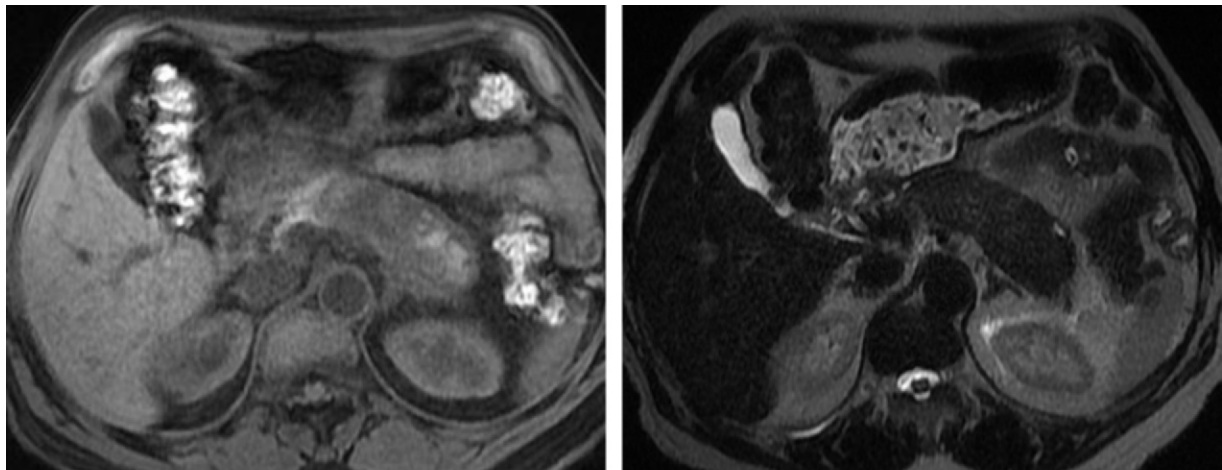
presence of a capsule-like rim or “halo” is common in patients with autoimmune pancreatitis and is believed to represent fluid, phlegmon, or fibrous tissue (Figs 8, 9) (5,41,45). When the pancreatic head is involved, narrowing of the intrapancreatic portion of the common bile duct typically is seen (Figs 6, 10).



a.

b.

Figure 7. Autoimmune pancreatitis involving the pancreatic body and tail in an 85-year-old man. **(a)** Arterial-phase CT image shows the affected pancreatic parenchyma (*), which appears hypoattenuating. **(b)** On a delayed-phase CT image, the affected pancreatic parenchyma appears hyperattenuating relative to the normal pancreas.



a.

b.



c.

Figure 8. Diffuse autoimmune pancreatitis in a 79-year-old man. **(a)** T1-weighted MR image shows a heterogeneously hypointense pancreas. **(b)** T2-weighted MR image shows the pancreas, which is diffusely hypointense. **(c)** Contrast-enhanced T1-weighted MR image, obtained in the portal venous phase, shows a hypointense halo (arrows) surrounding the pancreas.

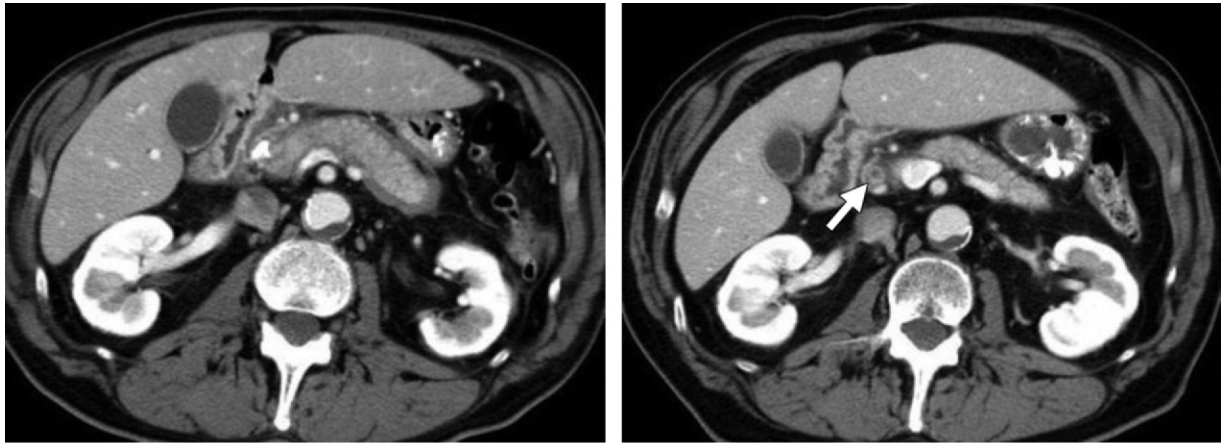


Figure 9. Diffuse autoimmune pancreatitis in a 75-year-old man. **(a)** Contrast-enhanced CT image shows a mildly heterogeneous pancreas surrounded by a hypoattenuating halo. **(b)** Follow-up CT image obtained 8 months later, after steroid treatment, shows the pancreas, which appears mildly atrophic with no halo. Thickening and enhancement of the common bile duct (arrow) are seen.

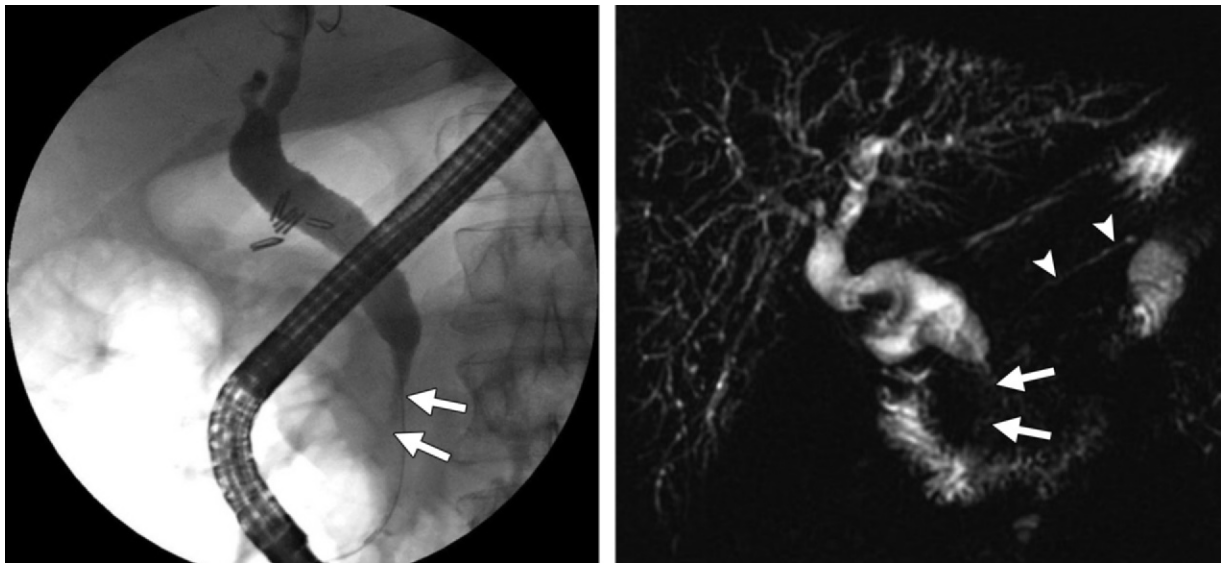
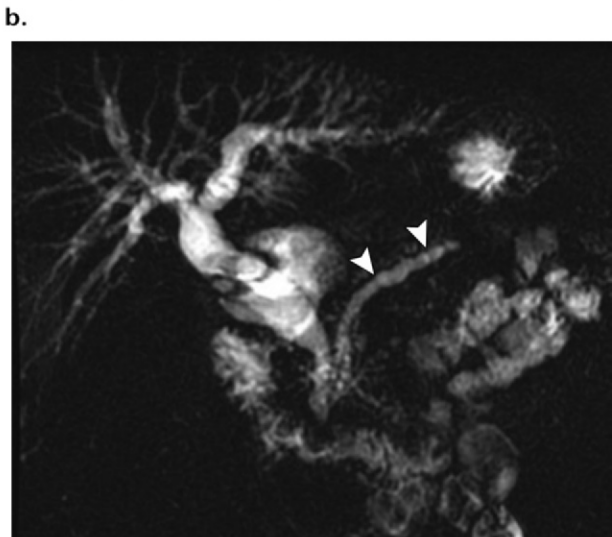


Figure 10. Narrowing of the common bile duct in a 61-year-old man with autoimmune pancreatitis. **(a)** ERCP image shows focal narrowing of the distal common bile duct (arrows). **(b)** MRCP image shows focal narrowing of the intrapancreatic portion of the distal common bile duct (arrows). Diffuse narrowing of the main pancreatic duct (arrowheads) also is seen. **(c)** MRCP image obtained 3 years later, after steroid therapy, shows that the narrowing seen in the common bile duct has improved, with development of diffuse dilatation of the main pancreatic duct (arrowheads).



c.

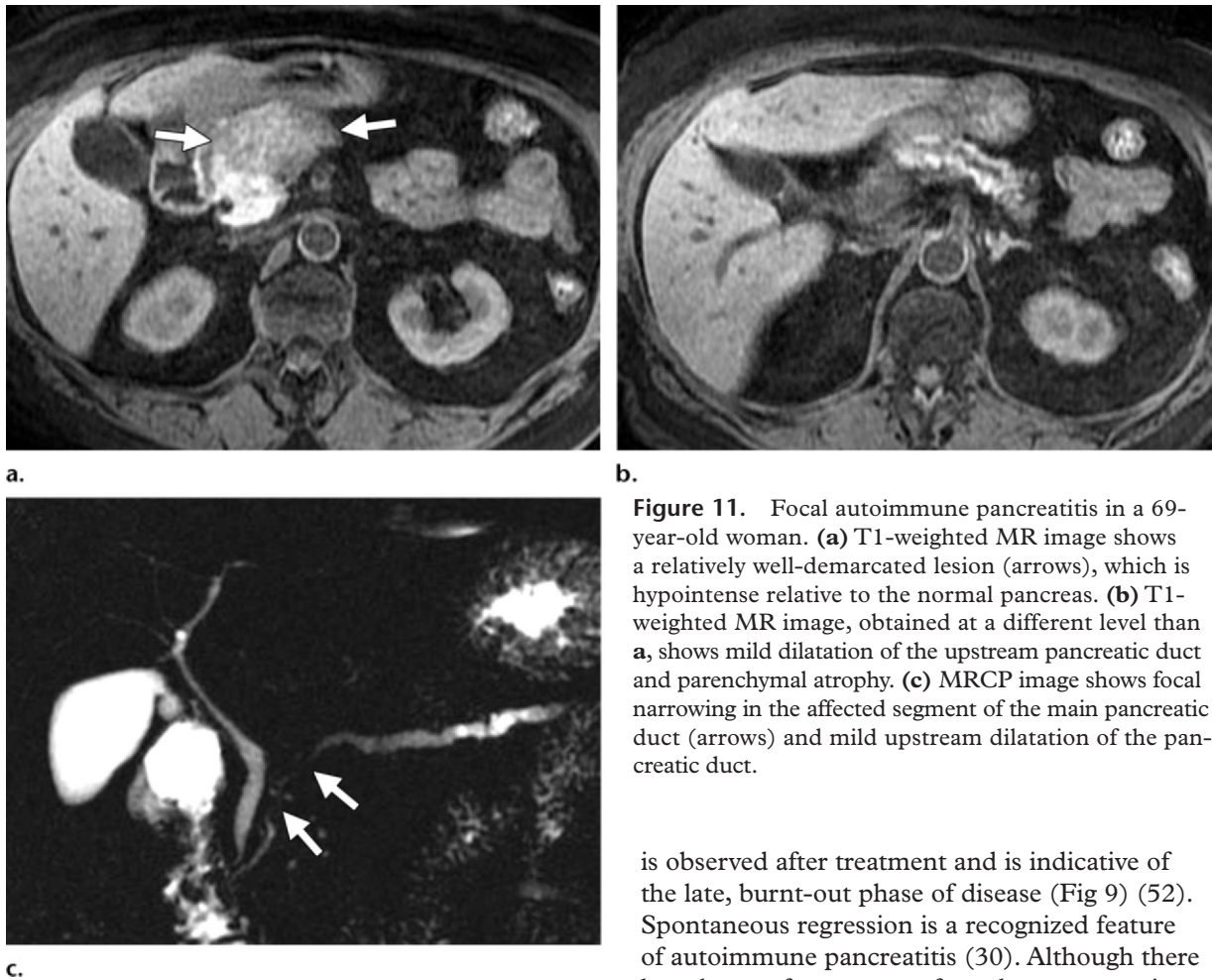


Figure 11. Focal autoimmune pancreatitis in a 69-year-old woman. **(a)** T1-weighted MR image shows a relatively well-demarcated lesion (arrows), which is hypointense relative to the normal pancreas. **(b)** T1-weighted MR image, obtained at a different level than **a**, shows mild dilatation of the upstream pancreatic duct and parenchymal atrophy. **(c)** MRCP image shows focal narrowing in the affected segment of the main pancreatic duct (arrows) and mild upstream dilatation of the pancreatic duct.

The main pancreatic duct typically is narrow and irregular in the segments affected by autoimmune pancreatitis, a finding that may be demonstrated at ERCP or MRCP (Figs 6, 10, 11) (30,41,46–48). Occasionally, peripancreatic lymphadenopathy is seen; however, pancreatic calcifications and pseudocyst formation, which are frequently seen in patients with chronic alcoholic pancreatitis, are rare (49,50). Severe peripancreatic stranding, a typical feature of acute pancreatitis, also is rare (5,45). Narrowing of peripancreatic veins is common (41,51). Features that favor a diagnosis of autoimmune pancreatitis over acute pancreatitis include minimal or no peripancreatic stranding, a lack of peripancreatic fat necrosis, and presence of a peripancreatic halo. The diffuse form of autoimmune pancreatitis may be mistaken for acute pancreatitis on images (50).

After corticosteroid therapy, pancreatic function and morphologic characteristics usually return to normal within 4–6 weeks, and narrowing of the pancreatic duct resolves. However, pancreatic atrophy of the affected segments often

is observed after treatment and is indicative of the late, burnt-out phase of disease (Fig 9) (52). Spontaneous regression is a recognized feature of autoimmune pancreatitis (30). Although there have been a few reports of synchronous autoimmune pancreatitis and pancreatic ductal adenocarcinoma, there are no data to support the idea that autoimmune pancreatitis is a predisposing factor for pancreatic malignancy (53,54).

In our study of 57 patients with autoimmune pancreatitis, 25 (44%) had diffuse disease, 28 (49%) had focal disease, and 4 (7%) had multifocal disease. A hypointense halo with delayed enhancement surrounding the affected pancreatic segments was seen in 32 patients (56%). Narrowing of the pancreatic duct in the affected pancreatic segments was demonstrated in all patients with autoimmune pancreatitis. Although no pancreatic calcifications were present in any patients, cystic lesions were present in seven patients. Two patients had mild ascites. Pancreatic atrophy was seen in 30 patients (53%) at follow-up imaging, 15 (50%) of whom underwent oral steroid therapy. One patient had synchronous autoimmune pancreatitis and ductal adenocarcinoma of the pancreas, and three patients had recurrent autoimmune pancreatitis.

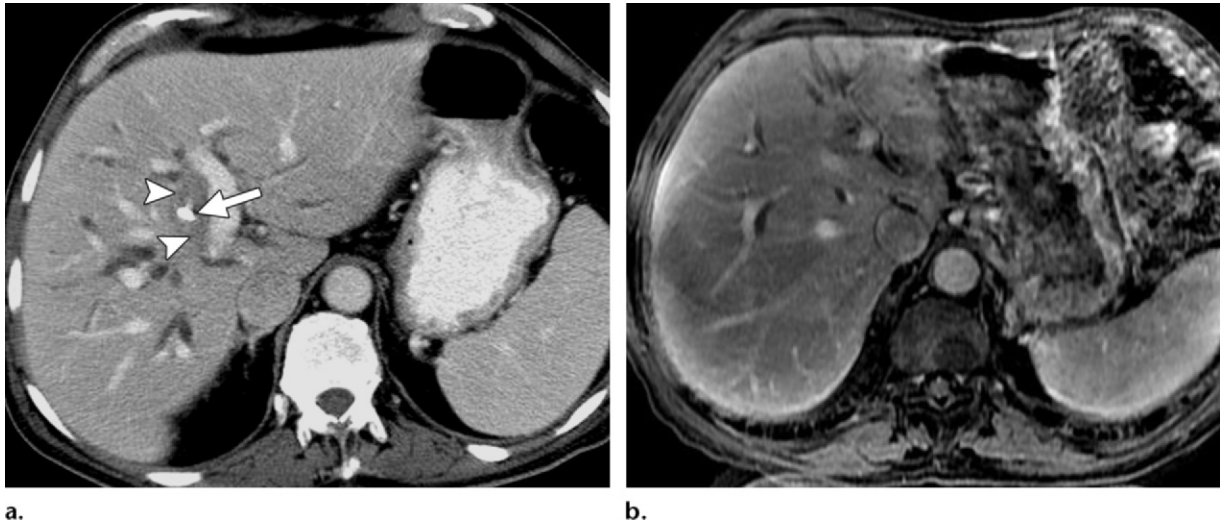


Figure 12. Biliary cirrhosis in a 72-year-old man with autoimmune pancreatitis. **(a)** Contrast-enhanced CT image, obtained in the venous phase, shows biliary involvement with autoimmune pancreatitis, which appears as diffuse thickening of the bile duct at its confluence with the hepatic hilum (arrowheads) with mild intrahepatic biliary dilatation. An endoscopic biliary stent (arrow) also is seen. **(b)** Contrast-enhanced T1-weighted MR image obtained 8 years later (the patient did not undergo treatment) shows atrophy of the left lobe of the liver. Histologic analysis of a specimen from the right lobe of the liver demonstrated grade III fibrosis.

Extrapancreatic IgG4-related Disease

Biliary Disease

IgG4-related sclerosing cholangitis is present in as many as 88% of patients with autoimmune pancreatitis, and, aside from the pancreas, the bile ducts are the most common organ involved with IgG4-related sclerosing disease. However, biliary disease may occur in patients with no pancreatic involvement (4,51). In patients with IgG4-related sclerosing cholangitis, the affected segments of the biliary tree demonstrate thickening, stenosis, irregularity, and contrast enhancement. The most commonly involved segment is the intrapancreatic segment of the common bile duct, which may lead to upstream biliary dilatation and obstructive jaundice (Figs 6, 10) (49). Multifocal intrahepatic biliary strictures may occur, but they are less common than typical primary sclerosing cholangitis (55). Without treatment, IgG4-related sclerosing cholangitis may be self-limited, or it may progress and lead to biliary cirrhosis (Fig 12).

Because the imaging appearances of primary sclerosing cholangitis and IgG4-related sclerosing cholangitis overlap, differentiating between the two conditions may be difficult. Clinically, primary sclerosing cholangitis tends to occur in younger patients (30–40 years old), and those with the disease usually are less symptomatic than those with IgG4-related sclerosing cholangitis early in the course of disease, with disease progression developing over a period of years. Patients with IgG4-related sclerosing cholangitis have a more acute presentation and a shorter duration of symptoms, and symptoms, imaging, and laboratory abnormalities often resolve with treatment. At ERCP, multifocal, short, bandlike strictures; a beaded or pruned-tree appearance; and diverticulum-like lesions involving the intra- or extrahepatic bile ducts, with alternating normal or slightly dilated segments, are characteristic of primary sclerosing cholangitis. In patients with IgG4-related sclerosing cholangitis, long and continuous strictures typically are seen, often with prestenotic dilatation. Isolated strictures of the distal common bile duct also are common (56). At cross-sectional imaging, a symmetrical, circumferential thick rind of tissue that encases

Teaching
Point

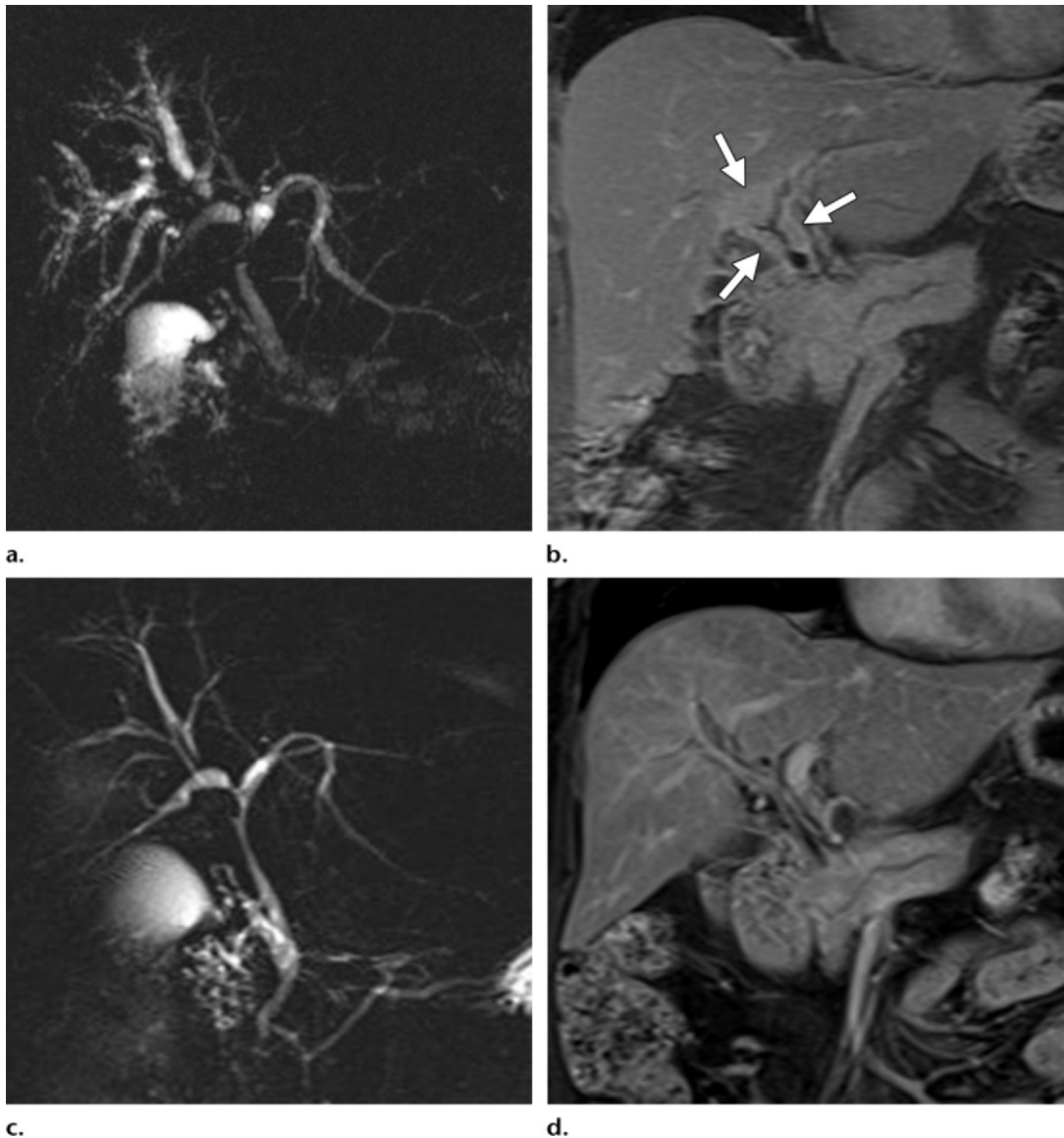


Figure 13. Biliary involvement in a 66-year-old woman with autoimmune pancreatitis. **(a)** MRCP image shows multiple strictures in the intrahepatic bile duct and a single stricture in the proximal common hepatic duct. **(b)** Coronal contrast-enhanced T1-weighted MR image, obtained in the delayed phase, shows marked soft-tissue thickening and enhancement of the confluence of the hilar bile duct and the common hepatic duct (arrows). **(c)** Follow-up MRCP image obtained 2 years later, after steroid therapy, shows the biliary strictures and dilatation, which demonstrate marked improvement. **(d)** Coronal contrast-enhanced T1-weighted MR image shows dramatic reduction in the thickening of the bile duct wall.

the affected duct is indicative of IgG4-related sclerosing cholangitis, although circumferential thickening of the involved bile ducts may be present to a milder degree in patients with primary sclerosing cholangitis or infectious cholangitis

(Fig 13). Finally, extrabiliary disease, especially involvement of the pancreas or kidneys, is highly suggestive of IgG4-related sclerosing cholangitis.

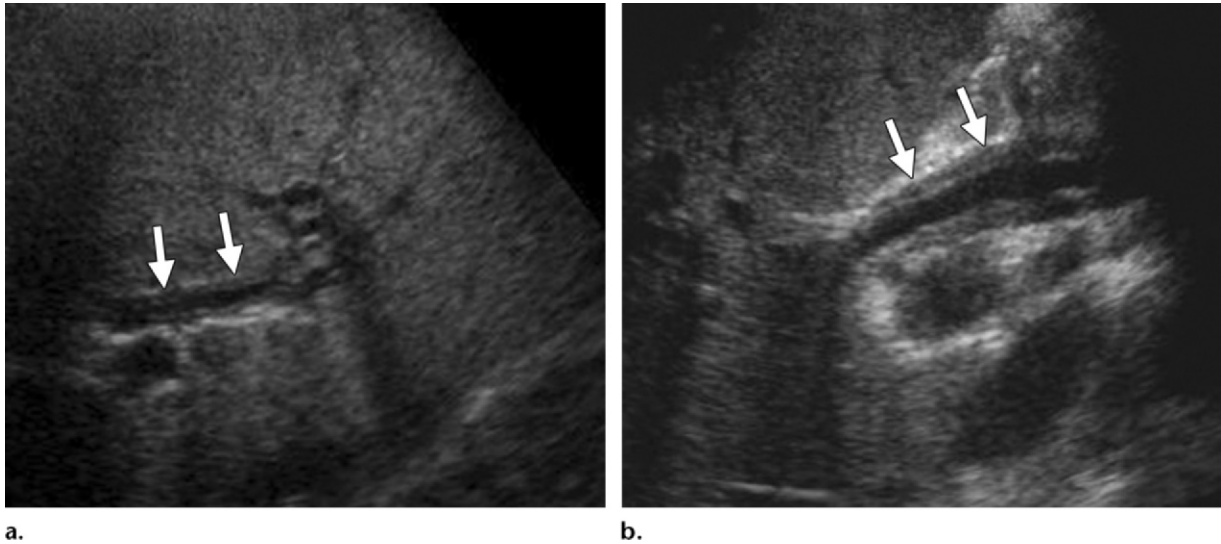


Figure 14. Biliary involvement in a 56-year-old man with autoimmune pancreatitis. **(a)** Transverse US image shows concentric thickening of the left hepatic duct (arrows). **(b)** Sagittal US image shows diffuse thickening of the common bile duct (arrows).

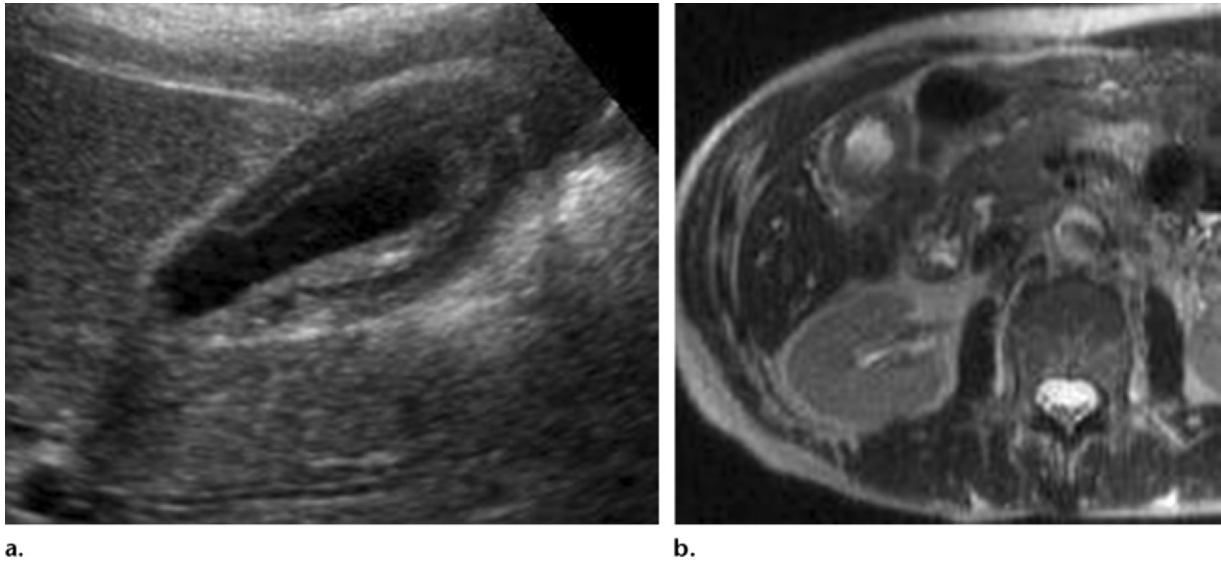
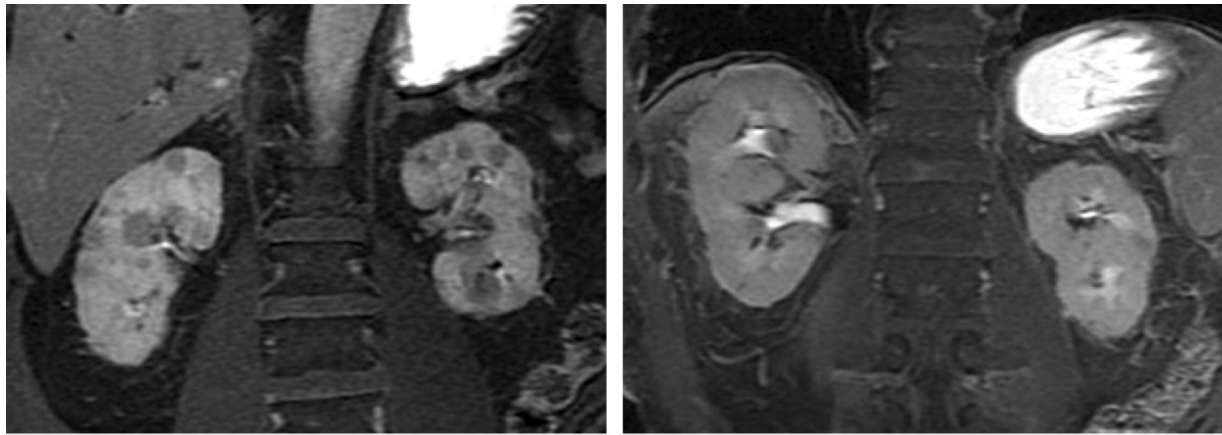


Figure 15. Gallbladder involvement in an 83-year-old man. **(a)** Sagittal US image shows marked thickening of the gallbladder wall, which appears hypoechoic. **(b)** At T2-weighted MR imaging, the thickened gallbladder demonstrates diffuse hypointensity.

At CT, biliary disease appears as focal or diffuse thickening of the bile duct walls, which also demonstrate enhancement (57). Biliary involvement is best depicted at MRCP or ERCP and demonstrates a favorable, and often dramatic, response to corticosteroid therapy (Fig 13) (56,58). However, relapses may occur, even while patients are undergoing maintenance corticosteroid therapy. When a hepatic hilar biliary stricture is present, especially in the presence of an associated soft-tissue mass,

its appearance resembles that of cholangiocarcinoma (Fig 13) (59).

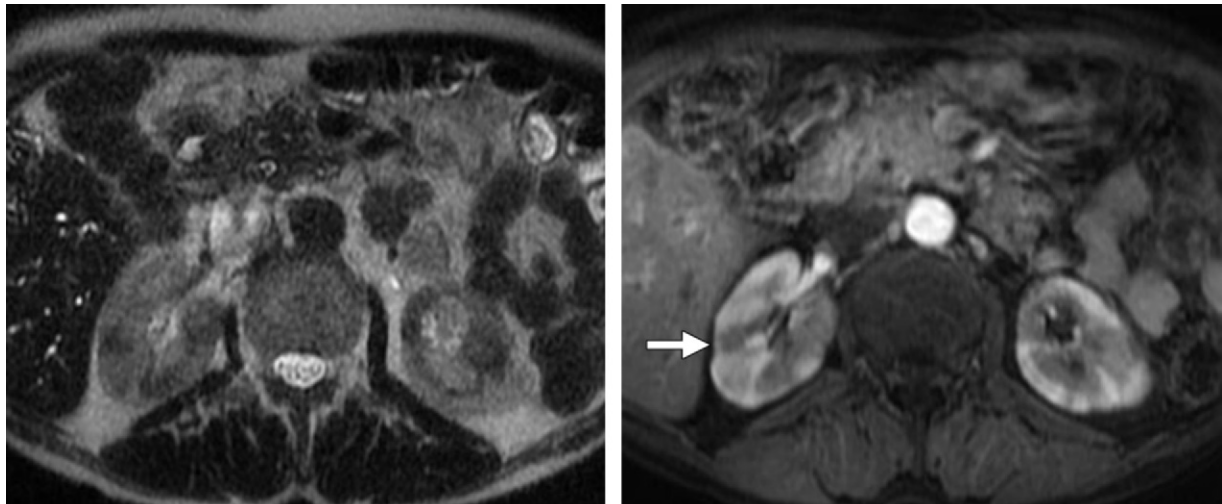
In our study, sclerosing cholangitis was present in 44 patients (77%) with autoimmune pancreatitis. Of those, only the extrahepatic bile duct was involved in 19 patients (43%), only the intrahepatic bile duct was involved in two patients (5%), and both the intra- and extrahepatic bile ducts were involved in 23 patients (52%) (Fig 14). In nine patients (20%), only the intrapancreatic portion of the common bile duct was involved. Placement of a temporary endoscopic biliary



a.

b.

Figure 16. Renal involvement in a 74-year-old man. **(a)** Coronal T2-weighted MR image shows multiple bilateral round, hypointense, cortical lesions in the kidneys. **(b)** Follow-up coronal T2-weighted MR image, obtained 1 year later, shows regression of the renal lesions. The patient did not undergo steroid therapy; however, right hemihepatectomy was performed for suspected cholangiocarcinoma, which turned out to be sclerosing cholangitis related to autoimmune pancreatitis, resulting in cranial migration of the right kidney.



a.

b.

Figure 17. Renal involvement in a 61-year-old man. **(a)** Axial T2-weighted MR image shows multiple bilateral wedge-shaped hypointense cortical lesions. **(b)** Axial contrast-enhanced T1-weighted MR image, obtained in the corticomedullary phase, shows the renal lesions (arrow), which are hypointense.

stent or percutaneous biliary drainage was performed in 26 patients (59%) to relieve jaundice.

Gallbladder involvement appears as diffuse wall thickening, a result of infiltration with IgG4-positive plasma cells and transmural fibrosis (29). The thickened gallbladder wall appears hypoechoic at US and hypointense at T2-weighted MR imaging and demonstrates substantial contrast enhancement that persists on delayed-phase images (Fig 15). Of the 57 patients in our study, gallbladder wall thickening, sometimes marked, with no associated cholelithiasis, was present in nine (16%). Wall thickening and enhancement

of the cystic duct were present in four patients (7%), all of whom had multifocal involvement of the biliary tract.

Renal Disease

Renal involvement is present in about one-third of patients with autoimmune pancreatitis (7,8). **There are four disease patterns: round or wedge-shaped renal cortical nodules, peripheral cortical lesions, masslike lesions, and renal pelvic involvement (Figs 16–19).** Renal cortical

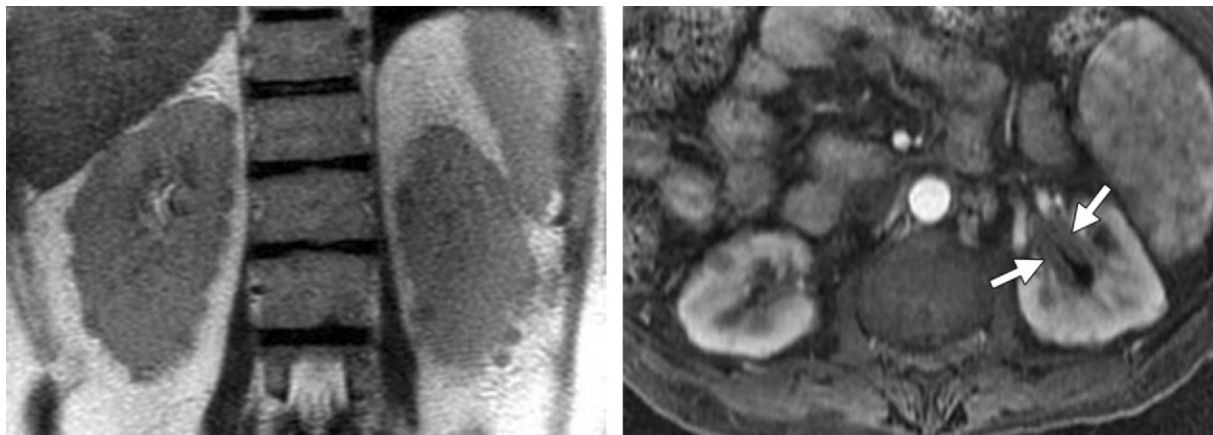


Figure 18. Renal involvement in a 61-year-old man. **(a)** Coronal T2-weighted MR image shows multiple bilateral hypointense cortical nodules in the periphery of the kidneys. **(b)** Transverse contrast-enhanced T1-weighted MR image, obtained in the corticomedullary phase, shows small bilateral hypointense nodules in the peripheral renal cortex and marked thickening of the left renal pelvis (arrows).

lesions usually are multiple and bilateral and are composed of lymphoplasmacytic infiltrate. When round or wedge-shaped nodules are present, the differential diagnosis includes pyelonephritis or metastases. Rarely, renal disease may manifest as a solitary lesion, which may mimic a neoplasm. At histologic analysis of the renal cortex, interstitial nephritis, which progresses to form scars, is seen. Nephritis may improve after corticosteroid therapy (8).

At CT, renal lesions typically are hypoattenuating on early-phase contrast material-enhanced images, with mild enhancement on delayed phase images (Fig 19). At MR imaging, renal lesions are iso- or hypointense on T1-weighted images and hypointense on T2-weighted images, and they demonstrate mild enhancement after administration of contrast material (Figs 16–18).

In our study, renal involvement was present in 20 patients (35%). Of these, 18 patients (90%) had bilateral lesions, and two (10%) had a unilateral tumorlike mass. Most renal lesions had progressed to cortical scars at follow-up evaluation, although some of the smaller lesions had disappeared completely. In one patient (5%), diffuse



Figure 19. Renal involvement and abdominal lymphadenopathy in a 46-year-old man. Contrast-enhanced CT image shows periportal lymphadenopathy (arrowheads). Bilateral hypoattenuating lesions also are seen in the kidneys (arrows), a finding indicative of renal involvement with autoimmune pancreatitis.

thickening of the renal pelvis was present in addition to the renal lesions (Fig 18). Eight patients (40%) had impaired renal function that did not require dialysis. Of these, five (63%) had bilateral renal cortical wedge-shaped lesions.

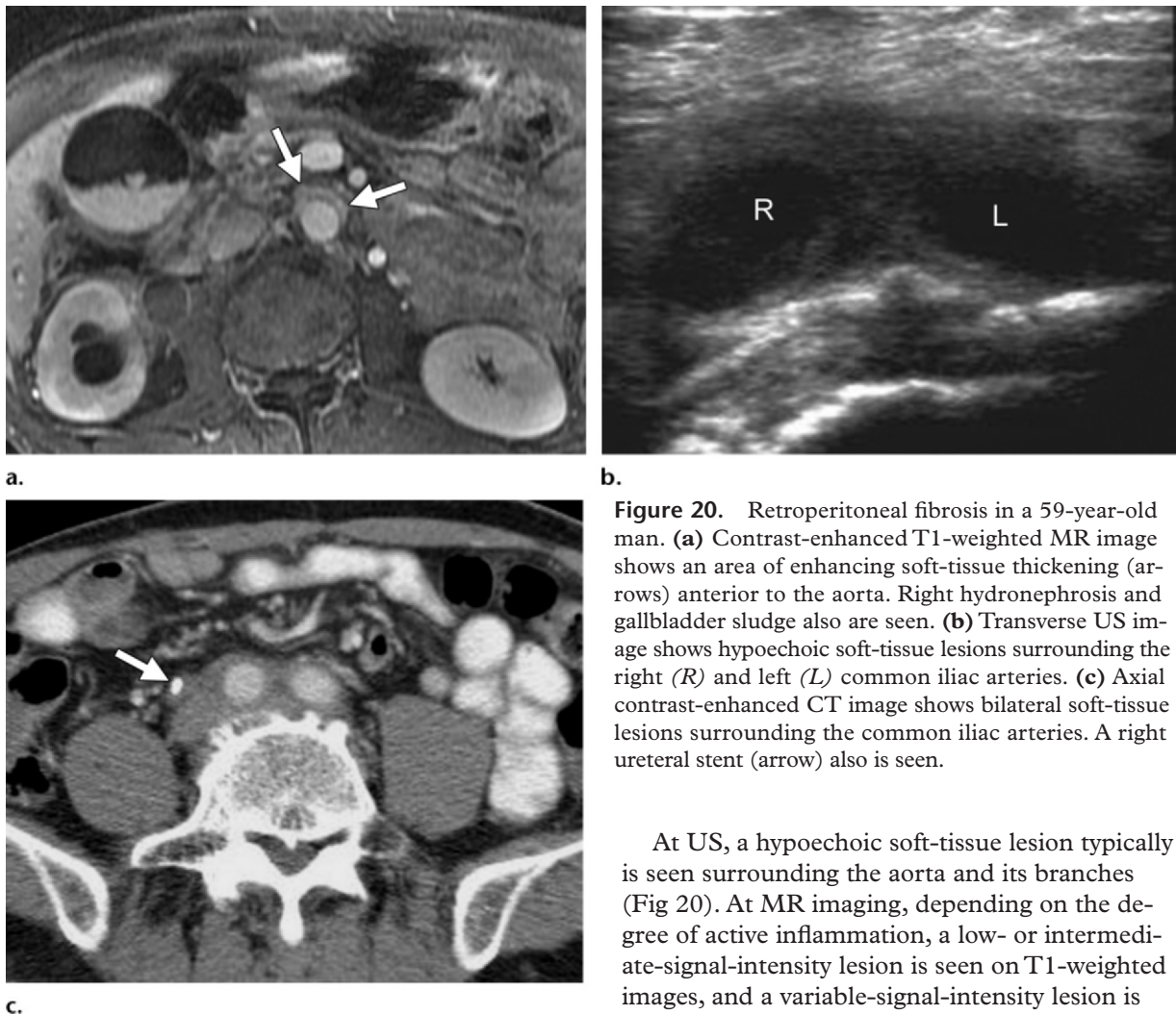


Figure 20. Retroperitoneal fibrosis in a 59-year-old man. **(a)** Contrast-enhanced T1-weighted MR image shows an area of enhancing soft-tissue thickening (arrows) anterior to the aorta. Right hydronephrosis and gallbladder sludge also are seen. **(b)** Transverse US image shows hypoechoic soft-tissue lesions surrounding the right (*R*) and left (*L*) common iliac arteries. **(c)** Axial contrast-enhanced CT image shows bilateral soft-tissue lesions surrounding the common iliac arteries. A right ureteral stent (arrow) also is seen.

Retroperitoneal Fibrosis

Retroperitoneal fibrosis is present in about 10%–20% of patients with autoimmune pancreatitis and has similar imaging characteristics as those of retroperitoneal fibrosis resulting from other causes (60–62). In patients with autoimmune pancreatitis, retroperitoneal fibrosis is characterized by a thick soft-tissue mass that is confined to the retroperitoneum and pelvic brim and typically covers the abdominal aorta and its branches. Hydronephrosis may result if the ureters are involved. Patients with IgG4-related retroperitoneal fibrosis usually respond to corticosteroid therapy.

At US, a hypoechoic soft-tissue lesion typically is seen surrounding the aorta and its branches (Fig 20). At MR imaging, depending on the degree of active inflammation, a low- or intermediate-signal-intensity lesion is seen on T1-weighted images, and a variable-signal-intensity lesion is seen on T2-weighted images. Contrast enhancement varies and depends on the maturity of the fibrous tissue.

Of the 57 patients with autoimmune pancreatitis in our study, five (9%) had retroperitoneal fibrosis, with circumferential or near-circumferential thickening around the aorta and iliac vessels (Fig 20). The disease resulted in ureteric obstruction in two patients, and in one patient, retroperitoneal fibrosis surrounded the iliac vessels and an inflammatory mass encased the inferior mesenteric artery (Fig 21). Follow-up images were available in five patients, three of whom

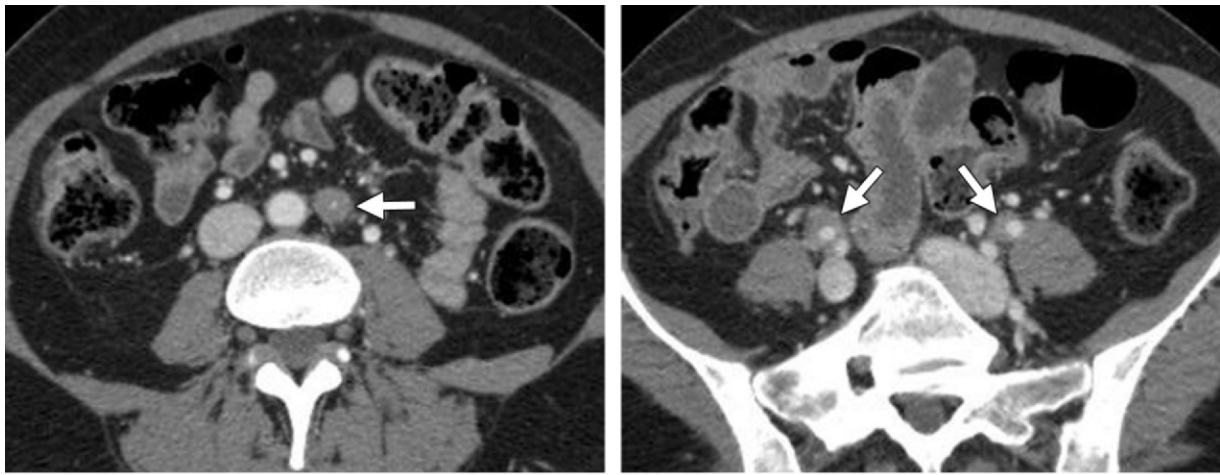


Figure 21. Retroperitoneal fibrosis in a 46-year-old woman. Contrast-enhanced CT images (**a** obtained at a higher level than **b**) show soft-tissue thickening surrounding the inferior mesenteric artery (arrow in **a**) and both common iliac arteries (arrows in **b**).

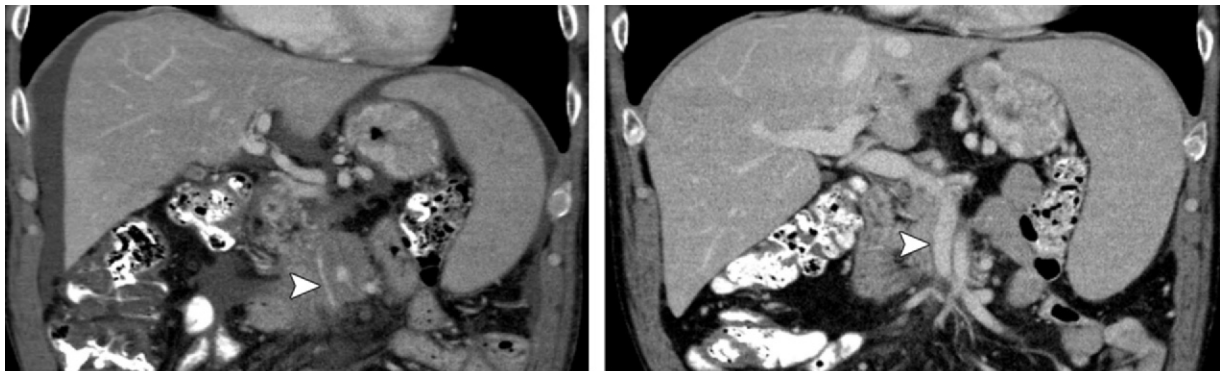


Figure 22. Sclerosing mesenteritis in a 73-year-old man. (**a**) Coronal contrast-enhanced CT image shows an enhancing soft-tissue mass in the root of the small bowel mesentery, resulting in narrowing of the superior mesenteric vein (arrowhead). Edematous thickening of the ascending colon also is seen, a result of venous congestion. (**b**) Follow-up CT image, obtained 3 months later after high-dose oral steroid therapy, shows regression of the soft-tissue mass and resolution of the narrowing of the superior mesenteric vein (arrowhead) and colonic wall thickening.

demonstrated a response to oral corticosteroid therapy, with decreased size of the perivascular soft-tissue lesions.

Sclerosing Mesenteritis

Sclerosing mesenteritis is a rare inflammatory condition that usually involves the root of the small bowel mesentery; an association with IgG4-related sclerosing disease has been reported (12,13). In a study by Akram et al (12) of 12 patients with sclerosing mesenteritis, marked infiltration with IgG4-positive plasma cells was pres-

ent in four patients (33%). At imaging, sclerosing mesenteritis typically appears as a soft-tissue mass encasing the mesenteric vessels, usually in the root of the small bowel mesentery. Often, the inflammatory soft tissues of sclerosing mesenteritis are spatially contiguous with lesions caused by autoimmune pancreatitis.

In our study of 57 patients with autoimmune pancreatitis, two patients (4%) had sclerosing mesenteritis: In one patient, the ileocolic mesentery was involved, with encasement of the mesenteric vessels, and in the other patient, the root of the small bowel mesentery was involved, with encasement of the superior mesenteric vein (Fig 22).

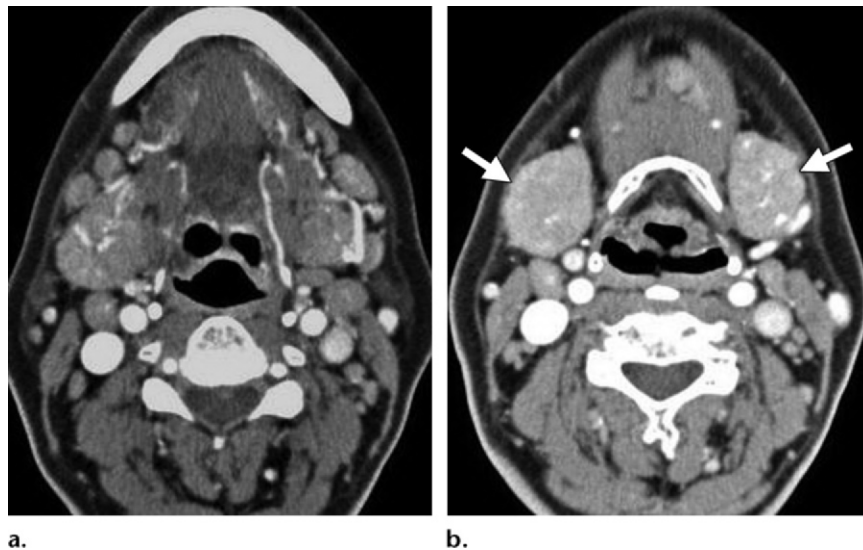


Figure 23. Salivary gland involvement in a 46-year-old man. Contrast-enhanced CT images (**a** obtained at a higher level than **b**) show diffuse enlargement of the submandibular glands (arrows in **b**) and bilateral cervical lymphadenopathy. At histologic analysis of a sample from the right submandibular gland, IgG4-related sialadenitis was confirmed.

Both patients demonstrated a response to corticosteroid therapy.

Inflammatory Bowel Disease

The association between inflammatory bowel disease and autoimmune pancreatitis is unclear. In the study by Ravi et al (25), inflammatory bowel disease was present in almost 6% of patients with proved autoimmune pancreatitis, a finding that implies a 12–15-fold increase in the risk for inflammatory bowel disease compared with that of the general population. In another study of 53 patients with autoimmune pancreatitis by Zamboni et al (63), 9 patients (17%) had ulcerative colitis or, less commonly, Crohn disease. Recently, two subtypes of autoimmune pancreatitis were described: lymphoplasmacytic sclerosing pancreatitis (type I, or “classic” autoimmune pancreatitis) and chronic duct-centric pancreatitis (type II autoimmune pancreatitis) (63–65). Duct-centric pancreatitis has different clinicopathologic features than lymphoplasmacytic sclerosing pancreatitis: It does not demonstrate a predilection for older men (younger patients are usually affected, with no gender predilection), it frequently is associated with inflammatory bowel disease, it demonstrates a weaker association with other sclerosing diseases, and patients with the disease tend to have normal serum IgG4 levels (66). Relapse is reported to only occur in patients with lymphoplasmacytic sclerosing pancreatitis (67).

In our study of 57 patients, 6 (10%) were confirmed to have inflammatory bowel disease. Of these, five patients had ulcerative colitis, with in-

volvement of the entire colon in four and involvement of the left hemicolon and rectum in one. One patient had right-sided inflammatory bowel disease, likely Crohn colitis. All six patients had pancreatic and extrapancreatic manifestations of IgG4-related sclerosing disease, and five were male. The mean age was 41 years old, lower than that for all patients with autoimmune pancreatitis. Three of the six patients were younger than 30 years old.

Lymphadenopathy

IgG4-related lymphadenopathy is characterized by dense infiltration of IgG4-positive plasma cells within the lymph nodes. Although the size of lymph nodes varies, they may be as large as 2 cm, and patients with lymphadenopathy usually respond to corticosteroid therapy (29). Abdominal (retroperitoneal, peripancreatic, mesenteric), mediastinal, hilar, and cervical lymphadenopathy have been reported, and peripancreatic and paraaortic lymphadenopathy are common (29,62,68).

Among the 57 patients in our study, lymphadenopathy was present in 19 (33%), most commonly in the abdomen. Peripancreatic lymphadenopathy was present in 12 (21%) (Fig 19), periportal and paraaortic lymphadenopathy were each present in four (7%), mediastinal or hilar lymphadenopathy was present in two (4%), and cervical lymphadenopathy was present in two (4%) (Fig 23). In four patients (7%), more than one lymph node group was involved.

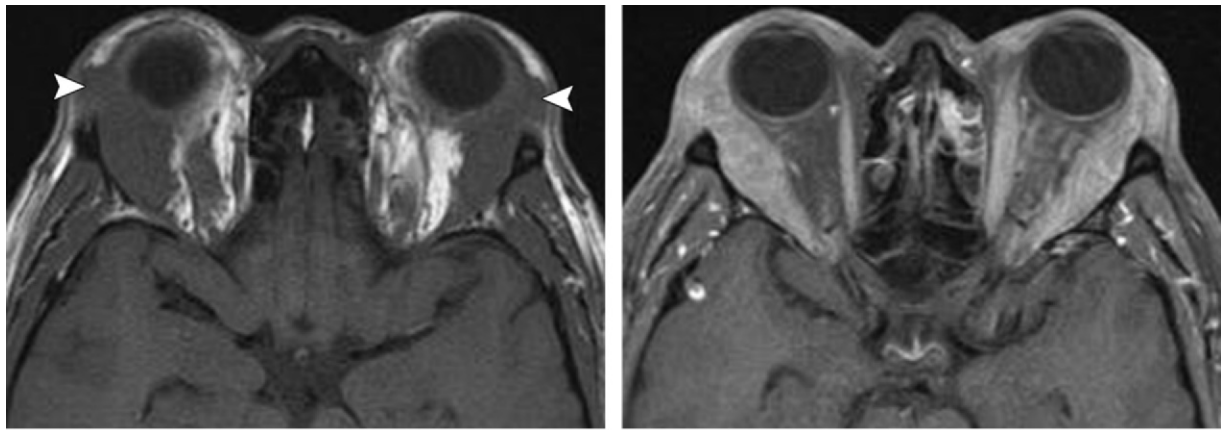


Figure 24. Ocular involvement in a 46-year-old man who presented with proptosis. Unenhanced (**a**) and contrast-enhanced (**b**) T1-weighted MR images show bilateral retro-orbital masses. Enlargement of the lacrimal glands (arrowheads in **a**) also is seen.



Figure 25. Thyroid involvement in a 46-year-old woman who presented with episodes of choking. (**a**) Transverse US image shows diffuse enlargement of the thyroid gland, with more severe involvement of the right lobe of the thyroid. (**b**) Contrast-enhanced CT image shows the enlarged thyroid gland partially encasing and mildly narrowing the lumen of the trachea, which is shifted to the left.

Head and Neck Disease

Swelling of the salivary glands has been reported in as many as 24% of patients with autoimmune pancreatitis and manifests as bilateral, painless, firm swelling of the salivary glands (Fig 23) (20). Reexamination of pathologic specimens from patients with sclerosing sialadenitis, also called a Kuttner tumor, has revealed that some of these cases represent a manifestation of IgG4-related sclerosing disease (19). The salivary glands demonstrate lymphoplasmacytic infiltration with

IgG4-positive plasma cells, which results in interstitial fibrosis, acinar atrophy, and subsequent impaired gland function (19). Swelling of the salivary glands is often associated with cervical or mediastinal lymphadenopathy and usually improves with corticosteroid therapy (20).

Orbital involvement is centered on the lacrimal glands and extends to adjacent structures (Fig 24). The extraocular muscles typically are spared. Ocular disease may be painful and leads to loss of vision, which results from compression of the optic nerve or retinal detachment (14). An association between IgG4-related sclerosing disease

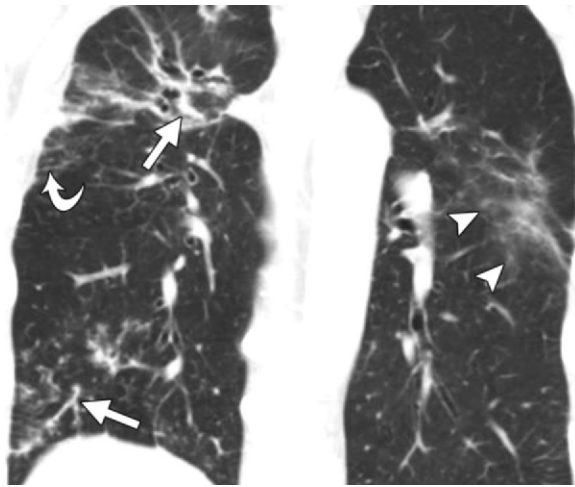


Figure 26. Pulmonary involvement in a 75-year-old man. Coronal CT image shows thickening of the bronchovascular bundles (straight arrows), with linear areas of opacification in the right lung. Mild thickening of the interlobular septa (curved arrow) also is seen, and an ill-defined area of ground-glass opacification (arrowheads) is seen in the left lung.

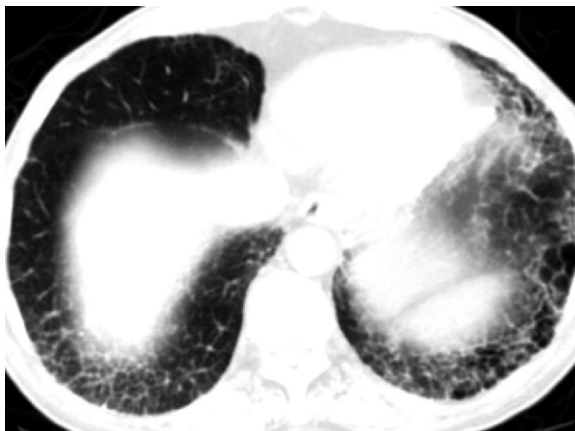


Figure 27. Pulmonary involvement in a 72-year-old man. CT image shows honeycomb changes in the lower lobes of both lungs.

and idiopathic orbital inflammatory disease has not been systematically explored.

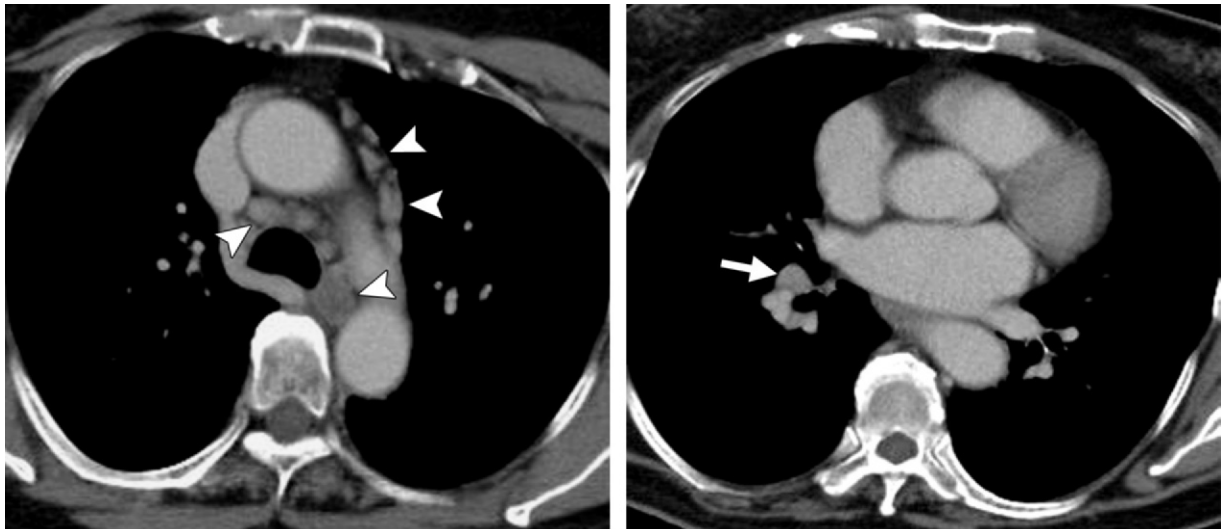
Mikulicz disease, a condition characterized by bilateral lacrimal and salivary gland swelling, is now believed to be part of IgG4-related sclerosing disease (17). Takahira et al (18) described four cases of Mikulicz disease, in which serum IgG4 levels were elevated, and infiltration of IgG4 plasma cells with sclerosing fibrosis in the lacrimal glands was present.

Hypothyroidism is relatively common in patients with autoimmune pancreatitis, and it has been shown that Riedel thyroiditis and even, in some cases, Hashimoto thyroiditis are part of the spectrum of IgG4-related sclerosing disease (15,29). IgG4-related thyroiditis demonstrates a higher degree of stromal fibrosis, lymphoplasmacytic infiltration, and follicular cell degeneration than non-IgG4-related thyroiditis (15). IgG4-related thyroiditis may lead to tracheal or esophageal encasement, sometimes with symptomatic compression, and it demonstrates a favorable response to corticosteroid therapy (Fig 25) (14). At US, the thyroid gland typically appears diffusely hypoechoic (15).

In our study of 57 patients, the salivary glands were enlarged in eight (14%). Of those eight patients, the submandibular gland was involved in four (50%), and the parotid gland was involved in four (50%). Both the submandibular and sublingual glands were involved in one patient (13%). Three patients (38%) underwent biopsy, at which dense infiltration of IgG4-positive plasma cells and fibrosis were seen. Bilateral orbital and lacrimal gland involvement was present in two patients (4%) (Fig 24). Thyroid involvement was present in seven patients (12%), all of whom had hypothyroidism, and four of whom (57%) presented with a firm, diffusely enlarged thyroid.

Pulmonary Disease

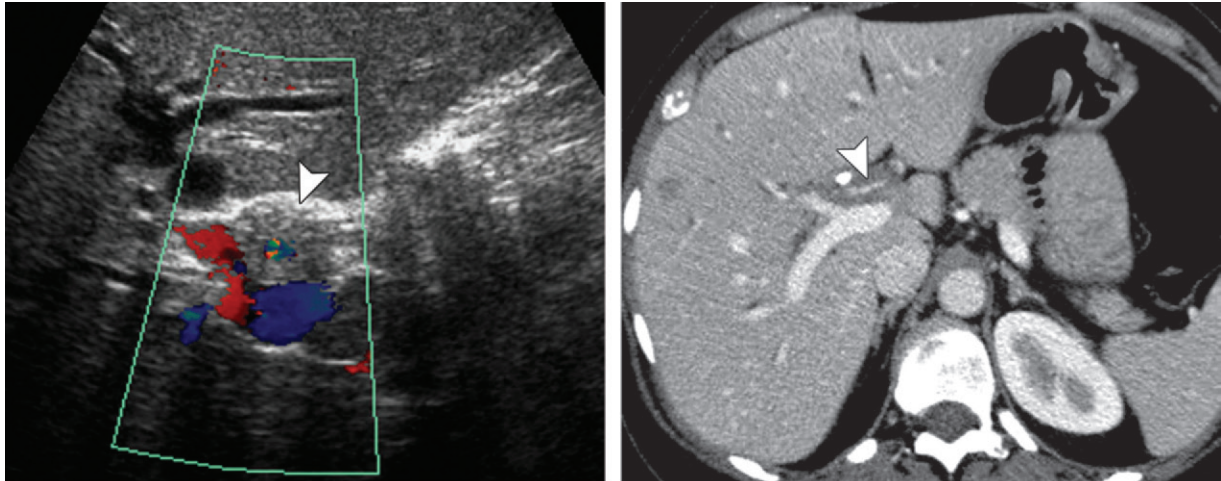
IgG4-related pulmonary disease has been reported in as many as 13% of patients with autoimmune pancreatitis (69). Pulmonary involvement may demonstrate a variety of imaging findings, including solid parenchymal nodules or masslike lesions; a bronchovascular pattern, which may be mistaken for sarcoidosis (Fig 26); a round area with ground-glass opacification that may mimic bronchioloalveolar carcinoma; an alveolar interstitial pattern, such as bronchiectasis and honeycombing (Fig 27); an area of diffuse ground-glass opacification that resembles nonspecific interstitial pneumonia; and air-space consolidation (22,23). Parenchymal nodules often have speculated margins, are confined to one lobe, and mimic the appearance of malignancy. Alveolar interstitial and bronchovascular disease usually involve all lung zones. All types of lesions are characterized by



a.

b.

Figure 28. Thoracic lymphadenopathy in a 54-year-old woman. Contrast-enhanced CT images (**a** obtained at a higher level than **b**) show multiple sites of mediastinal (arrowheads in **a**) and hilar (arrow in **b**) lymphadenopathy.



a.

b.

Figure 29. Hepatic arterial involvement in a 46-year-old woman. Transverse color Doppler US (**a**) and contrast-enhanced CT (**b**) images show a soft-tissue mass encircling the hepatic artery (arrowhead), which demonstrates mild irregular luminal narrowing.

diffuse infiltration with IgG4-positive plasma cells at histologic analysis. Enlargement of hilar or mediastinal lymph nodes is also common in patients with IgG4-related pulmonary disease (Fig 28) (22). Saegusa et al (70) reported that, among 23 patients with autoimmune pancreatitis, 16 (67%) demonstrated gallium 67 uptake in pulmonary hilar lymph nodes. Pulmonary lesions may occur in isolation, with no involvement of other organs; however, extrapulmonary lesions often precede pulmonary lesions (69,71).

Patients usually present with symptoms such as cough, shortness of breath, hemoptysis, and respiratory failure, although some patients are asymptomatic (69,71). Corticosteroid therapy effectively improves respiratory function and radiologic findings of pulmonary disease, and spontaneous improvement of lung disease has been reported (22,69,72). Pulmonary imaging was not routinely performed in our series. Among the 20 (35%) patients who underwent chest CT in our study, evidence of pulmonary involvement was present in three (15%).

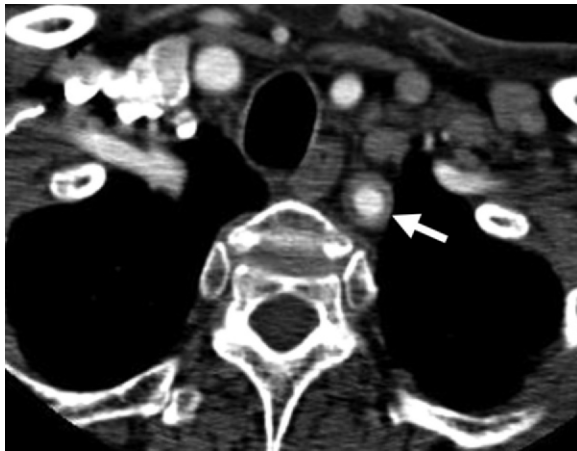


Figure 30. Subclavian arteritis in a 63-year-old woman. Contrast-enhanced CT image shows circumferential thickening of the left subclavian artery (arrow).



a.



b.

Figure 31. Narrowing of the splenic vein in a 32-year-old woman with autoimmune pancreatitis. **(a)** Contrast-enhanced CT image shows diffuse enlargement of the pancreas, which results in attenuation of the splenic vein (arrow). **(b)** Follow-up CT image obtained 12 months later, after steroid therapy, shows the pancreas, which is atrophic. The splenic vein (arrow) is normal in caliber.

Vascular Disease

There are a few reports of IgG4-related arteritis (27,73,74). Some inflammatory abdominal aortic aneurysms are related to IgG4-related sclerosing disease. At histologic analysis, arterial lesions consist of diffuse inflammatory cell infiltration of IgG4-positive plasma cells (74). In a study by Kamisawa et al (42), angiographic abnormalities, including irregular narrowing of the pancreatic arteries, were reported in 54% of patients with autoimmune pancreatitis. Lymphoplasmacytic infiltrate and fibroblast proliferation also has been observed in and around the walls of pancreatic veins, resulting in obliterative phlebitis in patients with autoimmune pancreatitis (Fig 2b). Kamisawa et al (42) also reported stenosis or obstruction of portal or splenic veins

with collateral vessel formation in 31% of patients with autoimmune pancreatitis.

Of the 57 patients in our study, seven (12%) had arteritis. The following vessels were involved: the aorta in three patients, the hepatic artery in two patients, the inferior mesenteric artery in one patient, and the left subclavian artery in one patient (Figs 29, 30). Both patients with hepatic arterial involvement were asymptomatic, with soft-tissue cuffing around the affected arteries and mild narrowing and irregularity at imaging. Narrowing of the splenic vein with collateral vessel formation was seen in nine patients (16%). In all nine patients, the splenic vein returned to a normal caliber after resolution of autoimmune pancreatitis (Fig 31).

Prostate Involvement

Rarely, autoimmune prostatitis is associated with autoimmune pancreatitis; only a few cases of histologically confirmed prostatic involvement have been reported. Patients often have an enlarged prostate and may present with lower urinary tract symptoms such as obstructive voiding symptoms and urinary frequency. It is important to differentiate the condition from prostate cancer, particularly because prostate-specific antigen levels may be elevated in the absence of adenocarcinoma in patients with IgG4-related disease involving the prostate (50,75). Histologic findings of prostatic involvement are similar to those of other organs affected by IgG4-related sclerosing disease and typically show partial or total replacement of the prostatic parenchyma, with dense fibrosis and infiltration of IgG4-positive cells in the stroma. No patients in our study had prostatic involvement.

Conclusions

IgG4-related sclerosing disease may involve various organs, such as the pancreas, biliary tree, kidneys, gallbladder, lymph nodes, salivary glands, thyroid gland, retroperitoneum, mesentery, blood vessels, lungs, orbits, and prostate. Autoimmune pancreatitis is the most common manifestation of IgG4-related sclerosing disease and frequently has typical imaging findings that help establish the diagnosis. Patients with autoimmune pancreatitis usually demonstrate a dramatic response to corticosteroid therapy; therefore, it is important to establish an accurate, timely diagnosis to avoid unnecessary invasive procedures. A combination of clinical history, characteristic imaging findings, multiorgan involvement, and serologic markers may aid diagnosis, and it is particularly important that radiologists recognize IgG4-related sclerosing disease to ensure that timely, effective treatment is provided.

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IgG4-related Sclerosing Disease: Autoimmune Pancreatitis and Extrapancreatic Manifestations¹

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Page 1380

The extrapancreatic organs that may be involved include the bile ducts, gallbladder, kidneys, retroperitoneum, mesentery, thyroid, lacrimal glands and orbits, salivary glands, lymph nodes, lungs, gastrointestinal tract, and blood vessels (2–27).

Page 1382

Characteristic imaging findings play an important role in the diagnosis of autoimmune pancreatitis in most classification systems, although the applicability of other findings varies.

Page 1388

Because the imaging appearances of primary sclerosing cholangitis and IgG4-related sclerosing cholangitis overlap, differentiating between the two conditions may be difficult.

Page 1391 (Figures 16–17 on page 1391. Figures 18–19 on page 1392)

There are four disease patterns: round or wedge-shaped renal cortical nodules, peripheral cortical lesions, masslike lesions, and renal pelvic involvement (Figs 16–19).

Page 1396 (Figure on page 1395)

Swelling of the salivary glands has been reported in as many as 24% of patients with autoimmune pancreatitis and manifests as bilateral, painless, firm swelling of the salivary glands (Fig 23) (20).