
PICTORIAL ESSAY

A Pictorial Review of Immunoglobulin G4-related Sclerosing Disease

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ABSTRACT

Immunoglobulin (Ig) G4-related sclerosing disease is a relatively new disease entity. Any organ system can be affected. Therefore, there is a wide range of possible clinical manifestations. Diagnosis is often difficult and relies on a combination of radiological features, laboratory data, and histology findings. IgG4-related sclerosing diseases are frequently found to be associated with autoimmune pancreatitis. There are several established diagnostic criteria that are used to diagnose autoimmune pancreatitis. In our centre, we use the Asian Diagnostic Criteria for Autoimmune Pancreatitis in 2008. A total of 10 cases with proven IgG4-related systemic disease from 2008 to 2012 were reviewed. This pictorial essay aimed to share our imaging findings among patients with proven IgG4-related sclerosing disease.

Key Words: Autoimmune diseases; Immunoglobulin G; Pancreatitis

中文摘要

免疫球蛋白G4相關性硬化病的圖文回顧

余燊明、陸國倫、楊芷珩、陸永恆、黃嘉敏

免疫球蛋白 (Ig) G4相關性硬化病是一種較新的疾病。該病可以影響任何器官系統，所以可能的臨床表現形式多樣。診斷通常困難，需要綜合影像學特徵、實驗室數據和組織學結果。IgG4相關性硬化病通常與自身免疫性胰腺炎有關。目前已建立了診斷自身免疫性胰腺炎的幾套標準。我們中心使用自體免疫胰臟炎2008年亞洲診斷標準。本文圖文回顧2008至2012年確診為IgG4相關全身性疾病的10宗病例，旨在分享該病的影像學表現。

INTRODUCTION

Immunoglobulin (Ig) G4-related sclerosing disease (IRSD) is a systemic fibroinflammatory condition. It predominantly affects middle-aged and elderly

males. Tissue fibrosis, obliterative phlebitis, and organ infiltration by IgG4-positive plasma cells and T-lymphocytes are characteristics of this disease. Serum IgG4 elevation is frequently observed. Any organ

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system can be affected.¹ As this disease often shows good response to steroid therapy,² awareness and prompt diagnosis help to avoid unnecessary investigations and invasive treatments.

PANCREATIC INVOLVEMENT

IRSDs are frequently found to be associated with autoimmune pancreatitis (AIP).¹ AIP is characterised by irregular narrowing of the main pancreatic duct and enlargement of the pancreas, elevation of serum γ globulin or IgG concentration, dense lymphoplasmacytic infiltration with fibrosis and obliterative phlebitis of the pancreas, and a favourable response to steroid therapy.³ Patients most commonly present with painless obstructive jaundice.² The pattern of involvement of AIP may be diffuse, focal, or multifocal. Diffuse disease is the most common, causing diffuse pancreatic enlargement. Focal disease is less common, and its appearance may mimic tumours because of focal mass-like lesions which often involve the head of pancreas. Pancreatic ductal dilation in AIP is typically milder than in pancreatic carcinoma.⁴ AIP may also be associated with extrapancreatic lesions such as sclerosing cholangitis, retroperitoneal fibrosis, and sialadenitis.⁵

The diagnosis of AIP is based on the Asian Diagnostic Criteria for Autoimmune Pancreatitis. Imaging, laboratory, and histopathological features are included as diagnostic factors in these criteria (Table⁶). The Research Committee of Intractable Pancreatic Diseases supported by the Ministry of Health, Labour and Welfare of Japan, and the Korean Society of Pancreatobiliary Diseases worked together to establish these criteria which were published in 2008.⁶

In resected pancreas with AIP, histopathological features include numerous IgG4-positive plasma cells, fibrosis with lymphoplasmacytic infiltration, periductal inflammation, and obliterative phlebitis.⁶ These histological changes likely explain the imaging findings in AIP including featureless pancreatic border, effacement of the lobulation of the pancreas, and diffuse decrease in pancreatic enhancement. Sometimes, a hypoattenuating rim can be observed (Figure 1). AIP can, however, also exhibit focal enlargement or a low-attenuating mass (Figure 2).⁷

The differentiation of AIP from pancreatic carcinoma can be difficult. The double duct sign is a common finding in both conditions (Figure 3). Abrupt cutoff of the dilated pancreatic duct and vascular encasement should favour the diagnosis of carcinoma.^{7,8} Diffuse parenchymal swelling, rather than a focal mass, is suggestive of AIP.⁹

It is important to look for associated extrapancreatic findings such as retroperitoneal fibrosis and renal involvement,^{10,11} which favour the diagnosis of AIP. Advanced imaging with positron emission tomography / computed tomography (CT) may help to differentiate carcinoma from AIP. According to Ozaki et al,¹² pancreatic lesions in AIP are much more commonly associated with heterogeneous fluorine-18 fluorodeoxyglucose (FDG) accumulation and multiple localisation; whereas pancreatic carcinoma is more commonly seen with homogeneous accumulation and solitary localisation. In their case series, FDG uptake was noted in the lacrimal glands, salivary glands, biliary ducts, and retroperitoneal space only in AIP patients but

Table. Diagnostic criteria for autoimmune pancreatitis (AIP).⁶

| Criteria | |
|---|---|
| I | Imaging (both criteria required) 1. Imaging of pancreatic parenchyma: diffuse / segmental / focal enlargement of the gland, occasionally with a mass and / or hypoattenuation rim 2. Imaging of pancreaticobiliary ducts: diffuse / segmental / focal pancreatic ductal narrowing, often with the stenosis of the bile duct |
| II | Serology (one criterion required) 1. High levels of serum immunoglobulin (Ig) G or IgG4 2. Detection of autoantibodies |
| III | Histopathology of pancreatic biopsy lesions Lymphoplasmacytic infiltration with fibrosis, with abundant IgG4-positive cell infiltration |
| AIP should be diagnosed when criterion I and one of the other two above criteria are satisfied, or when the histology shows evidence of lymphoplasmacytic sclerosing pancreatitis in the resected pancreas. | |
| Optional | Response to steroid therapy Diagnostic trials of steroid therapy should be conducted carefully by pancreatologists and only in patients fulfilling criterion I alone with negative work-up results for pancreatobiliary cancer |

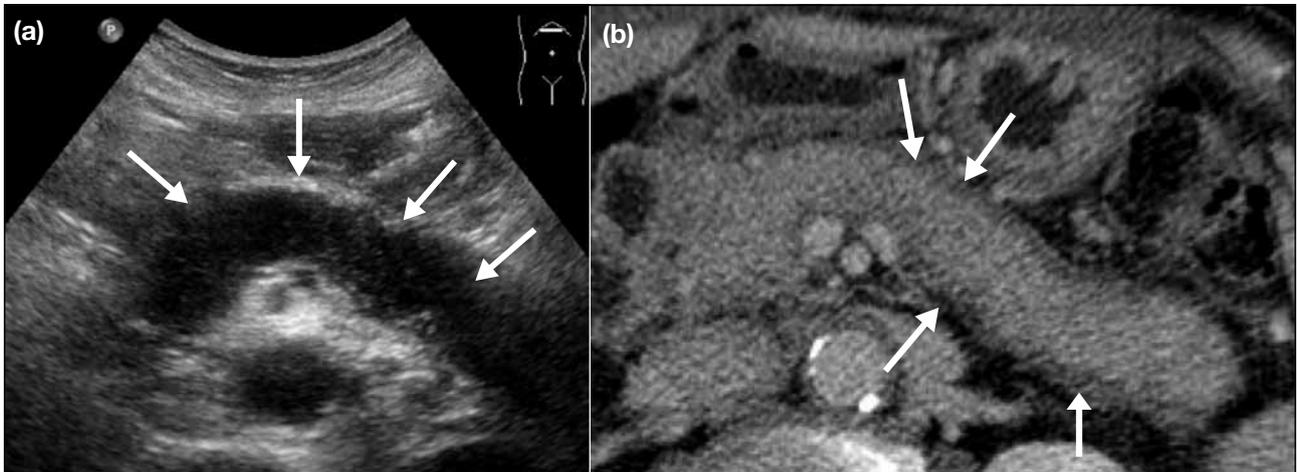


Figure 1. (a) A transverse ultrasonography image of upper abdomen shows a diffusely swollen and hypoechoic pancreas (arrows). (b) A corresponding axial contrast computed tomography image shows a swollen pancreas with characteristic hypoattenuating rim (arrows); there is associated diffuse obliteration of parenchymal cleft leading to a featureless appearance.



Figure 2. (a, b) Axial contrast computed tomography (CT) images show both diffuse and focal abnormalities with mildly diffuse pancreatic swelling, hypoattenuating rim, and a focal hypoenhancing lesion over the pancreatic tail (arrows). (c, d) The hypoenhancing lesion in the pancreatic tail resolves on follow-up CT study.

not in pancreatic cancer patients.¹²

Diffusion-weighted imaging (DWI) may also be helpful in the differentiation of these two conditions. Both AIP and pancreatic carcinoma show high-signal

intensity on DWI. Pancreatic carcinoma is likely to be a solitary nodular lesion, whereas AIP may show diffuse, solitary, or multiple lesions. AIP is likely to show lower apparent diffusion coefficient (ADC) values than pancreatic carcinoma, which shows lower

ADC values than normal pancreas. Kamisawa et al¹³ suggested an ADC cutoff value of $1.075 \times 10^{-3} \text{mm}^2/\text{s}$ to distinguish AIP from pancreatic cancer. Post-steroid therapy AIP lesions may show ADC values similar to those in normal pancreas.



Figure 3. An axial contrast computed tomography image shows dilated bile ducts and pancreatic duct — the double duct sign. Abrupt cutoff of the pancreatic duct is also present in this patient (arrow). Extrapancreatic disease is manifested as a hypoenhancing lesion in the left kidney.

BILIARY AND GALLBLADDER INVOLVEMENT

The biliary tree is probably the most commonly affected system by IRSD after the pancreas. IgG4-related sclerosing cholangitis is frequently associated with AIP. Bile duct wall enhancement is frequently seen on imaging. Ohara et al¹⁴ described the classification of cholangiogram in sclerosing cholangitis with AIP as follows: type 1 — stenosis present only in the distal common bile duct; type 2 — stenosis diffusely distributed in the intrahepatic and extrahepatic bile ducts; type 3 — stenosis localised to both the hilar hepatic area and the distal common bile duct; type 4 — strictures evident only in the hilar area. The radiological findings in IgG4-related sclerosing cholangitis can be very similar to those in primary sclerosing cholangitis (PSC). Clinical correlation is important for diagnosis, as PSC tends to occur in younger patients aged around 30 to 40 years,⁴ while IgG4-related cholangitis has a more acute presentation, a shorter duration of symptoms,⁴ and there is often association with inflammatory bowel disease and poor response to steroid therapy,¹ while

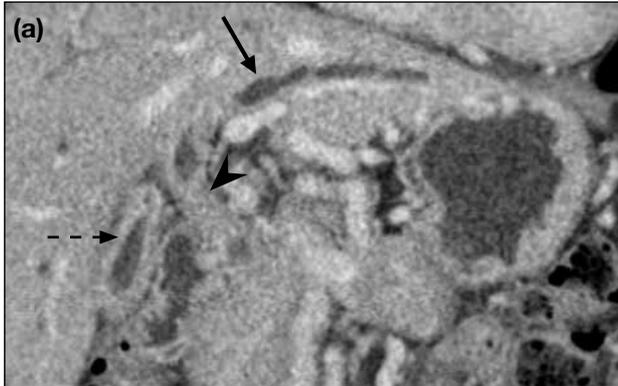
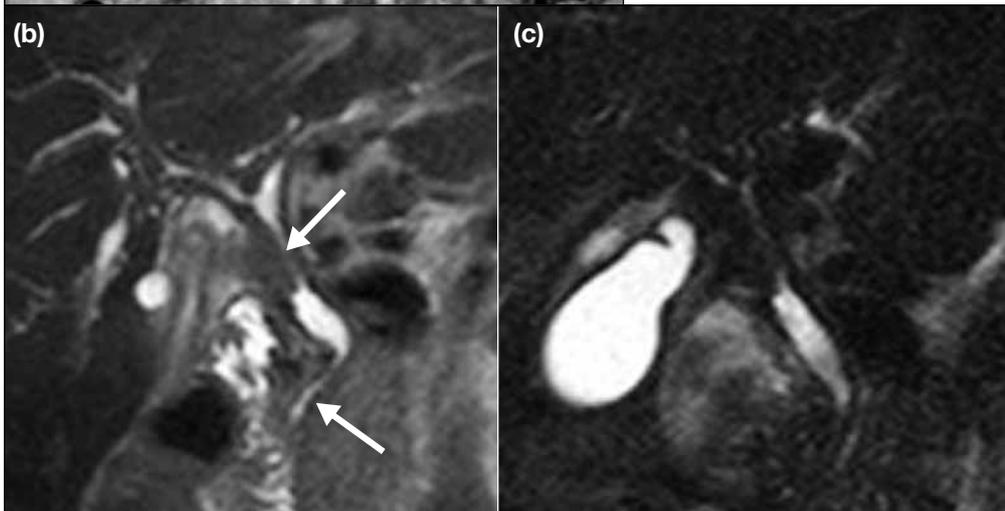


Figure 4. (a) A coronal contrast computed tomography image shows dilated intrahepatic ducts with wall enhancement (arrow) and segmental strictures in common bile duct (CBD) [arrowhead]. Note the diffuse involvement of the intrahepatic ducts, the hilum and the distal CBD regions. Small gallbladder with diffuse wall thickening is also seen (dashed arrow). (b) The biliary ductal stricture is better demonstrated in magnetic resonance cholangiopancreatography (MRCP) [arrows]. (c) The follow-up MRCP after steroid treatment shows improvement of the biliary ductal stricture and gallbladder wall thickening.



IgG4-related cholangitis tends to occur in middle-aged patients, frequently associated with AIP and other sclerosing disease such as sialadenitis,¹ and shows good response to steroids. Ohara et al¹⁴ also described the comparison of cholangiographic findings of PSC and sclerosing cholangitis with AIP. In their series, band-like stricture, beaded appearance, pruned-tree appearance, and diverticulum-like outpouchings were only found in PSC; long and segmental strictures with prestenotic dilatation were significantly more common in sclerosing cholangitis with AIP. Stricture of the distal common bile duct was observed in both conditions, but significantly more frequent among patients with sclerosing cholangitis with AIP (Figure 4).¹⁴ Extrabiliary disease with involvement of the pancreas or kidneys is highly suggestive of IgG4-related sclerosing cholangitis.⁴ When the gallbladder is involved in IgG4 disease, diffuse wall thickening is the main imaging finding (Figure 4).

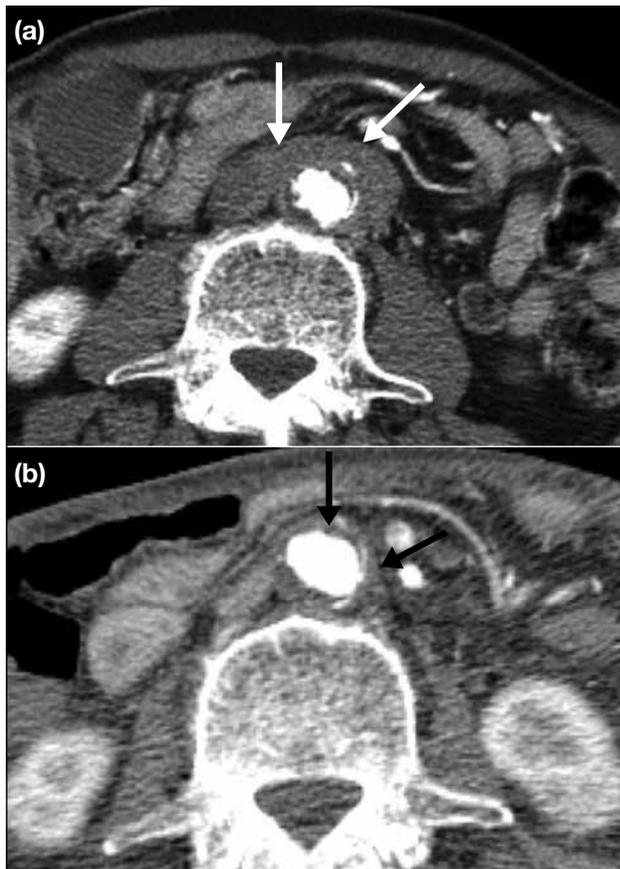


Figure 5. Axial contrast computed tomography (CT) images show (a) increased soft tissue density surrounding the abdominal aorta (arrows); there is a lack of elevation of aorta, which is a feature of periaortic lymphadenopathy. Overall features are compatible with retroperitoneal fibrosis; and (b) improvement of the retroperitoneal fibrosis after treatment on follow-up around 7 months later (arrows).

RETROPERITONEAL FIBROSIS AND AORTITIS

The aetiology of retroperitoneal fibrosis is unknown in the majority of cases. Retroperitoneal fibrosis can also be a part of the disease manifestation of IRSD, where the retroperitoneal mass shows dense infiltration of IgG4-positive plasma cells and obliterative phlebitis. Kamisawa and Okamoto¹ reported that retroperitoneal fibrosis was present in 8% of their patients with AIP. Imaging findings show a retroperitoneal mass encasing the abdominal aorta (Figure 5) and the ureters. In our experience, the fibrotic reaction may also involve the

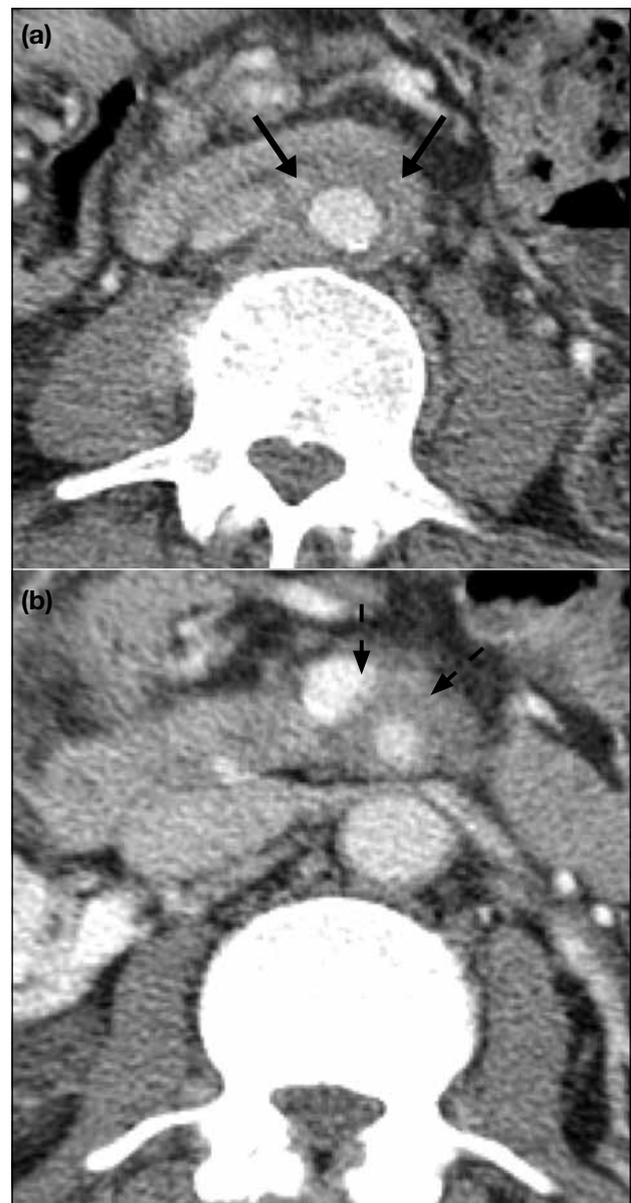


Figure 6. Axial contrast computed tomography images show (a) another case of retroperitoneal fibrosis (arrows) with (b) extension along the superior mesenteric artery (dashed arrows).



Figure 7. (a,b) Axial contrast computed tomography images show retroperitoneal fibrosis (arrows) complicated with abdominal aortic aneurysms (AAA) [dashed arrows]. (c) The retroperitoneal fibrosis (arrows) extends along the superior mesenteric artery. In this patient, relatively less-prominent atherosclerotic changes are noted along the rest of the aorta, whereas multiorgan involvement of autoimmune pancreatitis is present. Extension to the superior mesenteric artery is also present. AAA is, therefore, likely secondary to the retroperitoneal fibrosis.

superior mesenteric artery (Figures 6 and 7). Possible complications would include aortic aneurysm (Figure 7), ureteric obstruction, and renal failure.

IRSD can involve the ascending aorta as well as the descending aorta. Involvement of the ascending aorta with complication of dissection has been reported by Stone et al.¹⁵ Other associated findings of IRSD such as lymphadenopathy and pancreatic ductal dilation may offer clues to the diagnosis. In the case report by Stone et al,¹⁵ however, no significant pancreatic abnormality was associated with the condition.

SALIVARY AND LACRIMAL GLAND INVOLVEMENT

Salivary gland swelling due to IRSD can be differentiated from Sjögren's syndrome (SS) by the presence of abundant IgG4-positive plasma cell infiltrates and the absence of anti SS-A and SS-B antibodies.^{1,16}

Mikulicz's disease (MD) refers to bilateral symmetrical swelling of the lacrimal and salivary glands. It has been previously included as a subtype of SS, but there is clinical and histopathological evidence to suggest that



Figure 8. (a, b) Axial contrast computed tomography (CT) images show diffuse bilateral enlargement of the lacrimal (arrows) and parotid glands (dashed arrows), but no discrete mass lesion. (c) Coronal and sagittal contrast CT images show multiple enlarged bilateral cervical lymph nodes (arrows).

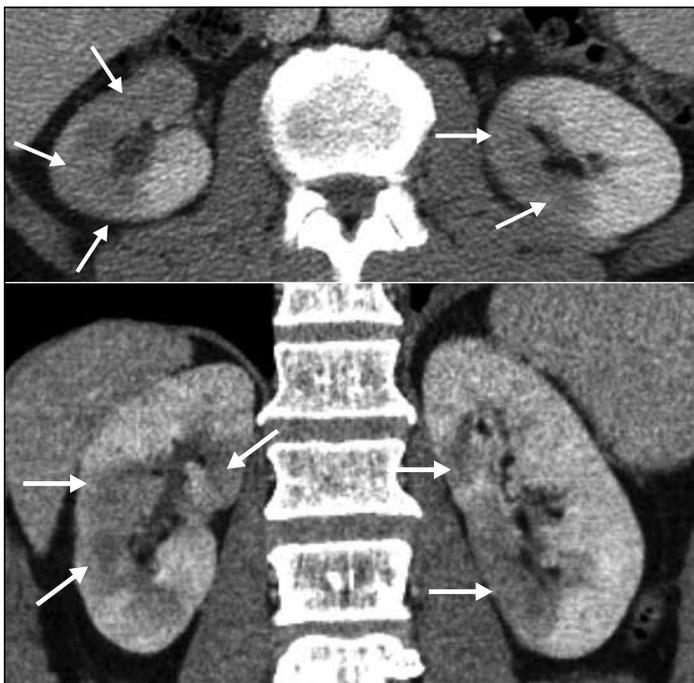


Figure 9. Axial and coronal contrast computed tomography images show bilateral renal involvement with patchy areas of decreased enhancement (arrows). Note the lack of mass effect and perinephric fat-stranding which may be seen in renal tumours and pyelonephritis.

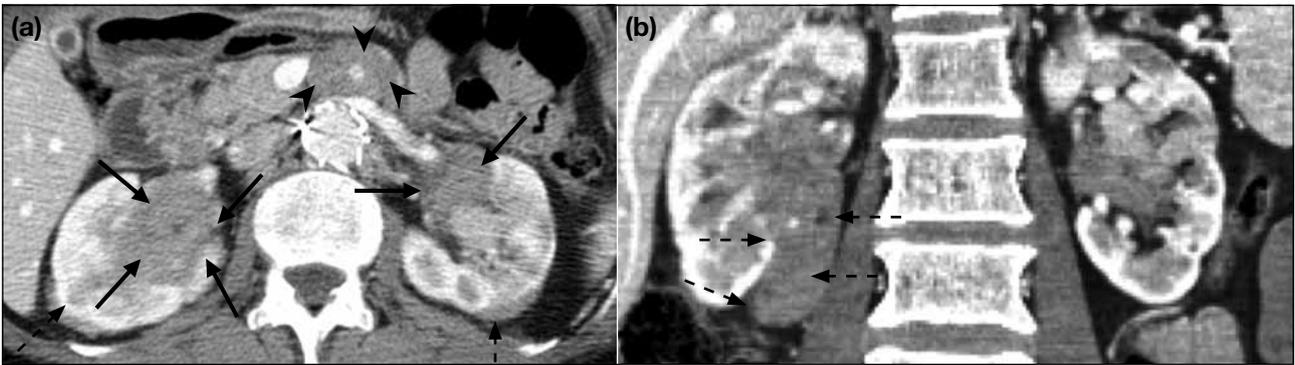


Figure 10. (a, b) Axial contrast computed tomography images show soft tissue infiltration of bilateral renal sinuses and pelvis (arrows). This pattern of renal involvement, sometimes, may have perinephric and extrarenal extensions (dashed arrows). Associated fibrosis around superior mesenteric artery is also seen (arrowheads).



Figure 11. Axial and coronal contrast computed tomography images show multiple enlarged lymph nodes (arrows) in the mediastinal and hilar regions.



Figure 12. Axial lung window computed tomography (CT) images show (a) a small subpleural nodule over left lung base (arrow), which resolves on (b) follow-up CT.

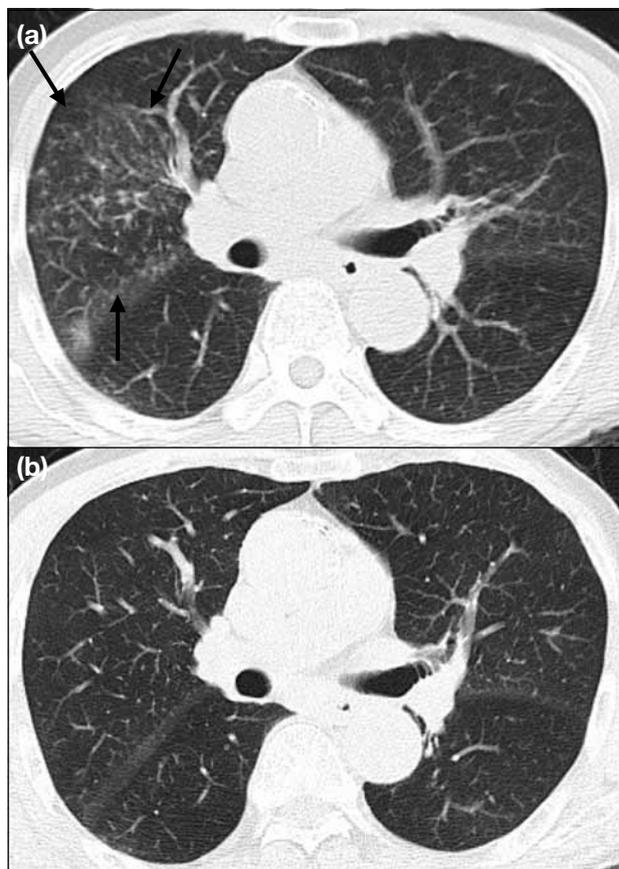


Figure 13. Axial lung window computed tomography (CT) images show (a) multiple small lung nodules over anterior segment of the right upper lobe (arrows), which resolve on (b) follow-up CT.

MD is a separate entity from SS. MD is characterised by prominent lacrimal and salivary gland infiltration by IgG4-positive plasma cells, responsiveness to steroid therapy, elevated serum IgG4 level, and lack of significant autoimmune reactions.¹⁷ Imaging findings include diffuse bilateral enlargement of lacrimal and salivary glands, sometimes also associated with cervical lymphadenopathy (Figure 8). Yamamoto et al¹⁷ reported that some of their MD patients had associated retroperitoneal fibrosis and tubulointerstitial nephritis.

RENAL INVOLVEMENT

Tubulointerstitial nephritis has been reported in IRSD. Patients may present with hypertension and proteinuria, and laboratory investigations may show elevated levels of serum creatinine. IgG4-positive plasma cell infiltrates are also found in the renal tissue. Of note, renal impairment has been shown to be a treatable disease showing favourable response to steroid therapy.¹⁸ The renal parenchymal lesions are usually multiple

and bilateral, showing decreased enhancement on CT compared with normal renal parenchyma (Figure 9). The renal parenchyma, renal sinus, or renal pelvic wall may be involved (Figure 10).⁷

OTHER ORGAN INVOLVEMENT

Lymphadenopathy related to IRSD has been observed in the neck, thorax, and abdomen (Figure 11). Kamisawa and Okamoto¹ reported that 24% of their AIP patients also had salivary gland swelling and lymphadenopathy; reduction in lymph node size may be observed after steroid treatment.

Interstitial pneumonia is not commonly observed in IRSD. Hirano et al¹⁹ reported that four out of their 30 patients with AIP had pulmonary involvement. Inoue et al²⁰ categorised IgG4-related lung disease into four types, namely, solid nodular, round-shaped ground glass opacity, alveolar interstitial and bronchovascular, based on the predominant CT findings (Figures 12 and 13).

CONCLUSION

IRSD is a systemic disease that can affect multiple organs. The imaging findings of the pancreas with IRSD may sometimes lead to the suspicion of pancreatic carcinoma, which leads to unnecessary surgery. Diagnosis of this condition requires correlation with laboratory and histological findings. Multisystem involvement is an important observation, but findings such as lymphadenopathy may be non-specific. Recognition of this disease entity and differentiation from malignancy is important as treatment with steroid in IRSD is associated with excellent response.

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