



IgG4-related Disease from Head to Toe¹

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Abbreviations: CBD = common bile duct, ERCP = endoscopic retrograde cholangiopancreatography, FDG = fluorodeoxyglucose, H-E = hematoxylin-eosin, IgG4 = immunoglobulin G4

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SA-CME LEARNING OBJECTIVES

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

- Identify the most commonly affected organs in IgG4-related disease.
- Describe characteristic imaging findings of pancreatic and extrapancreatic IgG4-related disease.
- Discuss the differential diagnosis in each affected organ.

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Immunoglobulin G4 (IgG4)-related disease is a relatively recently proposed clinical-pathologic entity that is characterized by fibro-inflammatory lesions rich in IgG4-positive plasma cells and, often but not always, elevated serum IgG4 concentrations. IgG4-related disease was recognized as a systemic disease in 2003, when extra-pancreatic manifestations were identified in patients with autoimmune pancreatitis. Since then, the disease has been reported as affecting virtually every organ system and has been identified in the biliary tree, salivary and lacrimal glands, periorbital tissues, lungs, lymph nodes, thyroid gland, kidneys, prostate gland, testicles, breasts, and pituitary gland. Its pathogenesis is poorly understood, but findings are consistent with both an autoimmune and an allergic disorder. Although definitive diagnosis requires histopathologic analysis, imaging plays an important role in demonstrating infiltration and enlargement of involved organs. Because of the systemic nature of the disease, imaging workup of IgG4-related disease should always include whole-body examinations to detect multiorgan involvement. Patients often present with subacute development of a mass in or diffuse enlargement of the affected organ, sometimes mimicking a neoplastic process. In every anatomic location, several inflammatory and neoplastic entities must be considered in the differential diagnosis. Because IgG4-related disease usually shows a marked response to corticosteroid therapy, radiologists should be familiar with its clinical and imaging manifestations to avoid a delay in diagnosis and unnecessary surgical interventions.

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Introduction

Immunoglobulin G4 (IgG4)-related disease is an increasingly recognized immune-mediated condition that comprises a group of disorders previously thought to be unrelated, but with common pathologic, serologic, and clinical features (Fig 1). These commonly shared features include infiltration by IgG4-positive plasma cells and lymphocytes with associated fibrosis, producing tumefactive lesions in one or more organs or organ systems. In addition, elevated serum IgG4 concentrations are found in most patients.

The pancreas is the most commonly affected organ in IgG4-related disease. Since 2001, it has been known that patients with sclerosing pancreatitis, a form of autoimmune pancreatitis called type 1, have high serum IgG4 concentrations and show infiltration by IgG4-positive

TEACHING POINTS

- IgG4-related lesions similar to those of autoimmune pancreatitis have been identified in many extrapancreatic organs, including the bile ducts, gallbladder, lymph nodes, retroperitoneum, mesentery, kidneys, lungs, breasts, prostate gland, and skin. The head and neck may also be involved, with the most commonly affected organs being the salivary and lacrimal glands, orbits, and thyroid gland, as well as the pituitary gland and meninges.
- A specific finding of autoimmune pancreatitis that (to our knowledge) has not been described in any other pancreatic disorder is a capsulelike rim or halo of low attenuation surrounding the pancreas at contrast material-enhanced CT and MR imaging. This finding is presumed to represent a fluid collection, a phlegmon, or fibrosis and has been observed in 12%–48% of patients at CT and 18%–47% of patients at MR imaging.
- Primary sclerosing cholangitis occurs in younger patients, is associated with inflammatory bowel disease, and is less acute with longer duration of symptoms. IgG4-related sclerosing cholangitis affects older patients, is frequently accompanied by pancreatic or extrapancreatic lesions, may include obstructive jaundice, and often resolves with steroid therapy.
- Nearly 40% of patients with IgG4-related pancreatitis also have salivary and/or lacrimal gland involvement, which is characterized by bilateral painless swelling of the glands. This manifestation may precede or accompany pancreatitis, but it may also occur in isolation.
- The presence of renal lesions in patients with pancreatic disease has been used to help differentiate autoimmune pancreatitis from pancreatic cancer, since their presence strongly suggests the former condition.

plasma cells in pancreatic specimens (1). However, it was not until 2003 that Kamisawa et al (2) proposed the concept of IgG4-related autoimmune disease and suggested that autoimmune pancreatitis is only a part of the spectrum of this systemic disease. Since then, IgG4-related lesions similar to those of autoimmune pancreatitis have been identified in many extrapancreatic organs, including the bile ducts, gallbladder, lymph nodes, retroperitoneum, mesentery, kidneys, lungs, breasts, prostate gland, and skin (3–10). The head and neck may also be involved, with the most commonly affected organs being the salivary and lacrimal glands, orbits, and thyroid gland, as well as the pituitary gland and meninges (9,10). Although autoimmune pancreatitis is present in most patients with IgG4-related disease, pancreatic involvement is no longer considered essential to diagnosis because cases with only extrapancreatic involvement have been reported (11,12). Extrapancreatic lesions may sometimes develop before or up to 15 years after pancreatitis.

Many different terms have been used in the literature to describe IgG4-related disease, including *IgG4-related sclerosing disease*, *IgG4-related systemic disease*, *IgG4-related autoimmune disease*, and *systemic IgG4-related plasmacytic syndrome* (13).

- Hypertrophic pachymeningitis
- Autoimmune hypophysitis
- Orbital pseudotumor
- Mikulicz's disease
- Kuttner's tumor
- Riedel's thyroiditis
- Hashimoto's thyroiditis
- Pulmonary pseudotumor
- Interstitial pneumonia
- Lymphadenopathy
- Autoimmune pancreatitis
- Sclerosing cholangitis
- Liver pseudotumor
- Retroperitoneal fibrosis
- Tubulointerstitial nephritis
- Inflammatory aortic aneurysm
- Prostatitis, testicular involvement
- Cutaneous pseudolymphoma

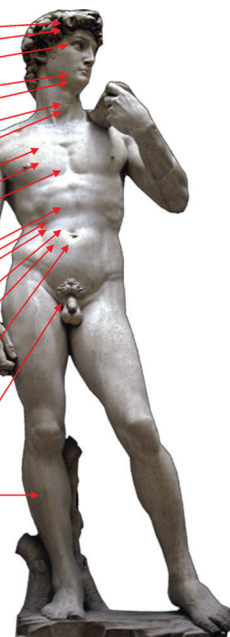


Figure 1. Previously recognized conditions that may form part of the IgG4-related disease spectrum.

Because the fibrosis is characteristically found in some organs but seldom in others, and because the disease may be systemic or may affect only a single organ, terms like *sclerosing* or *systemic* are not precise for referring to this spectrum of disease. A panel of Japanese investigators recently reached a consensus to simply use the term *IgG4-related disease* (14).

The pathogenesis of IgG4-related disease is poorly understood, and there are findings consistent with both an autoimmune and an allergic disorder. IgG4 is the least abundant IgG subclass (accounting for less than 5% of total IgG in healthy subjects), with serum concentrations generally stable in individual persons (15). Despite the ubiquity of IgG4 within involved organs, many unresolved questions remain regarding its role in the pathogenesis of the disease (16).

The Japanese group proposed three major diagnostic criteria for practical use: (a) clinical examination showing characteristic diffuse or localized swelling or masses in one or more organs; (b) hematologic examination showing elevated serum IgG4 concentrations (≥ 135 mg/dL); and (c) histopathologic examination showing marked lymphoplasmacytic infiltration and storiform fibrosis, as well as organ infiltration by IgG4-positive plasma cells (Fig 2). The diagnosis of IgG4-related disease is considered definite if all three criteria are met, probable if the first and third criteria are met, and possible if the first and second criteria are met (17). Because clinical symptoms and pathologic features depend on lesion location,

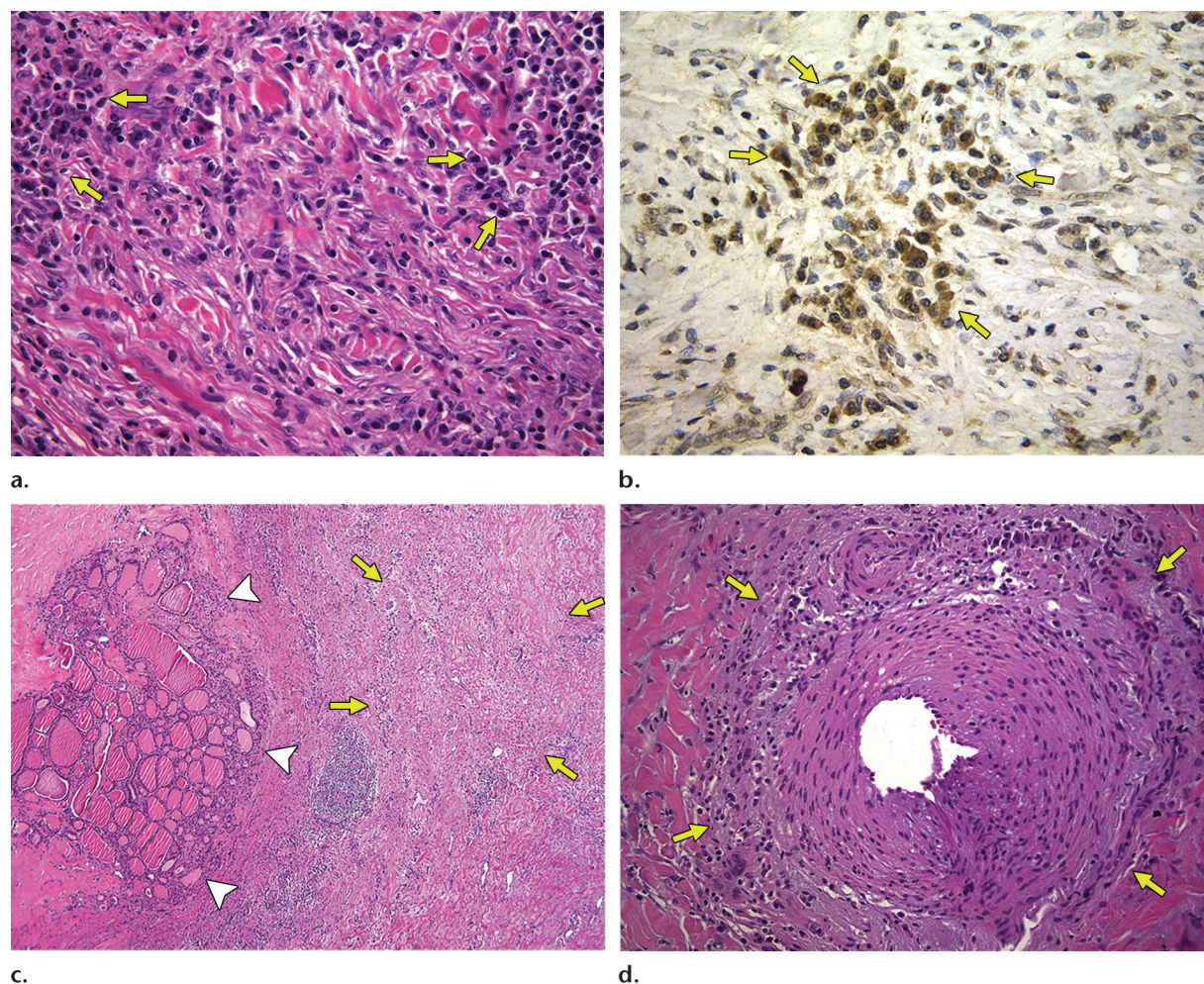


Figure 2. Histopathologic features of IgG4-related thyroiditis (Riedel thyroiditis). The histopathologic findings of IgG4-related disease share striking similarities regardless of the affected organ. (a) Photomicrograph of the thyroid parenchyma shows a dense lymphoplasmacytic infiltrate (arrows). (Original magnification, $\times 200$; hematoxylin-eosin [H-E] stain.) (b) Photomicrograph shows numerous IgG4-positive plasma cells (arrows). Brown = cytoplasm of plasma cells containing IgG4, blue = plasma cell nuclei. (Original magnification, $\times 400$; IgG4 immunostain.) (c) Photomicrograph shows storiform fibrosis (arrows) surrounding normal thyroid tissue (arrowheads). (Original magnification, $\times 40$; H-E stain.) (d) Photomicrograph shows obliteration of a venous channel by IgG4-positive plasma cells (obliterative phlebitis) (arrows). (Original magnification, $\times 100$; H-E stain.)

it is probably impossible to establish criteria that include all patients with IgG4-related disease. The aforementioned comprehensive diagnostic criteria are not organ specific but are intended to help physicians differentiate IgG4-related disease from other inflammatory or malignant diseases.

Although IgG4-related disease has a highly characteristic histologic appearance, it cannot be definitively diagnosed without immunohistochemical staining for IgG4. The presence of IgG4-positive plasma cells is required for diagnosis of IgG4-related disease, but some IgG4-positive plasma cells can also be detected in other inflammatory diseases. However, it has been suggested that dense infiltrates of IgG4-plasma cells (>10 – 50 per high-power microscopic field, depending on the affected organ) are highly specific for IgG4-related disease (18). A ratio of IgG4-positive to IgG-positive plasma cells higher than 40% is also

helpful in distinguishing between IgG4-related disease and non-IgG4-related inflammatory conditions (17–19). Elevated serum IgG4 concentration is common in but not specific for IgG4-related disease (20). On the other hand, serum IgG4 concentration may be normal in 20%–40% of cases of biopsy-proved IgG4-related disease (15,18,21). Thus, neither an increase in serum IgG4 concentration nor an elevated number of IgG4-positive plasma cells in tissue is specific for IgG4-related disease (18). Diagnosis of the disease requires careful correlation with the histopathologic features of the sample, as well as with clinical and radiologic findings.

Clinical symptoms of IgG4-related disease are generally mild, with no fever or elevation of C-reactive protein levels. The disorder is often identified incidentally when organ swelling is detected at radiology. Response to steroid therapy is

excellent in most patients, although some patients are refractory to such therapy (15). A few cases of cancer have been reported in patients with IgG4-related disease—mainly, lymphoma and pancreatic carcinoma—but the potential for malignant transformation of the disease is not clear (22).

In this article, we review the imaging findings of pancreatic and extrapancreatic involvement of IgG4-related disease and address the differential diagnosis in potentially affected organ systems.

IgG4-related Autoimmune Pancreatitis

Autoimmune pancreatitis is a specific form of chronic pancreatitis that occurs secondary to an autoimmune process. Recent studies suggest the existence of two distinct subtypes of autoimmune pancreatitis on the basis of pathologic findings: type 1 (lymphoplasmacytic sclerosing pancreatitis) and type 2 (idiopathic duct-centric chronic pancreatitis). Type 1 autoimmune pancreatitis is the pancreatic manifestation of IgG4-related disease, whereas type 2 has a distinctly different histologic and clinical profile, with no elevation of serum IgG4 concentrations or presence of autoantibodies (23).

IgG4-related autoimmune pancreatitis is the prototypical form of IgG4-related disease and is characterized by periductal infiltration by IgG4-positive plasma cells, which leads to periductal fibrosis. At presentation, the pancreas is either diffusely or focally enlarged, with irregular narrowing of the pancreatic duct and sometimes of the common bile duct (CBD) as well. Over time, atrophy of the parenchymal acini occurs, and extensive sclerosis results in loss of the lobular architecture (24).

IgG4-related autoimmune pancreatitis is seen in an estimated 2%–8% of patients with chronic pancreatitis (25). Middle-aged and elderly men are primarily affected, with 95% of patients older than 45 years and a male-to-female ratio of 3–7:1 (22,26). No specific symptoms are seen in patients with autoimmune pancreatitis, although some patients have little or no abdominal pain, obstructive jaundice, weight loss, new onset of diabetes, pancreatic enlargement, or accompanying extrapancreatic lesions (27). It was this observation—that patients with autoimmune pancreatitis had extrapancreatic fibroinflammatory lesions with similar histopathologic features—that led to the concept of IgG4-related disease.

Diagnosis of autoimmune pancreatitis is challenging because a subset of cases may closely mimic pancreatic adenocarcinoma; an estimated 3%–9% of patients who undergo resection for a presumed carcinoma have autoimmune pancreatitis (28). During the past decade, a number of authors from different countries have proposed various diagnostic criteria for autoimmune pancre-

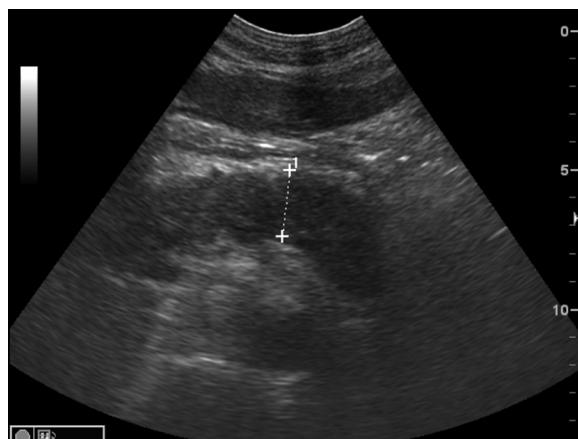


Figure 3. Diffuse autoimmune pancreatitis. Transverse US image shows an enlarged pancreas with hypoechoic parenchyma (cursors).

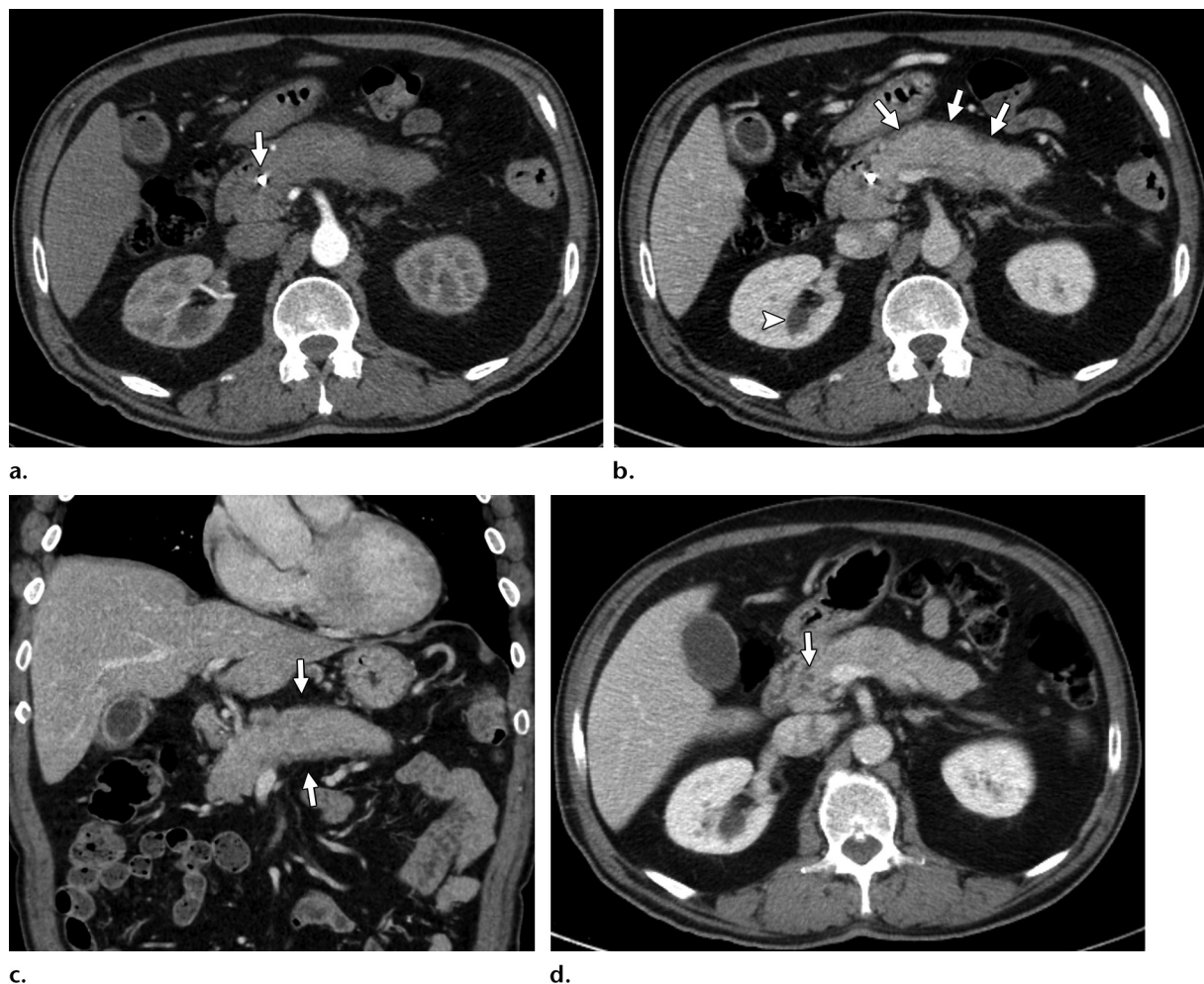
atitis. The Japanese Pancreatic Society established the first set of criteria in 2002 (29,30), consisting of imaging findings, serologic findings (elevated serum IgG4 concentration), and characteristic pathologic findings (the triad of lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis). Other authors introduced new diagnostic parameters (31,32), and in 2011, the International Association of Pancreatology released the International Consensus Diagnostic Criteria for autoimmune pancreatitis, which defined five cardinal features of type 1 autoimmune pancreatitis: pancreatic imaging findings (parenchyma and duct), serologic findings (IgG4), histopathologic findings and immunostaining, other organ involvement, and response to steroid therapy (33).

Pancreatic imaging findings play an important role in all of the proposed sets of diagnostic criteria for autoimmune pancreatitis, since laboratory and pathologic findings are often insufficient and sometimes nonspecific for the diagnosis. Cross-sectional imaging is also crucial in identifying multiorgan involvement.

There are two main recognized patterns of autoimmune pancreatitis: diffuse and focal (34,35). Diffuse disease is the more common pattern and is characterized by a uniformly enlarged pancreas with absence of pancreatic clefts. The pancreas has a sharp margin and loss of lobular contours, resulting in a featureless sausagelike appearance. Focal disease is characterized by enlargement of the pancreatic head or, less frequently, the pancreatic body or tail, resulting in a masslike appearance. Focal disease accounts for approximately 33%–41% of all cases, and its radiologic appearance may be difficult to differentiate from that of pancreatic carcinoma (36).

The affected area of the pancreas in patients with autoimmune pancreatitis typically appears hypoechoic at ultrasonography (US) (Fig 3),

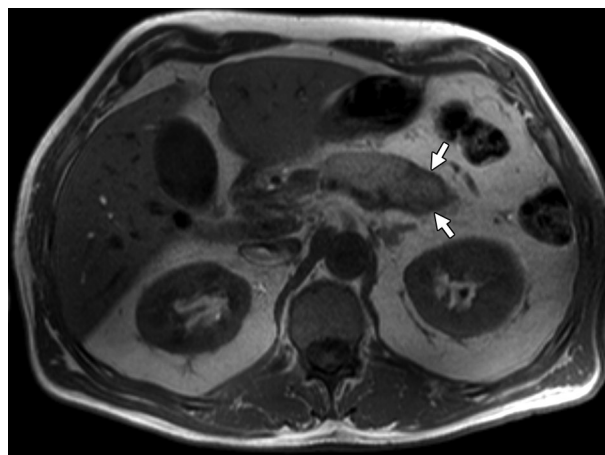
Figure 4. Diffuse autoimmune pancreatitis in a 72-year-old man who presented with jaundice. (a) Axial nonenhanced CT image shows an enlarged pancreas with loss of lobular contours (sausagelike appearance). Narrowing of the CBD led to endoscopic stent placement (arrow). (b) Axial contrast-enhanced CT image shows a characteristic hypoattenuating halo around the pancreatic body and tail (arrows), a finding that was barely visible on nonenhanced images. The round lesion in the right kidney (arrowhead) represents a cyst. (c) Coronal CT image shows the hypoattenuating halo and absence of peripancreatic stranding (arrows). (d) Follow-up CT image obtained 4 months later after steroid administration shows a marked response to treatment, with resolution of the hypoattenuating peripancreatic halo. Note the thickening and enhancement of the CBD (arrow) after biliary stent removal.



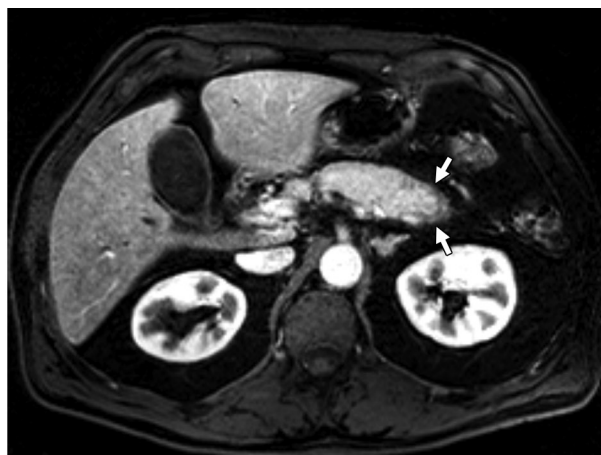
hypoattenuating at computed tomography (CT), mildly hyperintense at T2-weighted magnetic resonance (MR) imaging, and hypointense at T1-weighted MR imaging (34). Dynamic CT shows a distinctive delayed enhancement pattern due to the presence of parenchymal fibrosis (37). A specific finding of autoimmune pancreatitis that (to our knowledge) has not been described in any other pancreatic disorder is a capsulelike rim or halo of low attenuation surrounding the pancreas at contrast material-enhanced CT and MR imaging. This finding is presumed to represent a fluid collection, a phlegmon, or fibrosis and has been observed in 12%–48% of patients at CT and 18%–47% of patients at MR imaging (Figs 4–6) (34,37–39). A recent study reported that pancreatic perfusion was reduced in patients with autoimmune pancreatitis but improved

after steroid treatment (40). Other authors have suggested that diffusion-weighted MR imaging findings, in combination with other imaging findings, may be useful for distinguishing between autoimmune pancreatitis and pancreatic cancer. The apparent diffusion coefficient value of autoimmune pancreatitis was found to be significantly lower than that of pancreatic cancer because of the greater cellularity of the former condition (36,41). In addition, fluorodeoxyglucose (FDG) positron emission tomography (PET) has been reported to show abnormal pancreatic radiotracer uptake that disappears after steroid treatment, as in other organs affected by IgG4-related disease.

Diffuse or segmental narrowing of the main pancreatic duct and, sometimes, stenosis of the bile duct are characteristic imaging features of autoimmune pancreatitis, which may

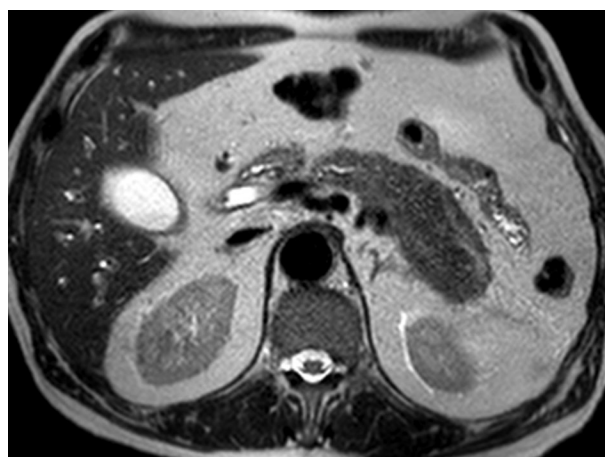


a.



b.

Figure 5. Diffuse autoimmune pancreatitis in the same patient as in Figure 4. (a) Axial T1-weighted MR image shows a hypointense halo of fibrosis and inflammation surrounding the pancreatic tail (arrows). (b) Axial contrast-enhanced arterial phase T1-weighted MR image shows intense enhancement of the pancreatic parenchyma, with less enhancement of the halo (arrows).

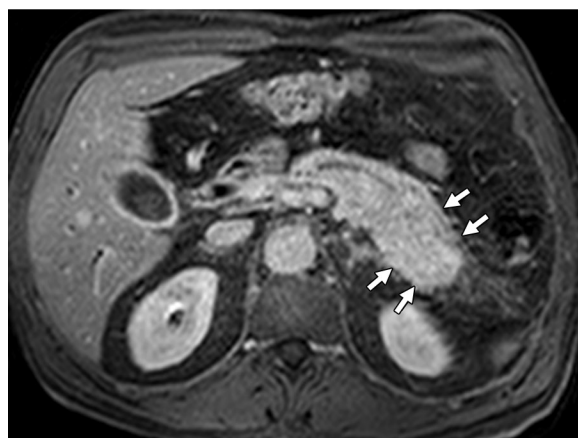


a.



b.

Figure 6. Diffuse autoimmune pancreatitis in a 77-year-old man. (a) Axial T2-weighted MR image shows enlargement of the pancreas, with absence of pancreatic clefts and a sharp outline (sausage-like appearance). (b) Axial contrast-enhanced arterial phase T1-weighted MR image shows intense parenchymal enhancement with a surrounding hypointense halo (arrows). (c) Axial contrast-enhanced T1-weighted MR image obtained 3 minutes after contrast material administration shows late enhancement of the pseudocapsule due to its fibrotic content; this area is now nearly indistinguishable from the adjacent pancreatic parenchyma (arrows).



c.

be demonstrated at endoscopic retrograde cholangiopancreatography (ERCP) and MR cholangiopancreatography (Fig 7). Penetration of the pancreatic duct through the mass (“duct-penetrating sign”) is a highly specific finding for benign strictures that is frequently encountered in patients with autoimmune pancreatitis but is not seen in those with pancreatic cancer (42). In addition, a smooth, tapered narrowing of the upstream pancreatic duct just distal to the pancreatic lesion (“ice pick sign”) is frequently seen in patients with autoimmune pancreatitis (Fig 7)

(39). In contrast, pancreatic carcinoma tends to produce abrupt obstruction of the main pancreatic duct, a rare event in patients with autoimmune pancreatitis. This is because, in pancreatic carcinoma, the tumor starts in the ductal epithelium and produces early obstruction,

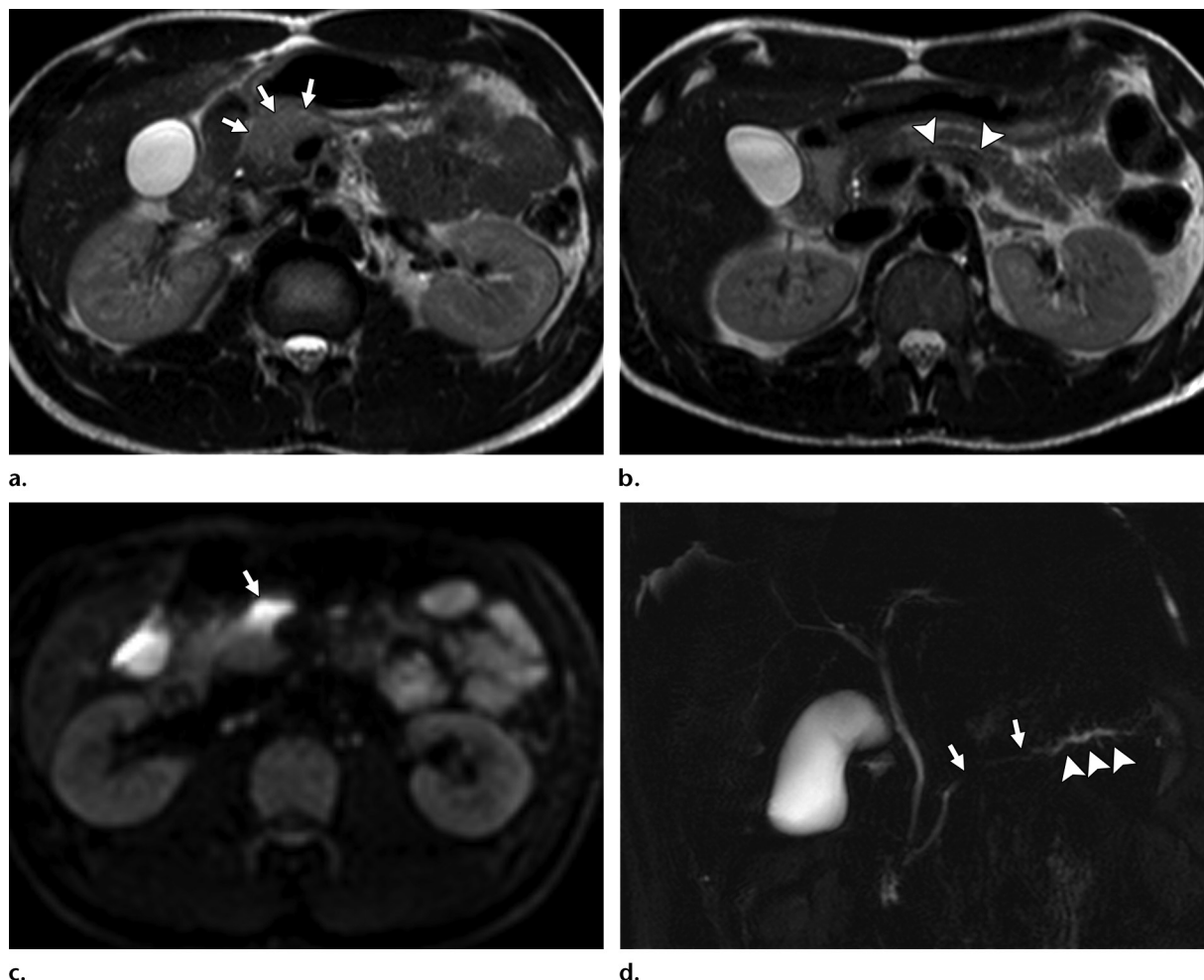


Figure 7. Focal autoimmune pancreatitis in a 47-year-old man. (a) Axial T2-weighted MR image shows well-demarcated focal enlargement with a mildly hyperintense appearance in the pancreatic isthmus (arrows), a finding that reflects an edematous component. (b) Axial T2-weighted MR image obtained at a higher level shows mild dilatation of the upstream pancreatic duct (arrowheads). (c) On an axial diffusion-weighted 3-T MR image ($b = 800 \text{ sec/mm}^2$), the lesion (arrow) is hyperintense relative to the pancreatic parenchyma because of inflammation. (d) Coronal MR cholangiopancreatographic image shows stenosis in the affected segment of the main pancreatic duct (arrows), with upstream dilatation (arrowheads). Note the smooth, tapered narrowing of the upstream pancreatic duct (ice pick sign).

whereas in autoimmune pancreatitis, the duct is extrinsically compressed by periductal fibrosis and inflammation (36,39). In cases of segmental narrowing, absent or mild upstream dilatation of the pancreatic duct helps distinguish between autoimmune pancreatitis and pancreatic cancer (43). Homogeneous enhancement after intravenous contrast agent administration and lack of parenchymal atrophy also aid in differentiation.

Findings that are often seen in chronic alcoholic pancreatitis, particularly pancreatic calcifications and pseudocyst formation, are rare in autoimmune pancreatitis (44). Severe peripancreatic stranding, a typical feature of acute pancreatitis, is also rare (Fig 4) (34).

IgG4-related autoimmune pancreatitis readily responds to oral steroid therapy, with marked improvement in pancreatic morphology and function seen within 4–6 weeks (Fig 4). How-

ever, atrophy of the affected pancreatic segments is observed after treatment in about 15% of patients, suggesting the burnout of inflammation, a late phase of the disease (45). Although some cases of synchronous autoimmune pancreatitis and pancreatic carcinoma have been reported, to our knowledge there are no data to support the contention that this IgG4-related disease increases risk for malignancy (46).

IgG4-related Sclerosing Cholangitis

Aside from the pancreas, the bile ducts are the most commonly involved organ in IgG4-related disease; about 60%–80% of patients with type 1 autoimmune pancreatitis have involvement of the hepatobiliary tract. However, IgG4-related sclerosing cholangitis can also occur without pancreatic involvement, making accurate diagnosis in these

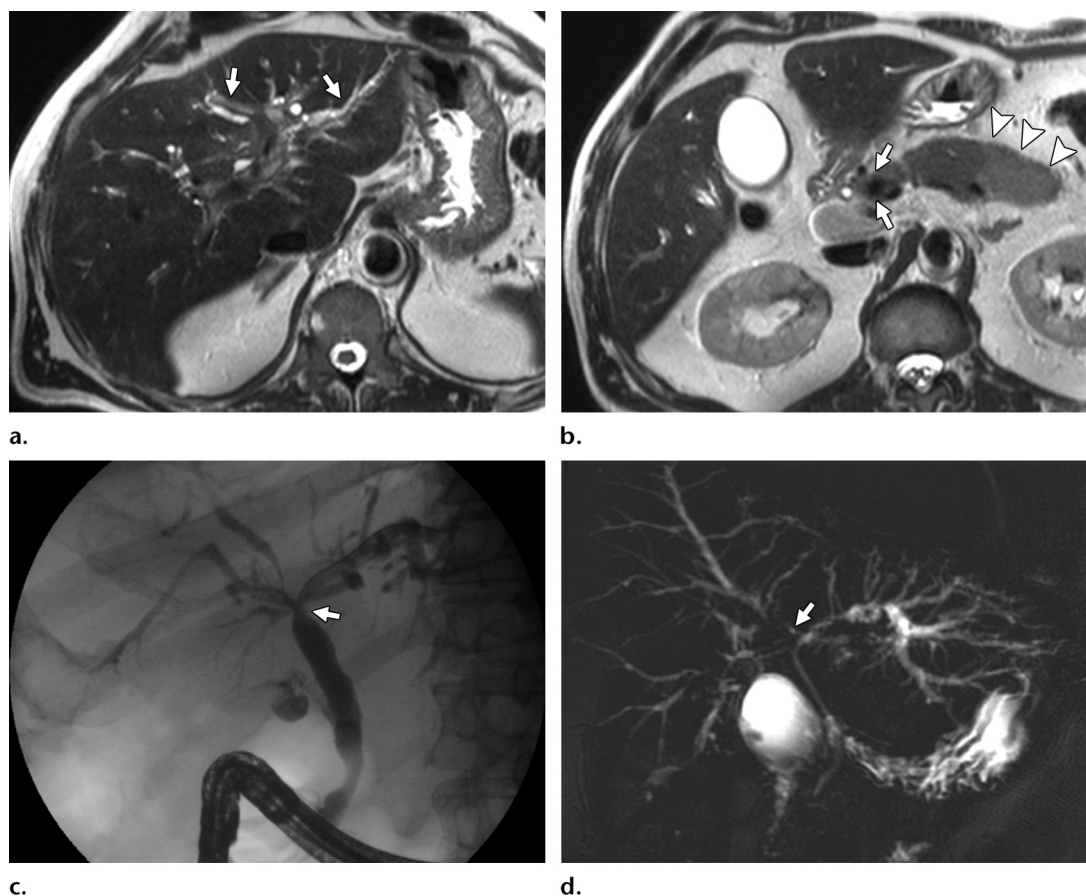


Figure 8. IgG4-related sclerosing cholangitis in a 71-year-old man with autoimmune pancreatitis. (a) Axial T2-weighted MR image shows diffuse dilatation of the intrahepatic biliary ducts (arrows). (b) Axial T2-weighted MR image obtained at a lower level shows mild wall thickening of the CBD (arrows). Note also the hyperintensity of the pancreatic tail (arrowheads) due to coexistent autoimmune pancreatitis. (c) ERCP image shows multiple strictures in the intrahepatic bile ducts with prestenotic dilatation, along with a single stricture in the proximal common hepatic duct (arrow). (d) Coronal MR cholangiopancreatographic image obtained 1 year later after steroid treatment shows persistent narrowing of the intrahepatic bile ducts (arrow) but resolution of the CBD dilatation.

patients particularly difficult (47,48). Both the intrahepatic and extrahepatic segments can be affected, producing dense bile duct infiltration by IgG4-positive plasma cells and extensive fibrosis. The result is focal or diffuse bile duct wall thickening, mostly associated with stenosis and upstream dilatation, findings that are readily depicted at ERCP and MR cholangiopancreatography (Fig 8) (49). The most commonly involved segment is the intrapancreatic portion of the CBD, since most cases of IgG4-related sclerosing cholangitis are associated with autoimmune pancreatitis. In these patients, the stenosis affecting the lower CBD is due to duct wall thickening and the effect of inflammation and/or edema of the pancreas (50).

The main differential diagnosis to be considered in patients with IgG4-related sclerosing cholangitis is primary sclerosing cholangitis. Primary sclerosing cholangitis occurs in younger patients, is associated with inflammatory bowel disease, and is less acute with longer duration of symptoms. IgG4-related sclerosing cholangitis

affects older patients, is frequently accompanied by pancreatic or extrapancreatic lesions, may include obstructive jaundice, and often resolves with steroid therapy (48,51). At ERCP, multifocal and short intrahepatic biliary strictures with beaded or “pruned-tree” lesions are characteristic of primary sclerosing cholangitis, whereas long and continuous strictures are typically seen in patients with IgG4-related sclerosing cholangitis. Isolated strictures of the distal CBD may occur (52). Differentiation from cholangiocarcinoma may be difficult, especially in the presence of a soft-tissue mass that produces stenosis of the hilar hepatic bile duct. In such cases, tumor infiltration is confined to the bile ducts, whereas in IgG4-related sclerosing cholangitis, luminal irregularities and stenosis involve both the biliary and pancreatic ducts. In addition, cholangiocarcinoma may produce hepatic capsular retraction due to desmoplastic growth (24).

In IgG4-related sclerosing cholangitis, CT and MR imaging depict a circular and sym-

metric rind of tissue encasing the bile duct wall, with relatively smooth margins and homogeneous enhancement in the delayed phase (Fig 8). These characteristic features are recognized not only in stenotic areas but also in areas without stenosis that appear normal at cholangiography (53). Gallbladder involvement occasionally occurs, appearing as diffuse wall thickening with decreased echogenicity at US and low signal intensity at T2-weighted MR imaging, with late intravenous contrast enhancement (54).

The disease usually demonstrates a favorable response to corticosteroid therapy, but it is strongly recommended that steroid trials be avoided and that the diagnosis be initially confirmed by obtaining biopsy specimens prior to initiating steroid treatment, since some malignant lesions may improve after treatment (49). Relapses may occur in some patients, even while they are undergoing maintenance corticosteroid therapy.

Salivary and Lacrimal Gland Involvement

Nearly 40% of patients with IgG4-related pancreatitis also have salivary and/or lacrimal gland involvement, which is characterized by bilateral and painless swelling of the glands (55). This manifestation may precede or accompany pancreatitis, but it may also occur in isolation. Patients present with either enlargement of the lacrimal and salivary glands (an entity previously known as Mikulicz disease) or chronic sclerosing sialadenitis of the submandibular glands (also known as Küttner tumor). In the past, both entities were erroneously viewed as subcategories of Sjögren syndrome; now, however, they are considered part of the spectrum of IgG4-related disease (56–58).

Mikulicz disease is an idiopathic condition that is characterized by painless bilateral swelling of the lacrimal, submandibular, sublingual, and parotid glands, with involvement of at least two of these glands needed to establish the diagnosis. Although both IgG4-related Mikulicz disease and Sjögren syndrome show glandular enlargement with lymphocytic infiltration, there are marked clinical and pathologic differences between the two entities (57). At CT, the lesions in Mikulicz disease usually demonstrate homogeneous attenuation and enhancement (Fig 9). At MR imaging, they have relatively low signal intensity on T2-weighted images owing to fibrosis, and low signal intensity with homogeneous enhancement on T1-weighted images (59).

Küttner tumor is a relatively uncommon cause of salivary gland enlargement and was originally described as a “hard swelling” of one

or both submandibular glands. The parotid gland may sometimes be involved. Küttner tumors are also referred to as IgG4-related sialadenitis owing to the typical histologic finding of markedly fibrous sclerotic lesions containing IgG4-positive plasma cells (56). Fibrosis tends to be more severe than in Mikulicz disease, but imaging findings are similar in both entities (14). With unilateral involvement, differentiation must be made from malignant salivary gland tumors, whereas with bilateral involvement, differentiation must be made from acute-phase Sjögren syndrome and lymphoma of the salivary gland (59).

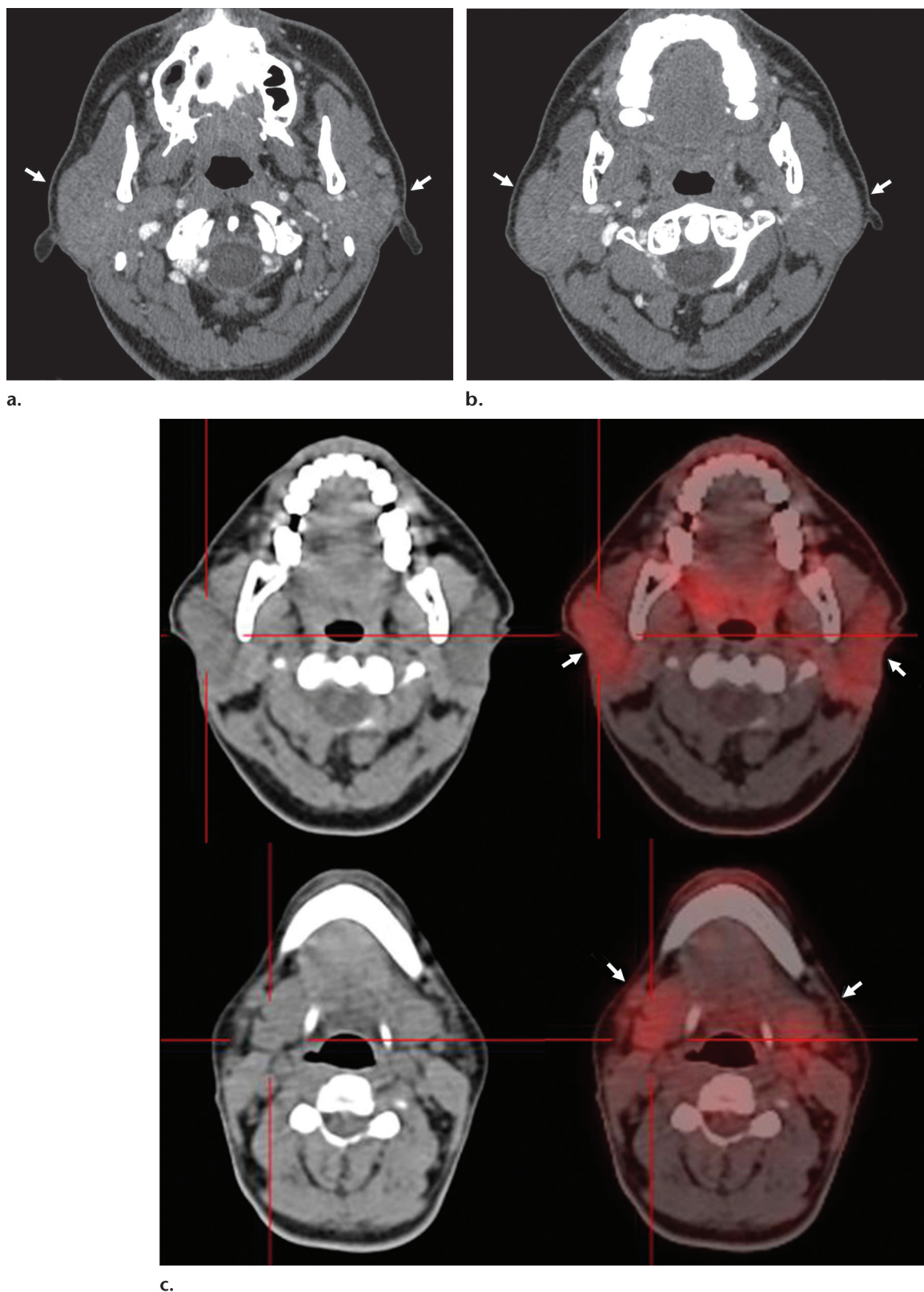
Orbital Involvement

Patients with IgG4-related ophthalmic disease primarily show involvement of the lacrimal gland (Fig 10). This IgG4-related dacryoadenitis is usually bilateral, and concurrent salivary gland enlargement (Mikulicz disease) is common. Histologic and serologic findings are similar to those in patients with sialadenitis. Some studies have found that IgG4-related chronic sclerosing dacryoadenitis may be a predisposing factor in the emergence of lymphoma (60). In addition, recent reports suggest that a substantial proportion of idiopathic orbital inflammations—also called orbital pseudotumors—are associated with IgG4-related disease (61). These orbital lesions may be unilateral or bilateral and can affect either the entire orbit or selected components, including the extraocular muscles, lacrimal system, and optic nerves. Perineural spread of IgG4-related orbital pseudotumors has been reported, often involving branches of the trigeminal nerve. Therefore, careful evaluation along the course of cranial nerves is mandatory for the radiologist when evaluating this entity (62,63). At CT, orbital pseudotumors show soft-tissue attenuation and homogeneous enhancement. At MR imaging, these pseudotumors demonstrate low signal intensity relative to brain on T2-weighted images (Fig 11) and tend to appear hyperintense on diffusion-weighted images because of fibrosis (64).

IgG4-related Thyroiditis

Two forms of thyroid involvement in IgG4-related disease have been described: Riedel thyroiditis and the fibrous variant of Hashimoto thyroiditis. Riedel thyroiditis is a rare form of chronic inflammatory process with extensive fibrosis, resulting in a rock-hard painless mass that involves the thyroid parenchyma and surrounding tissues. It is considered to be an IgG4-related thyroiditis, and one-third of patients also have fibrosclerosis in other organs (10,14). CT

Figure 9. IgG4-related sialadenitis in a 33-year-old man. (a, b) Axial intravenous contrast-enhanced CT images (a obtained at a higher level than b) show swelling of the parotid glands with homogeneous enhancement (arrows). (c) FDG PET/CT images show increased uptake in the parotid and submandibular glands (arrows). Biopsy of a parotid gland revealed dense lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells. (Case courtesy of José Antonio Narváez, MD, Barcelona, Spain.)



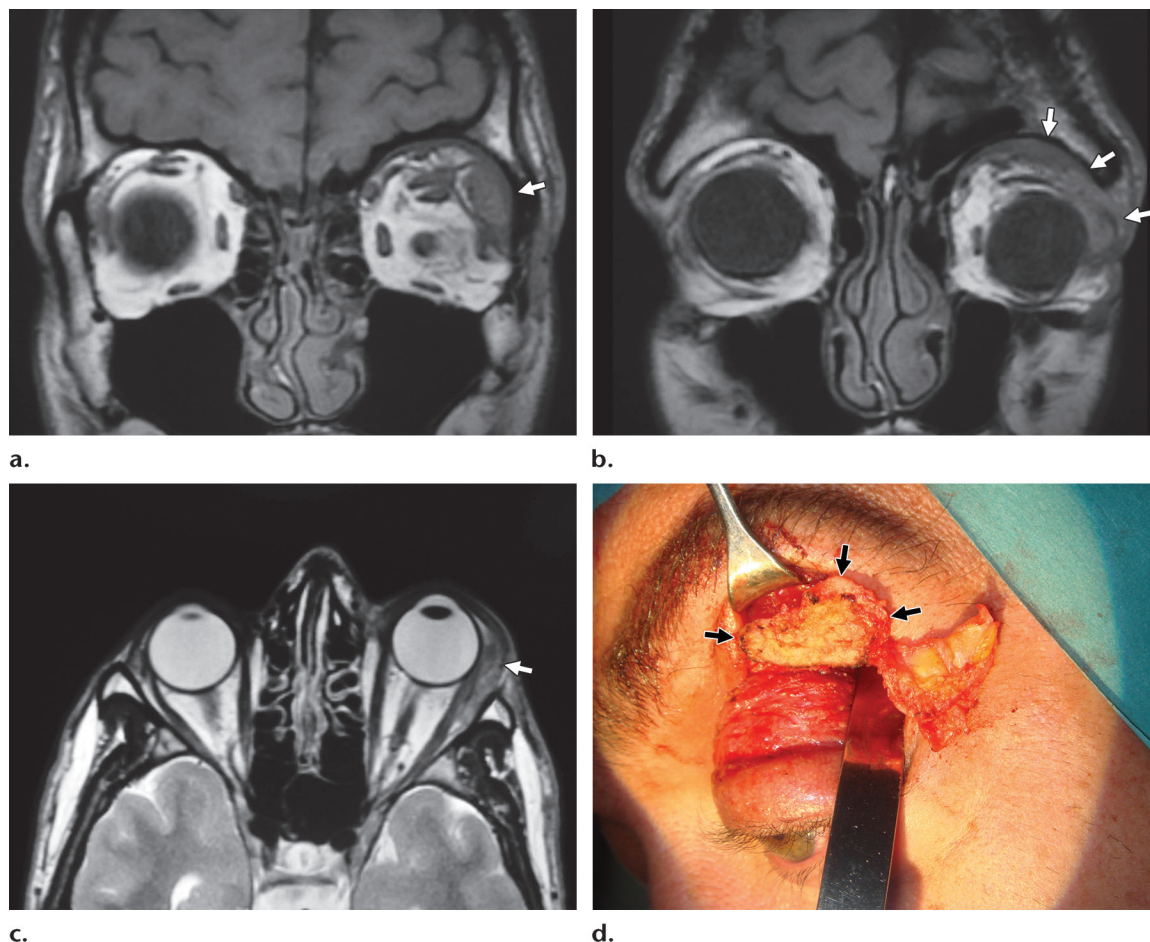


Figure 10. IgG4-related dacryoadenitis in a 37-year-old man. (a, b) Coronal T1-weighted MR images show swelling of the left lacrimal gland (arrows). (c) Axial T2-weighted MR image shows a mass (arrow) located external to the lateral rectus muscle with relatively low signal intensity due to fibrosis. (d) Photograph of the lacrimal gland (arrows) taken during surgical biopsy, the results of which confirmed IgG4-related dacryoadenitis. Histopathologic analysis demonstrated more than 100 IgG4-positive plasma cells per high-power field. (Case courtesy of José Vicente P. Moreiras, MD, Santiago de Compostela, Spain.)

demonstrates either focal or diffuse low attenuation of the thyroid, with minimal contrast enhancement relative to normal thyroid tissue (Fig 12) (59). In a small number of patients with Hashimoto thyroiditis, histologic features may be indistinguishable from those of IgG4-related disease (65). Steroid therapy for Riedel disease often results in marked reduction of the thyroid mass (Fig 12).

IgG4-related Renal Disease

Renal involvement may be present in up to 35% of patients with autoimmune pancreatitis (66,67). Five patterns of disease have been described: bilateral round or wedge-shaped peripheral cortical lesions (the most common) (Fig 13), diffuse patchy involvement (Fig 14), a rim of soft tissue around the kidney, bilateral nodules in the renal sinuses, and diffuse wall thickening of the renal pelvis (66). Biopsy usually reveals tubulointerstitial nephritis with fibrosis and abundant IgG4-positive plasma cell

infiltration. When the disease appears as multiple round or wedge-shaped cortical nodules, the differential diagnosis includes pyelonephritis, vascular insult, metastases, and lymphoma. In rare cases, when the disease manifests as a solitary round lesion, differentiation from renal cell carcinoma may be difficult. The presence of renal lesions in patients with pancreatic disease has been used to help differentiate autoimmune pancreatitis from pancreatic cancer, since their presence strongly suggests the former condition (67). Patients with IgG4-related nephritis have no hematuria and usually improve after undergoing corticosteroid therapy (66).

Renal lesions in IgG4-related disease are usually not visible at nonenhanced CT. After contrast material administration, they appear hypoattenuating relative to the normal renal cortex during the arterial phase, becoming isoattenuating relative to the surrounding parenchyma during later phases. At MR imaging, the lesions demonstrate low signal intensity on both T1- and T2-weighted images,

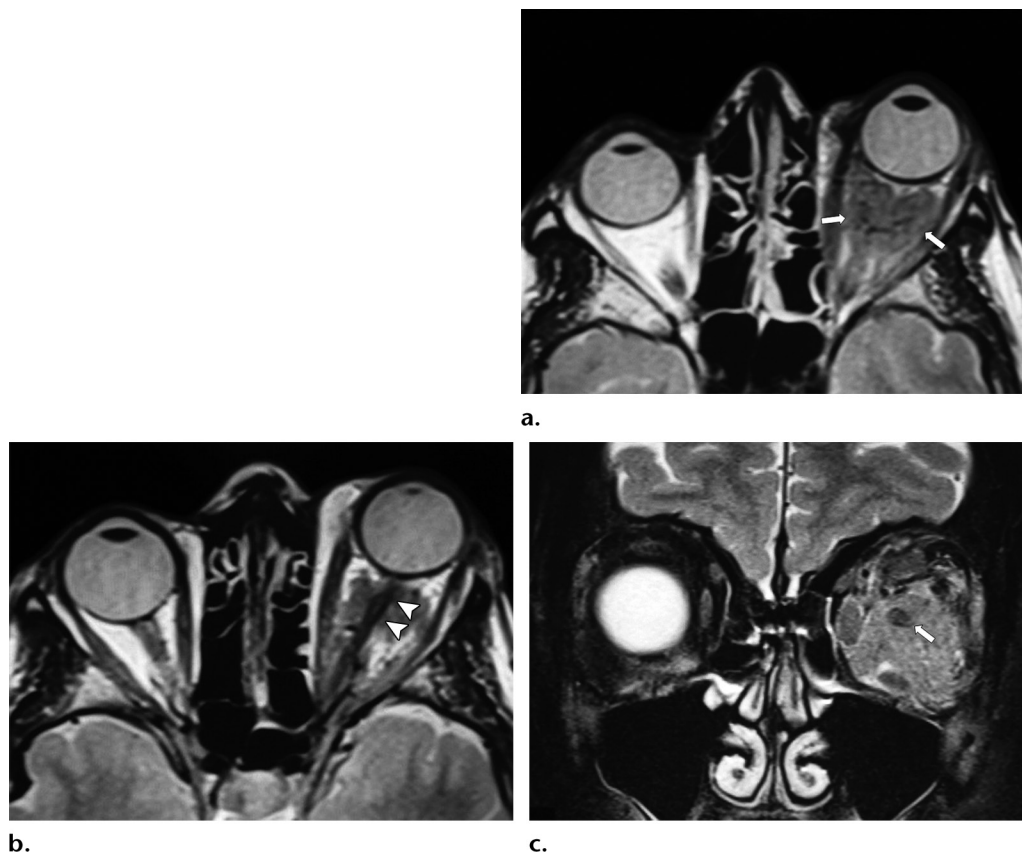


Figure 11. IgG4-related orbital pseudotumor in a 45-year-old woman. (a, b) Axial T2-weighted MR images show an intraconal mass lesion (arrows in a) surrounding the left optic nerve (arrowheads in b) and producing proptosis. (c) Coronal T2-weighted MR image reveals that the mass encases the optic nerve (arrow) and is hypointense relative to brain because of fibrosis. Surgery was performed, and histopathologic analysis revealed a lymphoplasmacytic infiltrate with an IgG4-positive to IgG-positive ratio of greater than 40%. (Case courtesy of José Vicente P. Moreiras, MD, Santiago de Compostela, Spain.)

with mild enhancement on T1-weighted images after contrast material administration (66,68).

IgG4-related Lymphadenopathy

Concomitant lymphadenopathy is often found in patients with IgG4-related disease. It sometimes represents the initial manifestation of the disease, but it is usually discovered at imaging of patients with known IgG4-related disease. Hamano et al (55) reported hilar lymphadenopathy in 80% of patients with autoimmune pancreatitis (Fig 15). Other commonly involved lymph nodes include mediastinal (Fig 15), axillary, cervical, and intra-abdominal nodes. When the lymphadenopathy is generalized, the differential diagnosis includes lymphoma, Castleman disease, and disseminated malignancy. In contrast, the lymph nodes in IgG4-related disease tend to be small (<2 cm), and patients experience no fever or weight loss. Histologic features in these patients differ from those in patients with extranodal disease in that there is usually no sclerosis or phlebitis (4,22).

IgG4-related Retroperitoneal Fibrosis

Retroperitoneal fibrosis is a chronic inflammatory condition that may have many underlying causes, including infection, radiation therapy, drugs, malignant tumor, and trauma. At presentation, about 20% of patients with autoimmune pancreatitis have retroperitoneal fibrosis, which is characterized by abundant IgG4-positive plasma cell infiltration seen in biopsy specimens (69). At cross-sectional imaging, IgG4-related retroperitoneal fibrosis appears as a soft-tissue mass that covers the abdominal aorta and its branches or entraps the ureters, producing hydronephrosis and hydroureter. Periaortic lesions, also known as IgG4-related periaortitis (Fig 14), are nonstenotic masses with irregular margins that show homogeneous late contrast enhancement at CT and may be associated with aortic dilatation (70, 71). Kasashima et al (72) reported that 57% of inflammatory abdominal aortic aneurysms are in fact a manifestation of IgG4-related disease. Lymphoma, large-vessel vasculitis, syphilis, and sarcoidosis-induced aortitis should also be included in the differential diagnosis.

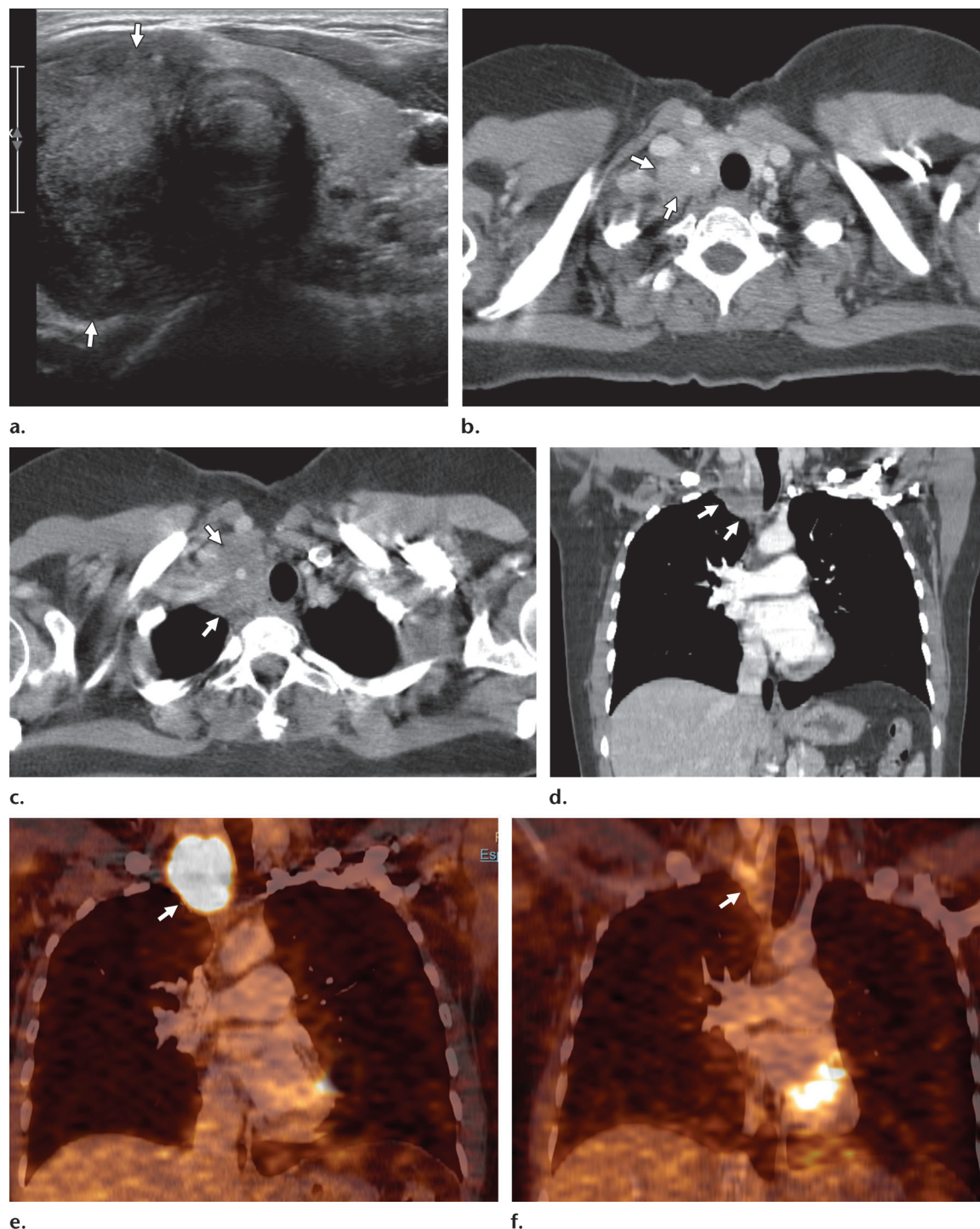


Figure 12. IgG4-related thyroiditis (Riedel thyroiditis) in a 45-year-old woman. (a) Transverse US image shows a large heterogeneous mass in the right lobe of the thyroid (arrows). (b, c) Axial contrast-enhanced CT images reveal that the mass (arrows) has ill-defined margins and encases the right carotid and subclavian arteries. (d) Coronal contrast-enhanced CT image better demonstrates the extension of the mass into the mediastinum (arrows). (e) Coronal fused FDG PET/CT image shows high uptake in the mass (arrow). (f) On a coronal fused FDG PET/CT image obtained after only 3 months of steroid therapy, the mass (arrow) shows a marked response to treatment, with a decrease in volume and radiotracer accumulation.

IgG4-related Sclerosing Mesenteritis

Sclerosing (or retractile) mesenteritis is a rare chronic disorder that leads to localized or diffuse fibrosis and inflammation of the small bowel mesentery. Although its physiopathology remains un-

known, sclerosing mesenteritis is often associated with other fibroinflammatory disorders, including autoimmune pancreatitis, sclerosing cholangitis, and retroperitoneal fibrosis. Recently, Kerdairat et al (73) reported that up to 61% of cases of sclerosing mesenteritis showed histopathologic

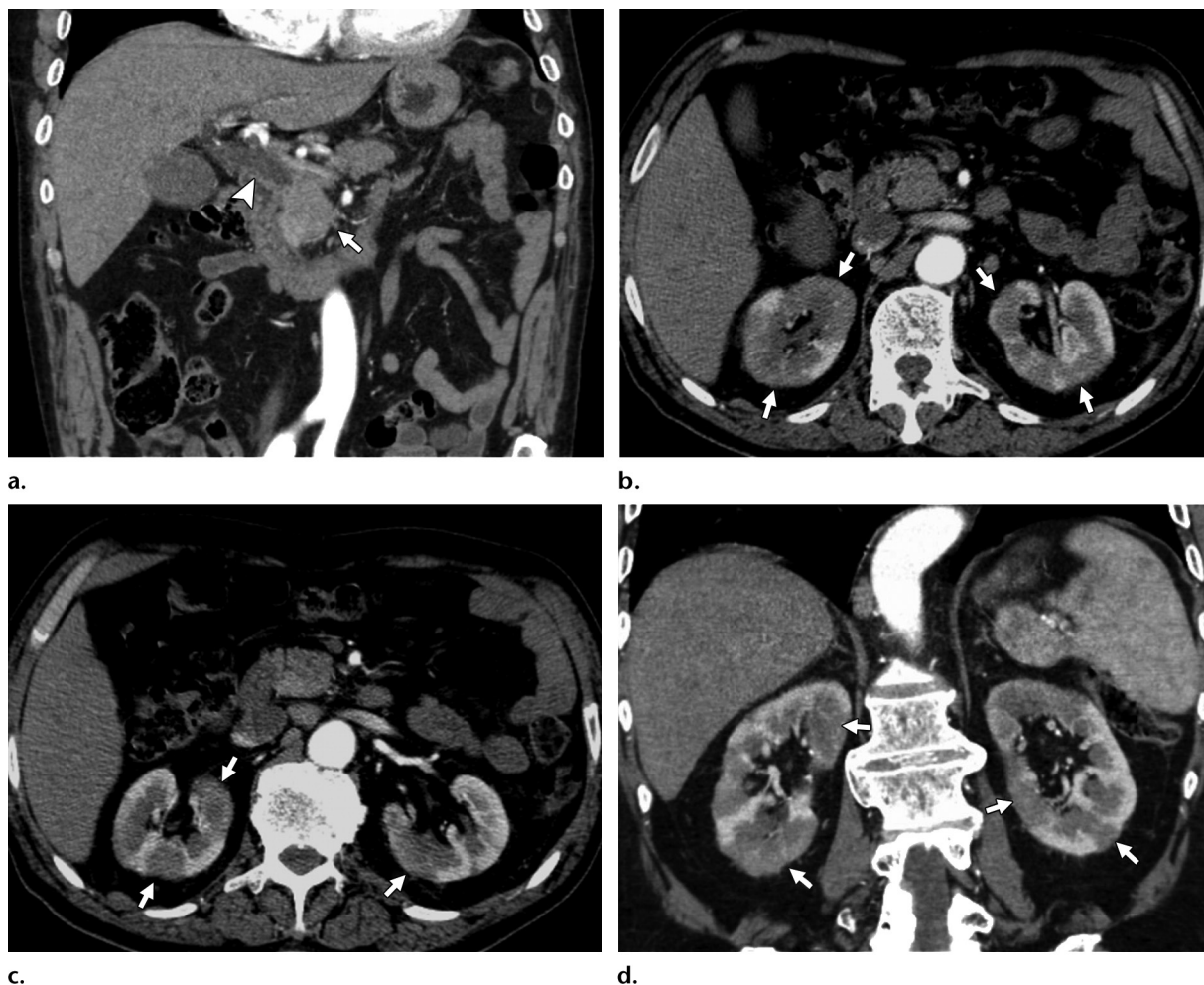


Figure 13. IgG4-related renal disease (multifocal type) in a 78-year-old man with autoimmune pancreatitis. (a) Coronal CT image shows swelling of the pancreatic head (arrow), with extrahepatic bile duct dilatation (arrowhead). (b–d) Axial (b, c) and coronal (d) contrast-enhanced corticomedullary phase CT images show multiple well-defined, wedge-shaped, low-attenuation lesions in both kidneys (arrows). Histopathologic analysis demonstrated tubulointerstitial nephritis. (Case courtesy of Filipe Caseiro, PhD, Coimbra, Portugal.)

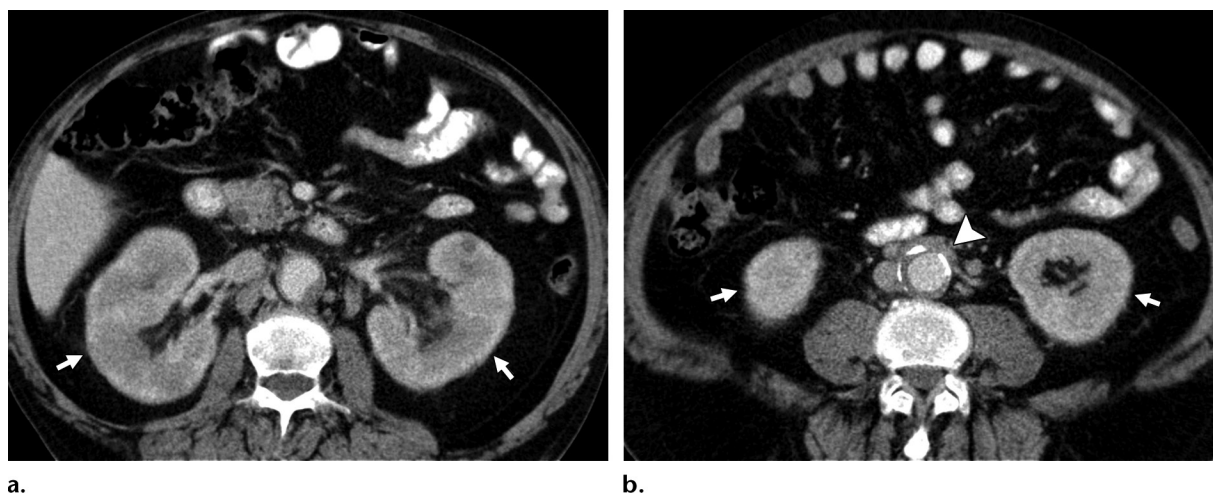


Figure 14. IgG4-related renal disease (diffuse type) in a 76-year-old man. Axial contrast-enhanced corticomedullary phase CT images show enlargement of both kidneys produced by diffuse low-attenuation areas (arrows). Note the small periaortic mass (arrowhead in b), a finding that represents IgG4-related retroperitoneal fibrosis. (Case courtesy of Eva Castañer, MD, Barcelona, Spain.)

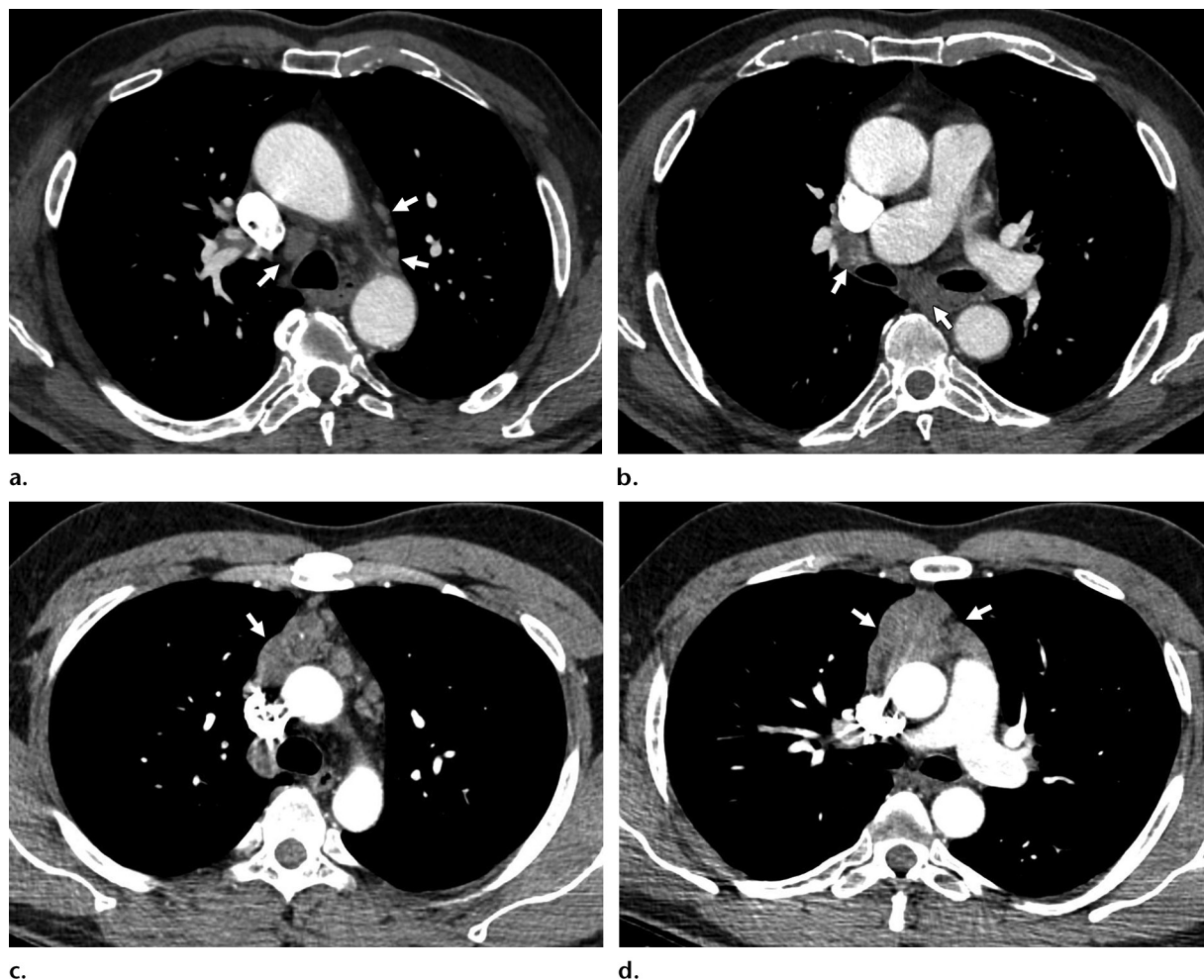


Figure 15. IgG4-related thoracic lymphadenopathy in two different patients. (a, b) Axial contrast-enhanced CT images in a 72-year-old man with autoimmune pancreatitis show an increased number of relatively small, relatively low-attenuation, confluent mediastinal and hilar lymph nodes (arrows). (c, d) Axial contrast-enhanced CT images in a 33-year-old man (same patient as in Figure 9) show multiple enlarged mediastinal lymph nodes and a well-defined anterior mediastinal mass (arrows). The sialadenitis and mediastinal involvement resolved completely after corticosteroid therapy. (Figs 15c and 15d courtesy of José Antonio Narváez, MD, Barcelona, Spain.)

features of IgG4-related disease such as lymphoplasmacytic infiltration, fibrosis, and obliterative phlebitis. At imaging, sclerosing mesenteritis appears as a soft-tissue mass enveloping the mesenteric vessels, mimicking other mesenteric processes such as lymphoma, carcinoid tumor, and carcinosarcoma. A useful CT finding that helps differentiate IgG4-related mesenteritis from these entities is preservation of fat around the mesenteric vessels, a phenomenon that is referred to as the “fat ring sign” (Fig 16) (73). Partial or complete obstruction of the small intestine may occur.

IgG4-related Lung and Pleural Disease

Hirano et al (74) found lung involvement in 13% of patients with autoimmune pancreatitis. Four major types of IgG4-related pulmonary disease have been defined: (a) a type characterized by solid nodular or masslike lesions, (b) a type char-

acterized by round ground-glass opacities, (c) alveolar interstitial disease, and (d) bronchovascular disease (75). Small nodules and masslike lesions may frequently be misdiagnosed as lung cancer (Fig 17). Occasionally, the histologic diagnosis is inflammatory pseudotumor. Some inflammatory pseudotumors of the lung belong to the spectrum of IgG4-related disease, with lymphoplasmacytic infiltration, fibrosis, obstructive phlebitis, and IgG4-positive plasma cell infiltration (76). When IgG4-related lung disease appears as a round ground-glass opacity at CT, imaging findings may suggest bronchoalveolar carcinoma. The alveolar interstitial pattern, a mixture of ground-glass and honeycombing components, must be differentiated from nonspecific interstitial pneumonia. In bronchovascular IgG4-related pulmonary disease, thickening of interlobular septa, combined with frequently associated enlargement of hilar and/or mediastinal lymph nodes, may resemble sarcoidosis

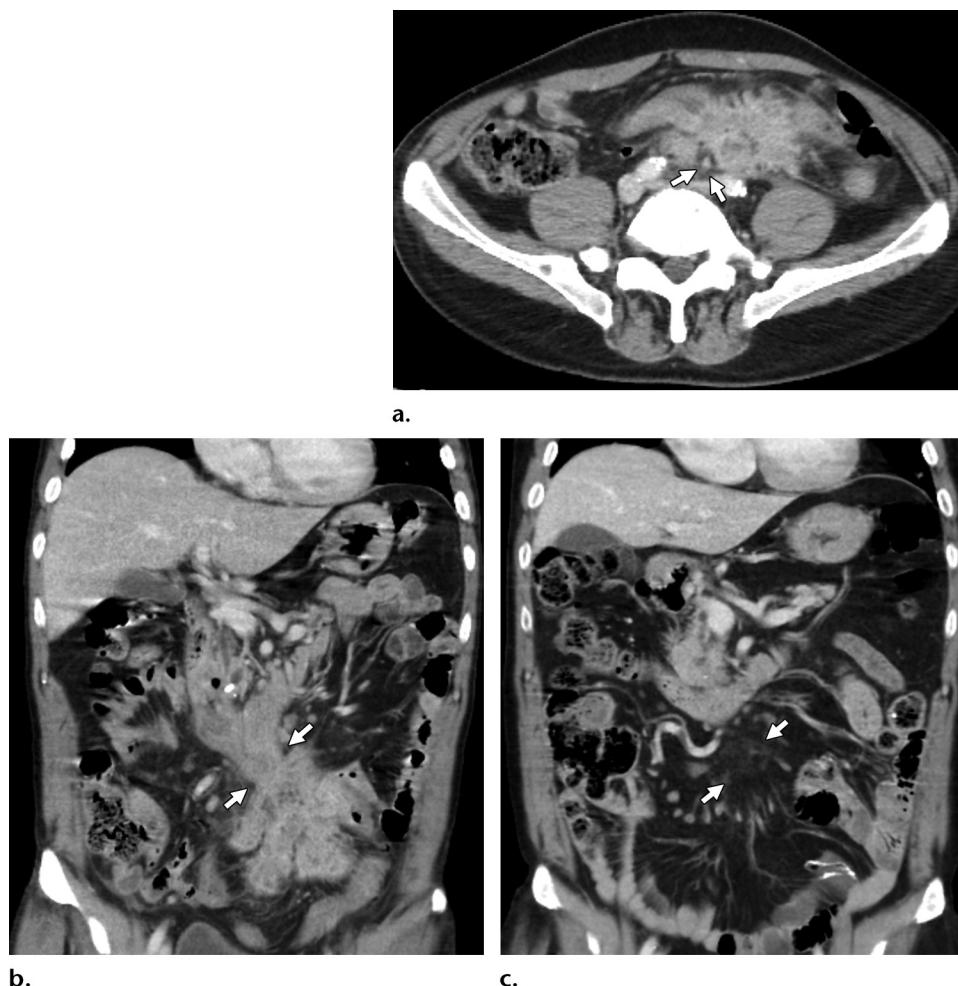


Figure 16. IgG4-related sclerosing mesenteritis in a 52-year-old man. (a) Axial CT image shows an ill-defined soft-tissue mass in the mesentery, with a preserved halo of fat around the superior mesenteric artery (fat ring sign) (arrows). (b) Coronal CT image better demonstrates the extension of the mass, with infiltration and retraction of the duodenum (arrows). (c) Follow-up coronal CT image obtained 9 months later after steroid therapy shows complete resolution of the mass (arrows).

(75). Visceral or parietal pleural thickening has been reported, sometimes involving the subpleural lung parenchyma (Fig 18) (76).

IgG4-related lung disease may manifest with or without involvement of other organs. Patients may be asymptomatic or may present with cough, dyspnea, hemoptysis, chest pain, or respiratory failure. Steroid therapy should improve the clinical symptoms as well as the radiologic abnormalities.

Other Organ Involvement

Rare cases of involvement of the gastrointestinal tract by IgG4-related disease, causing gastric wall thickening and ulcer formation, have been reported (77). A few cases of histologically proved IgG4-related prostatitis have also been reported, with patients demonstrating an enlarged prostate and obstructive urinary symptoms. Pathologic characteristics include chronic inflammatory cell infiltration with an increased number of IgG4-positive plasma cells, accompa-

nying glandular atrophy, and fibrosis. Other rare manifestations that share imaging and histologic characteristics with IgG4-related disease have been described in the testicles, breasts, pituitary gland, and meninges (24).

Conclusion

IgG4-related disease is a relatively recently established systemic disease that produces organ infiltration by fibroinflammatory tissue and sometimes mimics other inflammatory or neoplastic processes. This condition comprises a large number of medical disorders previously considered to be confined to single-organ systems. The pancreas is most commonly involved, but the list of extra-pancreatic manifestations is continually growing. Radiologists must be familiar with this disorder because patients usually demonstrate a marked response to corticosteroid therapy, and timely recognition may help avoid delays in diagnosis and unnecessary invasive procedures.

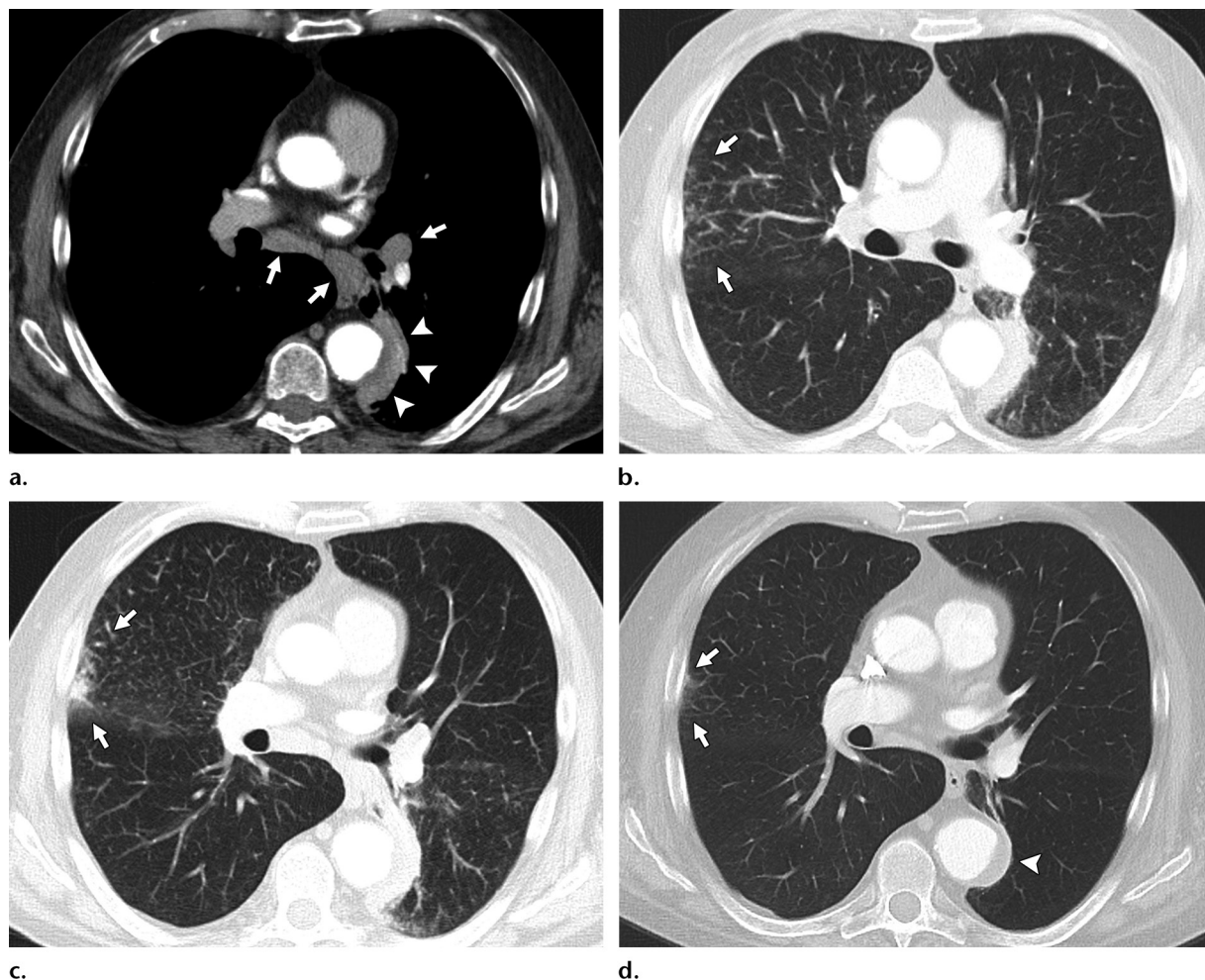


Figure 17. IgG4-related lung disease in a 76-year-old man. The patient presented with no symptoms but had an elevated serum IgG4 concentration (856 mg/dL) and imaging findings of renal involvement (cf Fig 14). (a) Axial contrast-enhanced CT image shows mediastinal and left hilar lymphadenopathy (arrows) and a paraaortic mass (arrowheads). (b, c) Axial CT images obtained at different levels reveal peripheral septal thickening in the right upper lobe and a small area of subpleural airspace disease (arrows in b–d). A presumptive diagnosis of IgG4-related disease was made, and corticosteroid therapy was administered. (d) On a posttreatment axial CT image, all lesions have diminished, including the paraaortic mass (arrowhead). (Case courtesy of Eva Castañer, MD, Barcelona, Spain.)

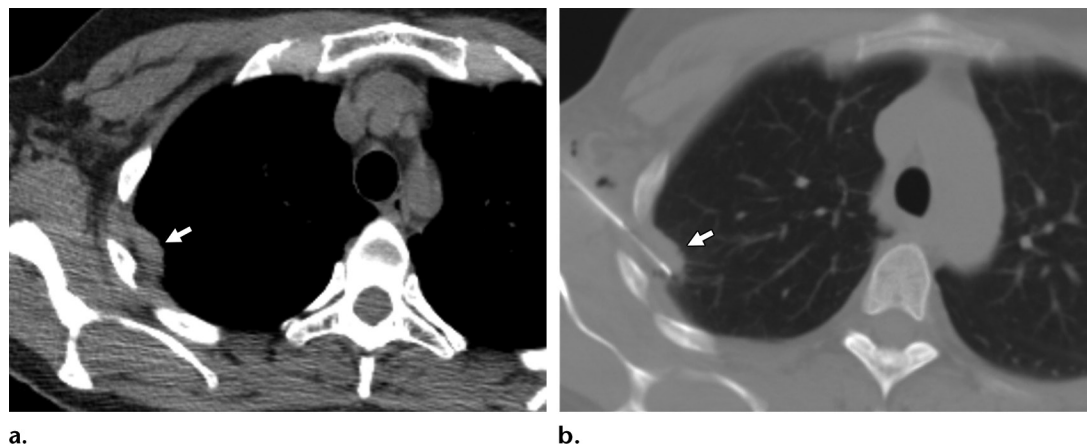


Figure 18. IgG4-related pleural disease in a 45-year-old woman. (a) Axial nonenhanced CT image shows a small pleural-subpleural lesion (arrow in a and b). (b) Axial CT image obtained during percutaneous biopsy, which demonstrated a lymphoplasmacytic infiltrate suggestive of IgG4-related disease.

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