

Systemic IgG4-Related Sclerosing Disease: Spectrum of Imaging Findings and Differential Diagnosis

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OBJECTIVE. The purposes of this article are to provide a practical review of the spectrum of imaging findings in patients with systemic IgG4-related sclerosing disease and to address the differential diagnoses.

CONCLUSION. IgG4-related sclerosing disease is a systemic disorder that can involve almost any organ. The imaging findings consist of diffuse and focal organ infiltration and encasement by inflammatory and fibrotic tissue. Awareness of the spectrum of imaging findings in IgG4-related disease should prompt further evaluation for systemic manifestations to avoid misdiagnosis.

Keywords: ¹⁸F-FDG PET, CT, IgG4-related disorders, MRI

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IgG4-related fibrosclerotic disease has been identified as a subgroup of disorders associated with multiorgan involvement mimicking inflammatory and neoplastic processes. The pancreas is most commonly involved, but the list of extrapancreatic manifestations is continuously growing. IgG4 is a subclass of IgG (normally, 3–6%) that does not activate complement and has a low affinity for targeted antigens. Its physiologic, in particular its pathophysiologic, role is not entirely understood. An important role in allergic reactions is hypothesized [1]. Currently, the main relevance of immunohistochemical detection of increased levels of IgG4 in involved tissues is that IgG4 is a surrogate marker, enabling exclusion of its neoplastic mimics. Proposed diagnostic criteria include an increased serum concentration of IgG4 (> 135 mg/dL), more than 45 IgG4-positive cells per high-power field, and an IgG4/IgG ratio greater than 30%, determined in involved tissues [1, 2]. The former criterion alone correlates with disease activity but unfortunately is insufficient for primary diagnosis because of its lack of specificity. Similarities to other fibrosing autoimmune disorders, such as panniculitis, Reidel struma, and mediastinal fibrosis, is observed both histologically and radiologically. Hence, only the number of IgG4-positive plasma cells and the ratio of IgG4- to IgG-positive plasma cells enable differentiation. Some authors consider these differential diagnoses potential types of burned-out IgG4-related sclerosing disease [2]. The spontaneous course

of IgG4-related sclerosing disease is inflammation shifting to dense sclerosis with severe consequences for the involved sites. Whereas response to glucocorticoids is excellent, often resulting in long-term remission, relapse, which can be treated with alternative agents (e.g., proteasome inhibitors and anti-CD20 antibodies), does occur [3]. Imaging workup of IgG-related sclerosing disease should always include whole-body examinations (e.g., CT, MRI, or ¹⁸F-FDG PET/CT) to document systemic involvement. Both morphologic and functional imaging are beneficial for evaluation of response to therapy [3].

Manifestations of IgG4-Related Sclerosing Disease

IgG4-Related Autoimmune Pancreatitis

IgG4-related autoimmune pancreatitis was the first described manifestation of this spectrum of diseases [4, 5]. Two clinicopathologic entities—lymphoplasmacytic sclerosing pancreatitis and idiopathic duct-centric chronic lymphoplasmacytic sclerosing pancreatitis—have been reported [1]. Elderly men are primarily affected. At presentation of the disease, the pancreas is either diffusely or focally enlarged with irregular narrowing of the main pancreatic duct and, often, concomitant stenosis of the common bile duct. Over time, atrophy and even parenchymal calcification occur. A sausage shape without normal pancreatic clefts and a peripheral smooth (capsule-like) rim of attenuation have been described as characteristic signs [6] (Figs. 1 and 2). In

IgG4-related autoimmune pancreatitis, pancreatic perfusion is reduced compared with perfusion in normal pancreatic tissue (Figs. 1B and 1C); signal intensity on T1- and T2-weighted MR images is nonspecific (Fig. 1D). On FDG PET images, active inflammation results in increased uptake (Fig. 1E). Imaging findings in combination with increased levels of IgG and a conjoint appearance with other autoimmune diseases should raise suspicion of IgG4-related autoimmune pancreatitis. Other differential diagnoses are pancreatic cancer, nonspecific acute or chronic pancreatitis, and primary sclerosing cholangitis. Homogeneous enhancement, lack of parenchymal atrophy, and the absence of vessel encasement and metastatic disease aid in differentiation from pancreatic cancer, whereas clinical and laboratory data enable exclusion of acute pancreatitis. The presence of primary sclerosing cholangitis should always raise the possibility of autoimmune pancreatitis.

Hepatobiliary Tract Involvement

Hepatobiliary tract involvement is found in 50–90% of patients with IgG-related autoimmune pancreatitis but can also occur as an entity of its own [7]. Both the intrahepatic and extrahepatic segments can be involved by IgG4 fibrosclerosis, which causes intramural and extramural lymphoplasmacytic infiltrates. The result is focal or diffuse bile ductal wall thickening, mostly associated with stenosis and upstream cholestasis [1]. Images show tumorlike infiltration involving the cystic, hepatic, choledochal, and small intrahepatic bile ducts (Figs. 3A–3D). Contrast enhancement of the thickened bile duct wall may be marked, especially in active disease, and decline after administration of corticosteroids (Fig. 4). ERCP (Fig. 3C) and MRCP nicely show luminal irregularities and stenosis of the biliary and pancreatic ducts. These findings are nonspecific, however, and primarily suggest cholangiocellular carcinoma. Thus a search for systemic IgG4-related manifestations is imperative. In cholangiocellular carcinoma, tumor infiltration is usually confined to either extrahepatic or intrahepatic bile ducts, frequently leading to focal cholestasis and liver capsule retraction due to desmoplastic growth. Periductal infiltration by breast cancer metastasis, lymphoma, and sarcoidosis should also be considered in the differential diagnosis in the appropriate clinical setting.

Liver involvement is more common in the form of a mass lesion at the hepatic hilum that

encases the bile ducts but may also be manifested by diffuse infiltration of the periportal spaces (IgG4-related hepatopathy) with or without interface hepatitis [1] (Fig. 1F). The latter is usually diagnosed when results of liver function tests are abnormal. Liver biopsy is generally necessary for diagnosis.

Lacrimal and Salivary Gland Involvement

The lacrimal and salivary glands are commonly involved in IgG4-related sclerosing disease, presenting with unilateral or bilateral diffuse or focal swelling. At imaging, the lacrimal gland is enlarged and homogeneously enhancing, but these findings are nonspecific (Fig. 5A). In the parotid and submandibular glands, sialadenitis can be focal and nodular in character, mimicking neoplasia. Bilateral hypoechoic nodular areas with considerable vascularization are found on sonograms, and a parenchymal defect may be seen on sialograms [8]. Abnormal FDG uptake in the bilateral lacrimal and submandibular glands affected by systemic sialadenitis (Mikulicz disease) has been reported [9] (Figs. 5B–5D and 6). Isolated involvement of the submandibular gland (Küttner tumor) presents as a firm swelling difficult to differentiate from a neoplasm [10]. Lymphoma, Sjögren disease, Wegener granulomatosis, and sarcoidosis should be considered in the differential diagnosis.

Retroperitoneal Fibrosis

Retroperitoneal fibrosis is a recognized manifestation of IgG4-related sclerosing disease resembling other types of fibrosis or vasculitis. Unlike giant cell vasculitis, IgG4-related sclerosing disease is usually located along the abdominal aorta and iliac vessels, presenting as nonstenotic vessel wall thickening with irregular margins (Figs. 5E–5G). In early disease stages, marked contrast enhancement and FDG uptake are seen (Fig. 5F). Later, however, fibrosis predominates, which may explain reported treatment failures. Inflammatory aortic aneurysm, lymphoma, large-vessel vasculitis, syphilis, sarcoidosis-induced aortitis, and other autoimmune diseases must be considered in the differential diagnosis.

Renal Involvement

Renal involvement is common in IgG4-related sclerosing disease (35% of cases) and predominantly involves the cortex [11]. Renal parenchymal lesions usually appear as bilateral peripheral cortical nodules, well-defined wedge-shaped lesions, or diffuse involvement.

Images may show cortical nodules coalescing to a perirenal rim of enhancing tissue (Fig. 5H). Enlargement of both kidneys is also frequent and reflects tubulointerstitial nephritis [1]. In the more focal infiltration pattern, multiple bandlike or broad-based triangular low-signal-intensity areas are seen in the peripheral cortex of both kidneys. These areas are particularly well demarcated on T2-weighted (Fig. 7A) and contrast-enhanced T1-weighted (Fig. 7B) MR images. IgG4-related sclerosing disease can also involve the renal sinus or renal pelvis wall [11]. The main differential diagnoses are lymphoma, which generally is not seen in a symmetric, perirenal distribution; extramedullary hematopoiesis; Erdheim-Chester disease; autoimmune diseases; and xanthogranulomatous pyelonephritis.

Paravertebral Masses

Paravertebral masses (Fig. 8) also occur in multisystemic disease but usually do not affect the adjacent spine. The differential diagnoses include lymphoma, Wegener granulomatosis, extramedullary myeloma or hematopoiesis, and metastasis. Biopsy is usually necessary for exclusion of malignancy.

Lymph Node Involvement

Lymph node involvement is detected on imaging studies in 80% of cases of IgG4-related sclerosing disease and may even be the initial manifestation [1]. It is believed that lymph node enlargement does not represent true IgG4-related sclerosing disease but rather reflects the immune disturbance accompanying this disease [1]. Focal or disseminated node enlargement with diffuse marked enhancement is usually found at imaging (Figs. 3E–3G). At FDG PET (Fig. 3G), increased uptake similar to that in lymphoma is expected. The list of differential diagnoses is broad and includes lymphoma, nodal metastasis, reactive lymph node enlargement, Castleman disease, and other autoimmune diseases.

Pulmonary Involvement

Pulmonary involvement in IgG4-related sclerosing disease consists of multiple lung nodules, peribronchiolar infiltration (Fig. 9A), round ground-glass opacities, or reticulointerstitial (Fig. 9B) or hilar adenopathy [1, 12]. Epithelial cells of glandular ducts are believed to represent the main target of IgG4-related sclerosing disease [12]. Differentiation from pneumonia, sarcoidosis, mucosa-associated lymphoid tissue (MALToma), and amyloidosis may be difficult and usually requires biopsy.

CNS Involvement

CNS involvement in IgG4-related sclerosing disease includes infundibulohypophysitis, hypertrophic pachymeningitis, pansinusitis, inflammatory orbital pseudotumor, and chronic subdural hemorrhage [13, 14].

Other Manifestations

Manifestations of IgG4-related sclerosing disease that share imaging and histologic characteristics have been described in the breast, prostate, and testicles and paratesticular region [15].

Conclusion

Cognizance of the broad spectrum of IgG4-related sclerosing disease should raise the level of suspicion and prompt a search for systemic manifestations of this disorder and thus avoid misdiagnosis with consecutive unnecessary surgical procedures.

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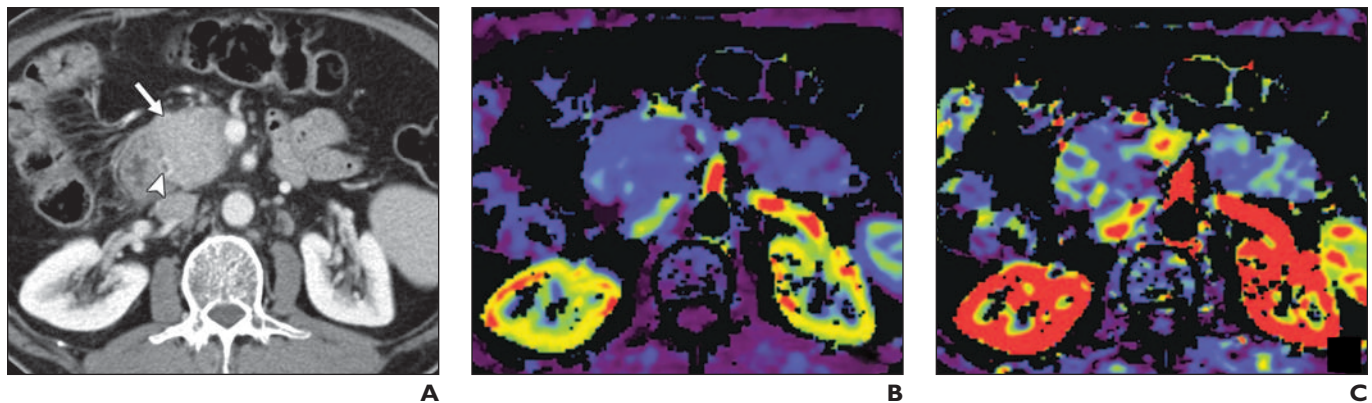


Fig. 1—67-year-old man with IgG4-related autoimmune pancreatitis.

A, Transverse contrast-enhanced CT image shows focal, slightly hypoattenuating enlargement of pancreatic head (arrow) and uncinate process and circular thickening and increased enhancement of the common bile duct wall (arrowhead). Normal pancreatic clefts and fine rim of hypoattenuation surrounding pancreatic head are absent.

B and C, Volume perfusion CT images show homogeneously decreased pancreatic head perfusion expressed by reduced blood flow (**B**) and volume (**C**) compared with kidneys.

(Fig. 1 continues on next page)

IgG4-Related Sclerosing Disease

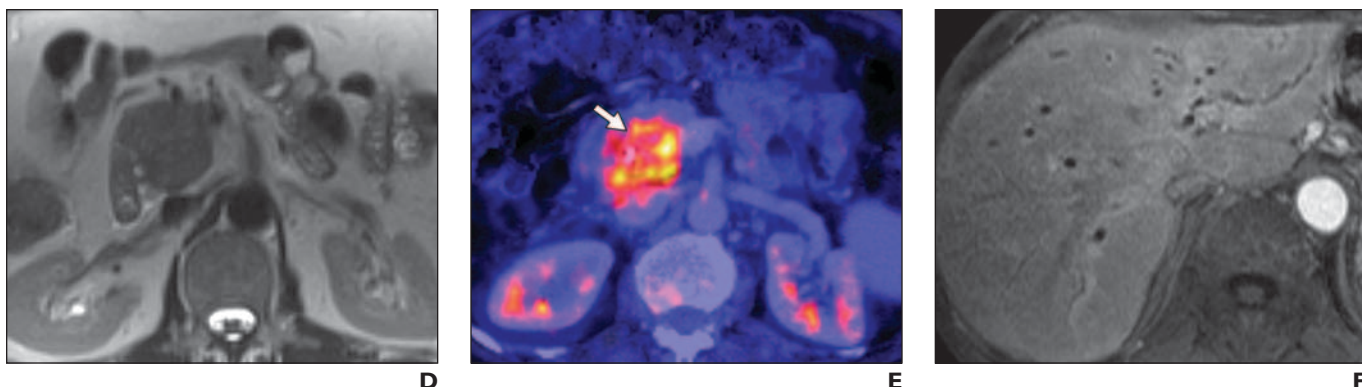


Fig. 1 (continued)—67-year-old man with IgG4-related autoimmune pancreatitis.

D, Transverse T2-weighted MR image of pancreatic head shows nonspecific low-signal-intensity parenchymal infiltration.

E, Transverse FDG PET/CT image shows nonspecifically increased uptake (mean standardized uptake value, 4.1) (arrow) compatible with inflammation or tumor.

F, Contrast-enhanced fat-saturated T1-weighted MR image shows enlargement and heterogeneous signal intensity of liver. Liver involvement was confirmed histologically.

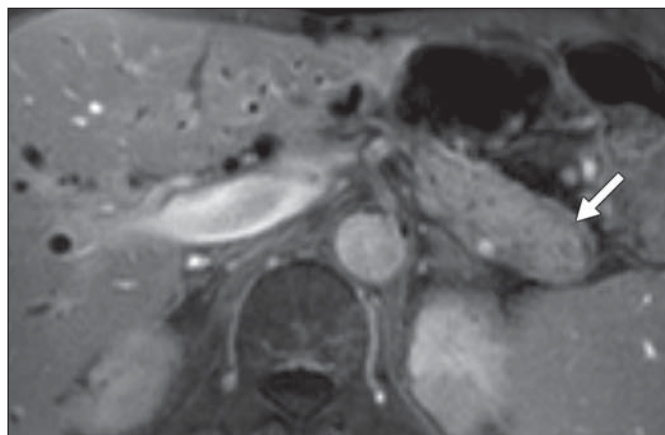


Fig. 2—78-year-old man with nonspecific abdominal pain and IgG4-related autoimmune pancreatitis. Contrast-enhanced fat-saturated T1-weighted MR image shows focal enlargement of pancreatic tail with homogeneous enhancement, absence of peripheral clefts, and peripancreatic hypoattenuating rim (arrow).

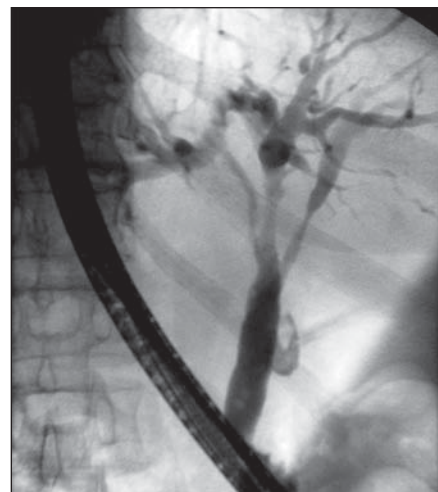
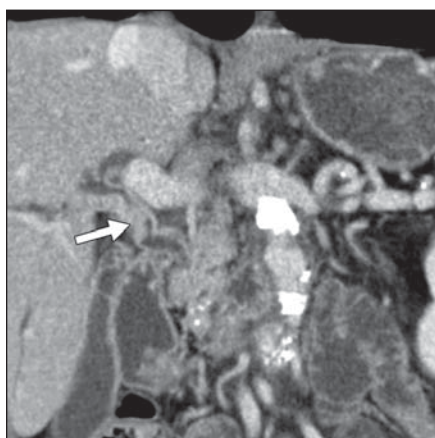


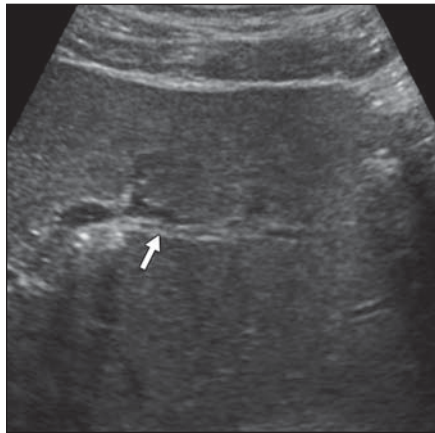
Fig. 3—67-year-old man with jaundice and abdominal discomfort. Condition was diagnosed as systemic IgG4-related disease. Generalized lymph node enlargement was diagnosed with whole-body CT.

A, Coronal contrast-enhanced CT image shows focal nodular thickening of common bile duct wall (arrow) with upstream cholestasis.

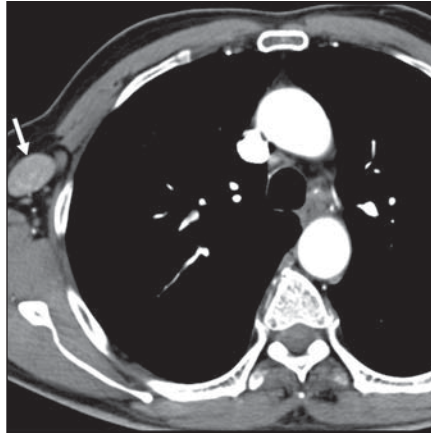
B, Transverse contrast-enhanced fat-saturated T1-weighted MR image shows irregularity of bile ductal wall (arrow) contours, thickening, and cholestasis.

C, ERCP image confirms findings in **A** and **B**.

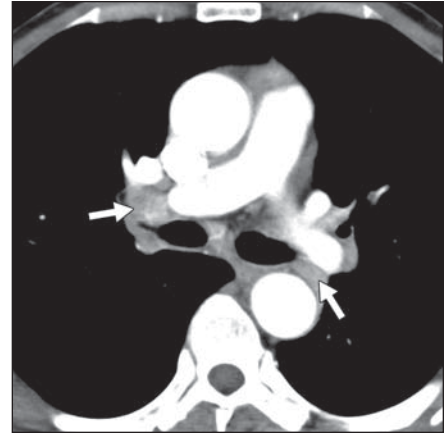
(Fig. 3 continues on next page)



D



E



F



G

Fig. 3 (continued)—67-year-old man with jaundice and abdominal discomfort. Condition was diagnosed as systemic IgG4-related disease. Generalized lymph node enlargement was diagnosed with whole-body CT.

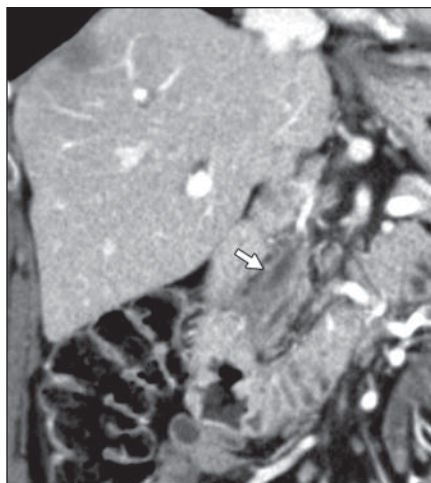
D, Transverse ultrasound image of left hepatic lobe depicts diffuse thickening of intrahepatic bile duct wall (arrow).

E and F, Transverse contrast-enhanced CT images of left axillary region (**E**) and mediastinal lymph nodes (**F**) shows isoattenuating enlargement (arrows).

G, FDG PET/CT image shows nonspecific increased FDG uptake in mediastinal lymph nodes (arrowhead) and increased periaxillary FDG uptake (arrow) with involvement of right iliac artery.



A



B

Fig. 4—70-year-old woman with systemic IgG4-related sclerosing disease and jaundice at initial presentation.

A, Coronal contrast-enhanced CT image at primary diagnosis shows diffuse infiltration of bile duct (arrows) resulting in stenosis and upstream cholestasis.

B, Coronal contrast-enhanced CT image 5 months after **A**, after initiation of glucocorticosteroid therapy, shows marked decline in both bile duct wall thickness and enhancement (arrow).

IgG4-Related Sclerosing Disease

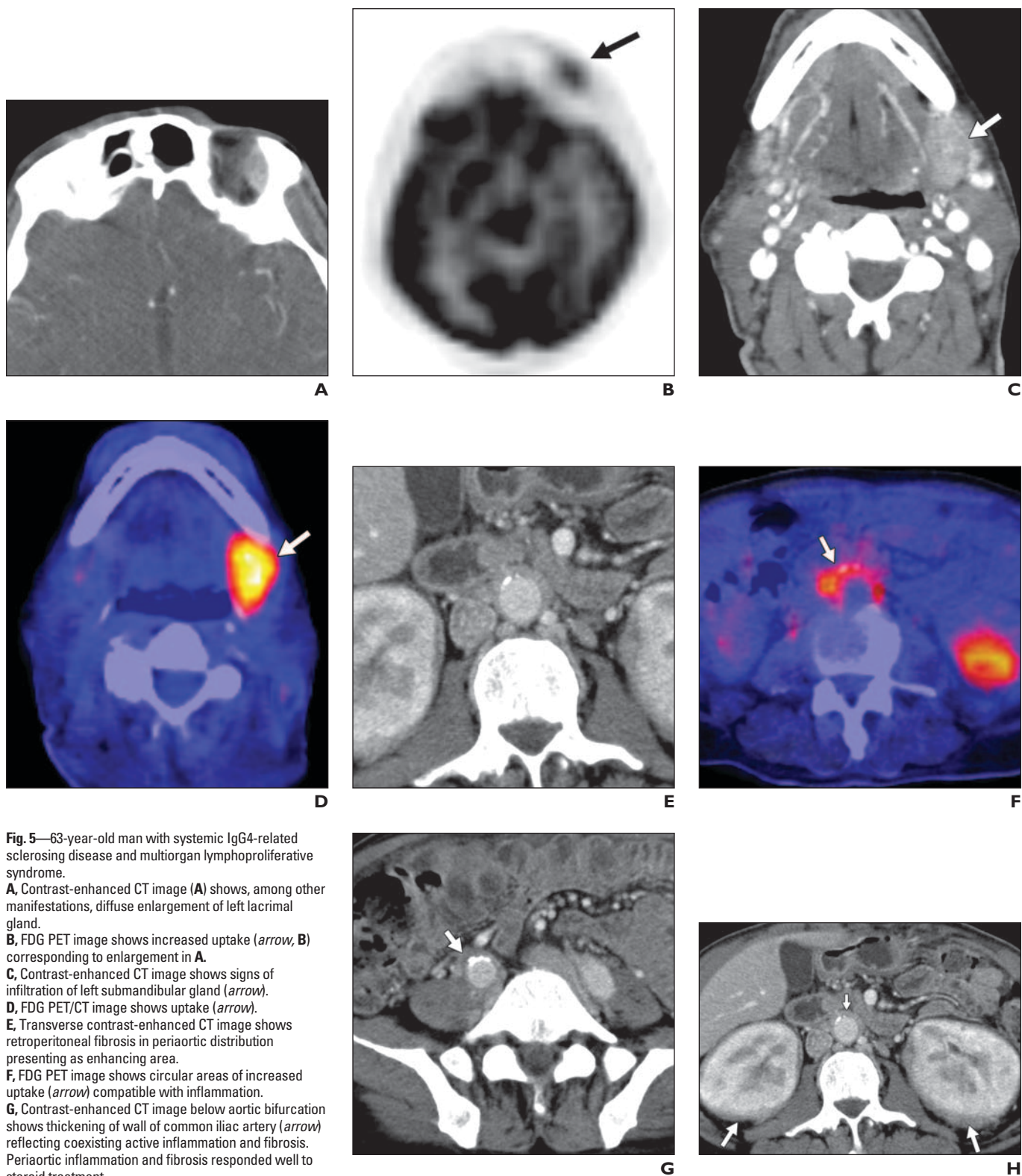


Fig. 5—63-year-old man with systemic IgG4-related sclerosing disease and multiorgan lymphoproliferative syndrome.

A, Contrast-enhanced CT image (**A**) shows, among other manifestations, diffuse enlargement of left lacrimal gland.

B, FDG PET image shows increased uptake (*arrow*, **B**) corresponding to enlargement in **A**.

C, Contrast-enhanced CT image shows signs of infiltration of left submandibular gland (*arrow*).

D, FDG PET/CT image shows uptake (*arrow*).

E, Transverse contrast-enhanced CT image shows retroperitoneal fibrosis in periaortic distribution presenting as enhancing area.

F, FDG PET image shows circular areas of increased uptake (*arrow*) compatible with inflammation.

G, Contrast-enhanced CT image below aortic bifurcation shows thickening of wall of common iliac artery (*arrow*) reflecting coexisting active inflammation and fibrosis. Periaortic inflammation and fibrosis responded well to steroid treatment.

H, Triple-phase contrast-enhanced CT image shows renal involvement with diffuse enlargement (*large arrows*) and enhancement of coalescing perirenal inflammatory and fibrotic tissue, which was confirmed at biopsy. Small arrow indicates thickening of arterial wall.

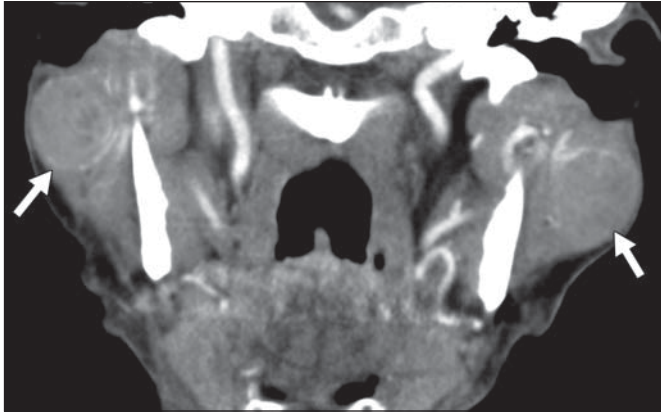
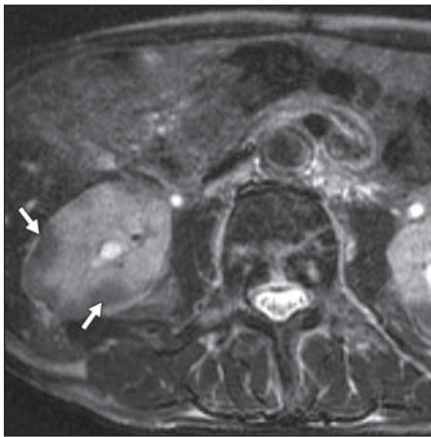
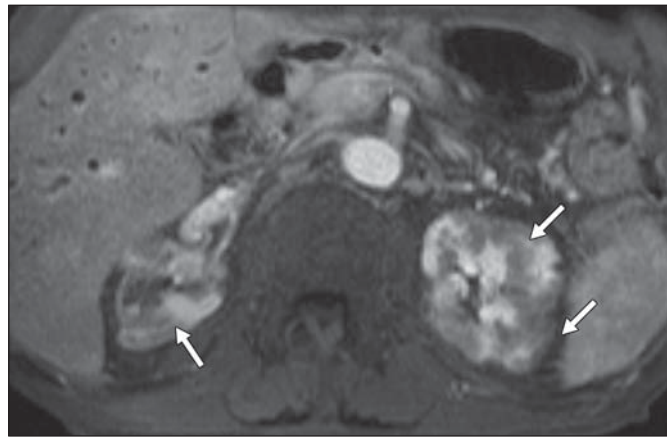


Fig. 6—78-year-old man with systemic IgG4-related sclerosing disease. Coronal contrast-enhanced CT image shows bilateral nodular isoattenuating masses (arrows) in parotid glands.



A

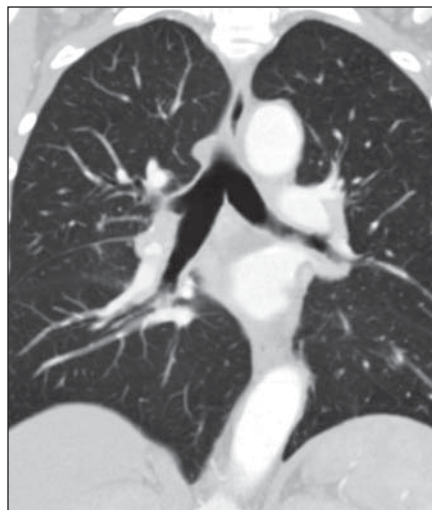


B

Fig. 7—78-year-old man with systemic IgG4-related sclerosing disease. **A** and **B**, Transverse T2-weighted (**A**) and fat-saturated T1-weighted contrast-enhanced (**B**) MR images show multiple bandlike or broad-based, triangular, low-signal-intensity areas (arrows) in peripheral cortex of both kidneys.



Fig. 8—70-year-old woman with systemic disease. Transverse contrast-enhanced CT image shows well-defined several-centimeter-large isoattenuating mass. IgG4-related sclerosing disease was confirmed at biopsy.



A



B

Fig. 9—63-year-old man with systemic IgG4-related sclerosing disease. **A** and **B**, Coronal (**A**) and transverse (**B**) chest CT images show peribronchial spread of inflammation and reticular interstitial and bronchiolar infiltration in right perihilar region.