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GENERAL RADIOLOGY

PICTORIAL ESSAY

The pancreatic and extrapancreatic manifestations of IgG4-related disease

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ABSTRACT

The association between immunoglobulin IgG4 and autoimmune pancreatitis was first shown in 2001. Since then many previously established fibrosclerotic diseases demonstrating synchronous or metachronous multiorgan involvement have been included within the ambit of IgG4-related disease. Diagnostic criteria have been proposed involving 1) serum IgG4 level elevated beyond 135 mg/dL, 2) IgG4+ to IgG+ plasma cell ratio >40% and >10 IgG4+ cells per high power field of biopsy sample and 3) a constellation of imaging features which involve a variety of organ systems. We present a pictorial essay demonstrating the spectrum of imaging findings for IgG4-related disease, including dacryosialadenitis, variety of renal lesions, tumefactive thickening of the extraocular muscles and orbital nerve, sclerosing cholangitis, and type I pancreatitis. Imaging plays an important role in diagnosis, screening for multiorgan involvement, and follow-up of the disease.

Hamano et al. (1) first described the relationship between IgG4 and autoimmune pancreatitis in 2001. Since then, the spectrum of IgG4-related disease (IgG4-RD) has increased and diseases involving multiple systems have been included. Several previously classified diseases are being included within this category and the list continues to grow. These are fibrosclerotic diseases that demonstrate synchronous or metachronous multiorgan involvement mimicking inflammatory or neoplastic lesions. Umehara et al. (2) have proposed two diagnostic criteria based on their experience: first, serum IgG4 level elevated >135 mg/dL and second, the ratio of IgG4+ to IgG+ plasma cells >40% and >10 IgG4+ cells per high power field of biopsy sample. Imaging with computed tomography (CT) and magnetic resonance imaging (MRI), as well as positron emission tomography (PET) continues to perform a vital role in diagnosis and management of the disease. Once diagnosis is suspected or has been established, whole body screening may be performed to look for systemic involvement, using a CT scan due to its speed and cost advantages compared with an MRI. The natural history of the disease includes inflammation gradually leading to dense sclerosis. The inflammatory stage of IgG4-RD shows good response to glucocorticoids, often going into remission; however, recurrence involving the same or different organ is frequently seen. We present an extensive pictorial essay demonstrating the spectrum of IgG4-RD with involvement of multiple organ systems.

Head and neck

IgG4-RD frequently affects the head and neck and now includes many previously classified diseases. Diseases such as Riedel thyroiditis, Mikulicz disease, Küttner tumor, idiopathic orbital inflammation (inflammatory pseudotumor), orbital lymphoid hyperplasia, and pituitary hypophysitis are examples of some of the previously classified diseases that have been added to the spectrum of IgG4-RD (3). On imaging, the findings are nonspecific with unilateral or bilateral enlargement of the lacrimal gland (Fig. 1) and/or parotid glands with uniform enhancement (4). Apart from diffuse enlargement, IgG4-RD may present as a focal enhancing nodule within the parotid gland. Küttner disease shows isolated involvement of the submandibular gland and biopsy may be needed to differentiate it from neoplasm.

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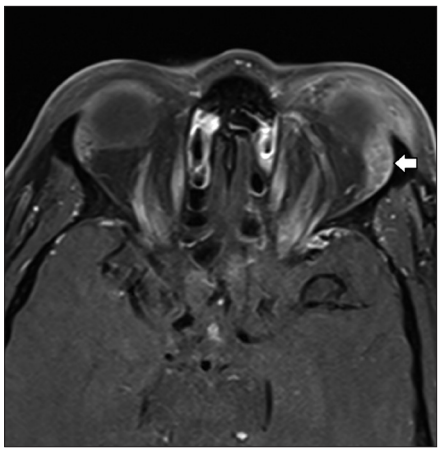


Figure 1. Axial T1-weighted contrast-enhanced MRI of the orbits showing asymmetric thickening and enhancement of the left lacrimal gland *(left arrow)*. Incisional biopsy showed IgG4-related sclerosing dacroadenitis.

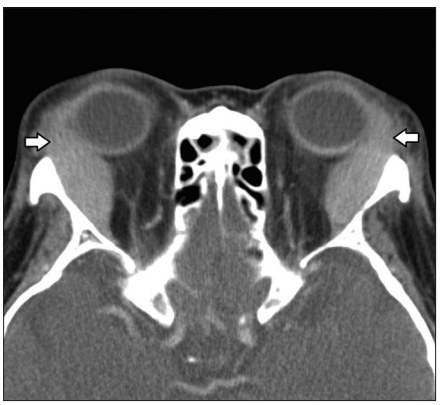


Figure 2. CT image of the orbits shows symmetrical thickening and enhancement of bilateral lacrimal glands, one of which was biopsied later to reveal IgG4-RD *(horizontal arrows)*.

Main points

Diagnostic criteria for IgG4-related disease include:

- Organ involvement:
  - i. Dacryosialadenitis: swelling of two pairs of glands
  - ii. Lungs: solid nodular, round-shaped ground glass opacities, alveolar interstitial, or bronchovascular lesions
  - iii. Eyes: extraocular muscle and orbital nerve mass-like thickening
  - iv. Kidneys: tubulointerstitial nephritis, cortical nodules, peripheral cortical lesions and renal pelvis involvement
  - v. Sclerosing cholangitis (with response to steroid trial)
  - vi. Type I pancreatitis (with response to steroid trial)
  - vii. Others: retroperitoneal fibrosis, lymphadenopathy, sclerosing mesenteritis
- Serum IgG4 >135 mg/dL
- IgG4+ / IgG+ cell ratio >40% and >10 IgG+ cells per high power field of biopsy sample

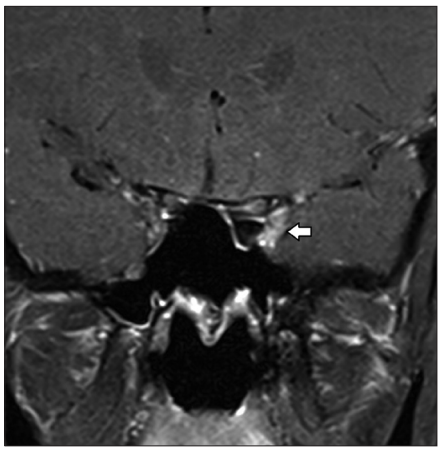


Figure 3. T1-weighted contrast-enhanced image of the brain shows thickening and enhancement of the left V1 (first branch of trigeminal nerve) *(left arrow)*.

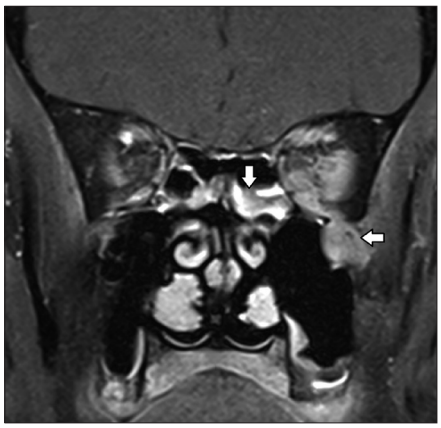


Figure 4. T1-weighted contrast-enhanced image of the brain shows thickening and enhancement of the left infraorbital nerve *(left arrow)*. Also note sinusitis in this patient *(down arrow)*.

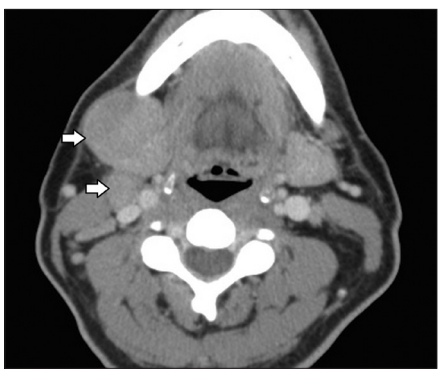


Figure 5. Axial CT image shows right 2A cervical lymphadenopathy *(lower arrow)* with the submandibular gland pushed medially *(upper arrow)*. Excision biopsy showed lymphoid hyperplasia with reactive plasmacytosis consistent with IgG4-RD.

The intraorbital findings of the IgG4-RD may include orbital inflammatory pseudotumor, which may present as unilateral or bilateral intraconal, conal, or extraconal masses,

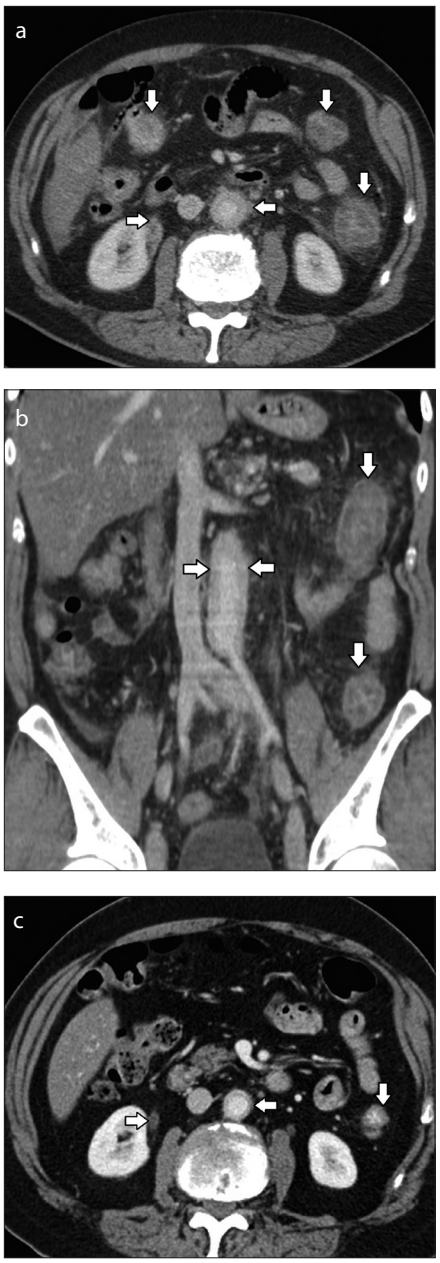


Figure 6. a–c. Axial **(a)** and coronal **(b)** CT images show thickening of the abdominal aortic wall with surrounding inflammatory changes in keeping with aortitis *(left arrow)*. The image also shows thickening of the colonic wall with pericolic inflammatory fat stranding *(down arrow)*. Also note thickening of the right proximal ureter walls *(right arrow)*. Axial CT **(c)** through similar level after 3 months of corticosteroid therapy. Note decrease in aortic wall thickening, right ureter thickening, and resolution of bowel wall thickening and inflammation.

as shown in Fig. 2. Although inflammatory pseudotumor may be within the spectrum of IgG4-RD, most cases have a different etiology (4). Thickening of the cranial nerves may be encountered, with trigeminal nerve and its branches being the most commonly involved nerve (Figs. 3, 4). It presents as tubu-

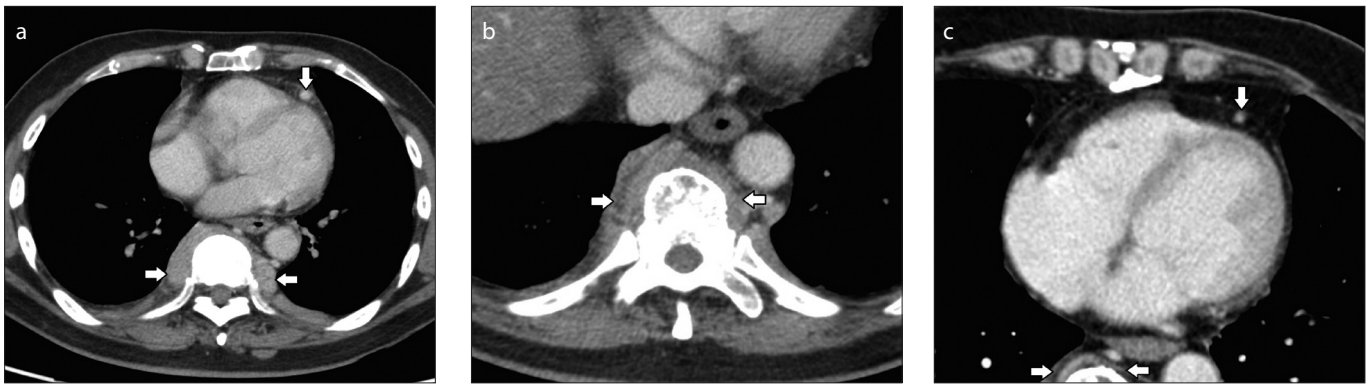


Figure 7. a–c. Axial CT image **(a)** through the mediastinum shows inflammatory fat stranding along the left anterior descending artery *(down arrow)* soft tissue thickening along the thoracic vertebra at T4 vertebral level *(horizontal arrows)*. Axial CT image **(b)** shows paravertebral soft tissue thickening along the lower thoracic vertebra at T10 vertebral level *(horizontal arrows)*. Axial CT image **(c)** in the same patient after corticosteroid therapy shows resolution of vasculitis as well as paravertebral soft tissue thickening *(arrows)*.

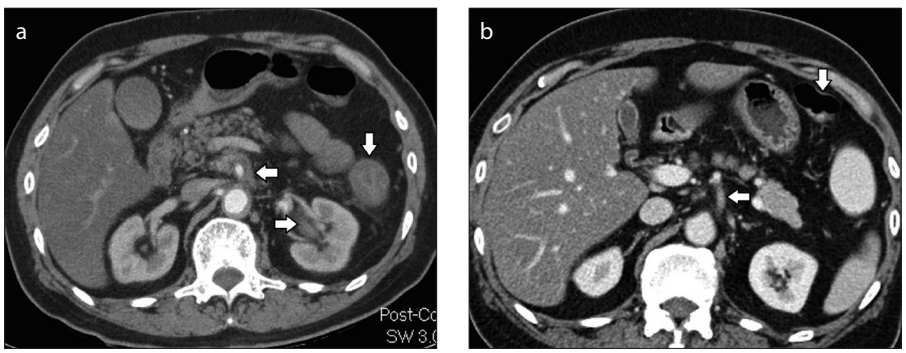


Figure 8. a, b. Axial CT image **(a)** through the upper abdomen shows soft tissue along the superior mesenteric artery (SMA) *(left arrow)*. Also note inflammation around left renal pelvis *(right arrow)* and inflammatory changes in the descending colon *(down arrow)*. Axial CT image **(b)** at a similar level shows resolution of soft tissue along the SMA after treatment with corticosteroids.

lar thickening with uniform enhancement of one of the branches of the nerve in the skull base. Within the calvarium, pachymeningeal thickening and pituitary hypophysitis are some of the manifestations now included within the spectrum. Pansinusitis shown in Fig. 4, Riedel thyroiditis, and lymphadenopathy shown in Fig. 5 have also been demonstrated to be associated with IgG4-RD.

Lungs

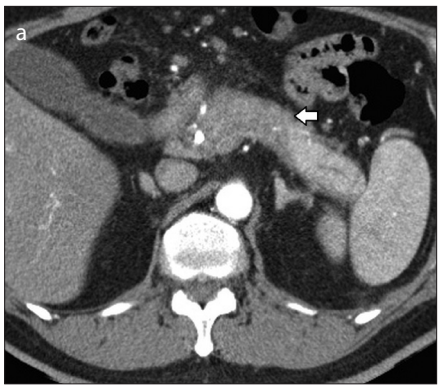
Knowledge on pulmonary manifestations of IgG4-RD is mostly based on case reports and case series. Inoue et al. (5) attempted to categorize the pulmonary findings of the disease into four subcategories: solid nodular, round-shaped ground glass opacities, alveolar interstitial, and bronchovascular. In their case series based on CT findings, carcinoma, sarcoidosis, and lymphoproliferative disorders were the differential diseases considered. Fibrosing mediastinitis has similar radiologic features with the features of IgG4-RD elsewhere in the body. This is corroborated by the fact that a subset of fibrosing mediastinitis cases exhibit the histopathologic and immunologic characteristics consistent with IgG4-RD (6). Differential diagnosis of fibrosing mediastinitis includes granulomatous infection, sarcoidosis, and prior radiotherapy to the thorax (7, 8).

Vascular system

Aortitis comprises a set of inflammatory conditions characterized by chronic inflammation of the aortic wall and could either be infective or inflammatory, as shown in Figs. 6 and 7 (9). Noninfectious aortitis may be a consequence of systemic rheumatologic disease such as rheumatoid arthritis, ankylosing spondylitis, Behcet disease, giant cell, and Takayasu arteritis. However, it is now noted that these diseases are frequently hallmarked by variable but prominent lymphoplasmacytic infiltrate, sclerosis, and phlebitis, which are indistinguishable to those of IgG4-RD. Noninfectious aortitis has been more commonly associated with thoracic aorta, while aneurysm in these cases is more commonly seen in the abdominal aorta (9). The CT features of aortitis include thickened aortic wall with periaortic inflammation. Besides aortitis, vasculitis can be seen in other mid-sized arteries (e.g., celiac, superior mesenteric, cardiac, or renal arteries) as shown in Fig. 8.

Hepatopancreatobiliary system

Autoimmune pancreatitis is a chronic inflammatory condition that has distinct clinical, radiologic, and histologic features. The IgG4-RD, as we know it today, was first described as an association between autoimmune pancreatitis and elevated IgG4 and to this date the pancreas remains the most commonly involved organ. IgG4-RD classically presents as chronic pancreatitis with absence of acute attacks of pancreatitis (10, 11). The three sets of diagnostic criteria that are currently used worldwide are, the Mayo clinic criteria, the Korean criteria and the Japanese criteria, each with its own merit (12). There is diffuse or patchy enlargement of the organ, giving it a mass like appearance often mimicking pancreatic carcinoma (12). Often a capsule-like rim demonstrating delayed enhancement, which is thought to be secondary to fibrotic changes, is seen surrounding the pancreas as shown in Fig. 9. On MRI, the involved segments of the pancreas show decreased T1-weighted signal intensity, and homogeneous enhancement is noted in the contrast-enhanced sequences (Fig. 9) (13). Diffuse pancreatic enlargement with featureless borders, delayed enhancement, with or without a capsule, has been described as "sausage" pancreas (Fig. 10) (14). Segmental or diffuse irregular stenosis of the main duct of the pancreas can be identified on both endoscopic retrograde cholangiopancreatography (ERCP) and



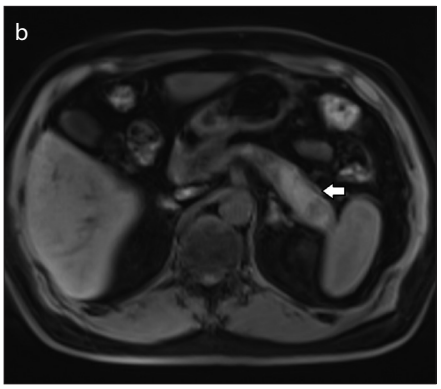


Figure 9. a, b. Axial CT image **(a)** shows autoimmune pancreatitis *(left arrow)*. The pancreatic tail is bulky with enhancement and loss of fat cleft. A hypodense rim surrounding the pancreatic tail is thought to represent fibrous tissue. Axial T1-weighted image **(b)** shows bulky pancreatic tail with T1-weighted hyperintensity. Surrounding fibrotic tissue is seen as T1-weighted hypointense rim, better depicted on MRI than on CT.

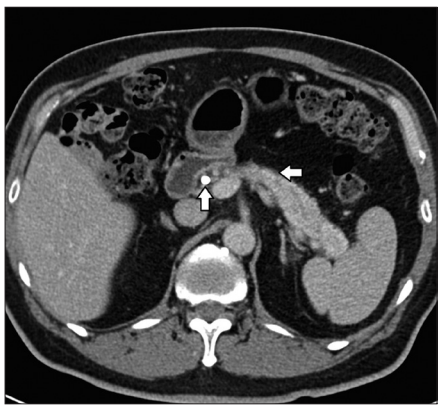


Figure 10. A patient with fine-needle aspiration cytology (FNA)-proven autoimmune pancreatitis depicting loss of fat cleft in the pancreas, sausage pancreas *(left arrow)*. A stent is seen in the common duct, also see Fig. 11 *(up arrow)*.

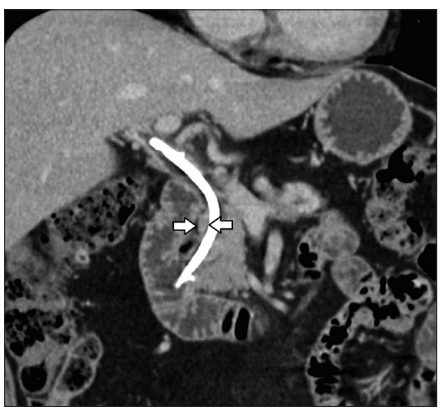


Figure 11. Same patient as in Fig. 10. Coronal CT image shows thickened and irregular proximal common duct walls, with surrounding inflammation *(horizontal arrows)*.

magnetic resonance cholangiopancreatography (MRCP). It is important to identify autoimmune pancreatitis early in the course of management as it shows good response

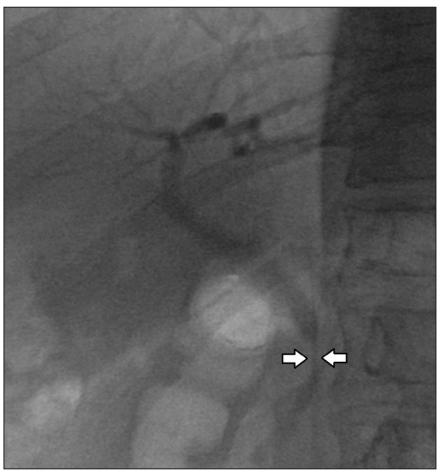


Figure 12. Spot ERCP image of a patient with autoimmune pancreatitis involving pancreatic head shows narrowing of the distal common duct wall *(horizontal arrows)*.

to medical management and unnecessary intervention may be avoided in some cases.

Sclerosing cholangitis is a disease known to be caused by various etiologic factors such as choledocholithiasis, biliary tumor, and infection. When no association is identified it is termed as primary sclerosing cholangitis. IgG4-related sclerosing cholangitis exists in up to 88% of patients with autoimmune pancreatitis, making bile duct the second most common site of involvement (Fig. 11) (11). Intrapancreatic common duct is the most commonly involved segment (Fig. 12). Multifocal strictures may occur within the intrahepatic biliary tree (Fig.13), but is a less common feature of IgG4-RD compared with primary sclerosing cholangitis. In patients with IgG4-RD, the involved segments of the bile ducts show mural thickening, irregular luminal narrowing, and contrast enhancement. Segmental narrowing of the duct is

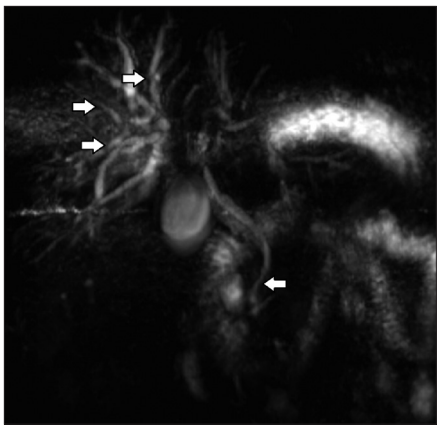


Figure 13. 3D MRCP image of the same patient as in Fig. 12 one year later shows recurrence with persistent narrowing of the distal common duct *(left arrow)*. Also, note the beaded appearance of the intrahepatic bile ducts *(right arrows)*.

seen on ERCP or MRCP with proximal dilatation of the biliary ducts, as shown in Figs. 12 and 13. If left untreated, the cholangitis may go into remission or progress further to cause biliary cirrhosis. IgG4-related sclerosing cholangitis responds well to glucocorticoid therapy and early diagnosis is prudent in the management of the disease. When a biliary stricture is seen, especially with the presence of a mass, differentiation from malignancy may be difficult. Within the liver, IgG4-RD may present with a pseudotumor; however, a strong degree of suspicion (particularly if there is involvement of other organs along with clinical-pathologic correlation) is often necessary for prompt diagnosis and management of this entity.

Kidneys

The kidneys are involved in about a third of individuals with IgG4-RD. Tubulointerstitial nephritis is the most dominant renal expression of IgG4-RD and may manifest as acute or chronic renal dysfunction (15). Radiologically, four types of disease patterns can be recognized within the kidneys, namely mass-like lesions, peripheral cortical lesions, round or wedge-shaped renal cortical nodules, and renal pelvic involvement, as shown in Figs. 14 and 15. Differential diagnosis is based on the type of radiologic pattern and vary from acute pyelonephritis to malignancy. The lesions are usually hypoattenuating during the arterial phase and show mild enhancement in the delayed phase. With MRI, these lesions are iso- to hypointense on T1-weighted and hypointense on T2-weighted sequences, with mild contrast enhancement (15).

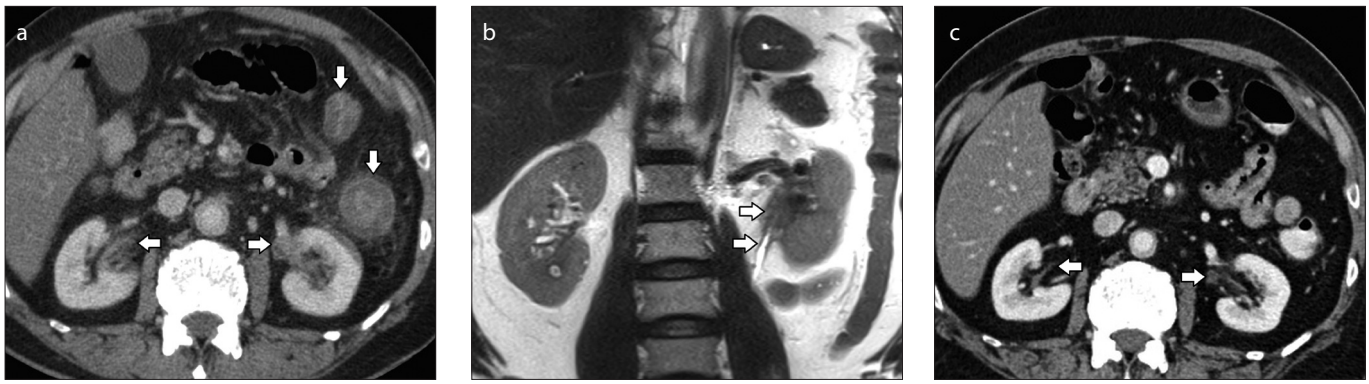


Figure 14. a–c. Axial CT **(a)** showing asymmetric thickening of the ureteric wall, more prominent on the left than on the right *(horizontal arrows)* and colonic edema *(down arrows)*. Coronal T2-weighted image **(b)** through the left renal pelvis in the same patient shows mass-like thickening of the ureter wall, which later decreased on the left and resolved on the right with corticosteroid treatment (**c,** *horizontal arrows)*.

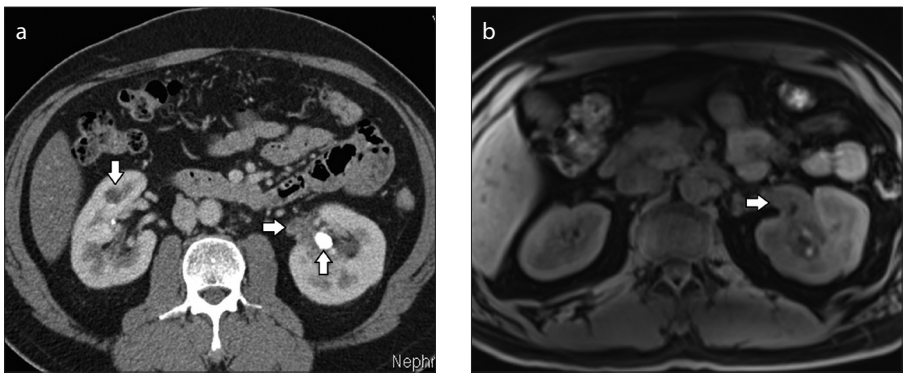


Figure 15. a, b. Axial CT **(a)** in a patient with autoimmune pancreatitis shows mass-like thickening of the walls of the left renal pelvis and the proximal ureter *(right arrow)*; a renal stone is also seen *(up arrow)*. Pathogenesis could be IgG4-related or due to inflammation secondary to renal stone. Also note a hypodense nodule in the right kidney *(down arrow)*. T1-weighted image **(b)** of the same patient at a higher level, during a 2-month follow-up shows persistent thickening of the left renal pelvis wall *(right arrow)*. The nodule in the right kidney has resolved.

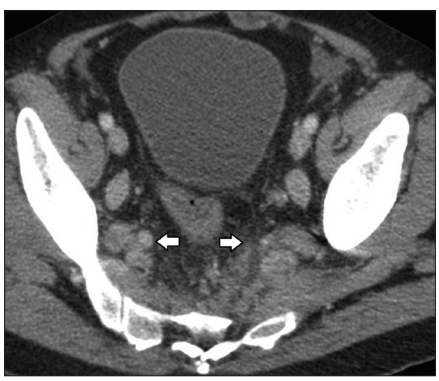


Figure 16. Axial CT image through the pelvic cavity in the same patient as in Fig. 10 shows bilateral internal iliac lymphadenopathy *(horizontal arrows)*.

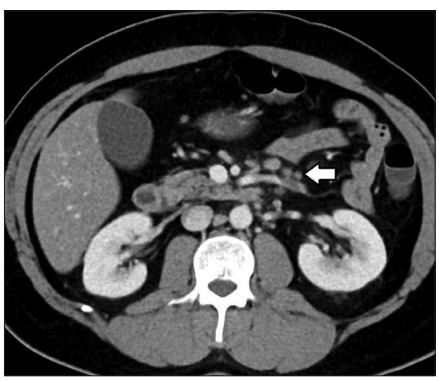


Figure 17. Axial CT image through the abdomen in a patient with sclerosing mesenteritis shows mesenteric fat stranding, haziness, and a few adjacent enlarged mesenteric lymph nodes *(left arrow)*.

Others

Retroperitoneal fibrosis is seen in approximately 10%–20% of patients with autoimmune pancreatitis. IgG4-RD retroperitoneal fibrosis is hallmarked by a large mass with soft tissue density, limited to the retroperitoneum and pelvic brim. The abdominal aorta is plastered to the vertebra rather than being elevated in case of lymphadenopathy. Lymphadenopathy is seen in up to 33% of patients growing up to 2 cm and shows good response to corticosteroid therapy (Figs. 15 and 16) (16). Paravertebral soft tissue is seen in some cases; however, the vertebrae themselves are spared. Other diseases like sclerosing mesenteritis (Fig. 17) and inflammatory bowel disease have also been shown to be associated with IgG4-RD.

Conclusion

IgG4-RD is a comparatively novel entity, and since an association between IgG4 and autoimmune pancreatitis was established, many diseases have been added to the gamut. It shows good response to treatment with corticosteroids; therefore, early diagnosis using the criteria described in this article would expedite treatment and potentially prevent significant organ damage. Imaging along with serial serum IgG4 levels plays an important role in the assessment of disease activity (17). Additionally, PET imaging has been proven to be useful in detecting disease which may not have significant manifestations on CT and MRI (18). Further studies are needed to explore more about the pathology of the disease and its management.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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