CME ARTICLE

Imaging findings of immunoglobulin G4-related disease: from the head to the pelvis

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INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is predominantly diagnosed through serum IgG4 levels and biopsy findings, although imaging findings can provide clues to the diagnosis. IgG4-RD is a systemic disease characterised by abundant infiltration of IgG4-positive plasma cells and lymphocytes as well as storiform fibrosis.¹,² The serum IgG4 level is often, but not always, elevated in patients with IgG4-RD. However, serum IgG4 level may also be elevated in other diseases, including microscopic polyangiitis and granulomatosis with polymygitis; therefore, elevation of serum IgG4 level is not a specific finding for IgG4-RD.³ IgG4-RD often involves multiple organs and may mimic malignancy, infection or other autoimmune diseases. Differentiating IgG4-RD from malignancy is crucial, because many cases show good response to corticosteroid therapy. IgG4-RD can cause organ failure⁴ and thus must be diagnosed promptly and accurately. It is important to be familiar with the imaging findings of IgG4-RD, as it may present with characteristic findings on computed tomography (CT) and magnetic resonance (MR) imaging. The most important step in diagnosing IgG4-RD is performing a systematic survey while carefully considering all the varied presentations of the disease, because some imaging findings are non-specific for IgG4-RD. We should be aware of the fact that most cases have multi-organ lesions, especially in autoimmune pancreatitis. Thus, this study aims to describe the wide range of CT and MR imaging findings of IgG4-RD across the whole body.

INTRACRANIAL FINDINGS

Hypertrophic pachymeningitis

Hypertrophic pachymeningitis is a rare but increasingly recognised manifestation of IgG4-RD. The most common symptom is headache, and visual or hearing impairment can occur owing to local dural involvement in the periorbital areas or vestibular structures.⁴ On CT and MR imaging, it may appear as a linear dural thickening with homogeneous enhancement (Fig. 1a). The dural thickening appears relatively hypointense on T2-weighted (T2-W) imaging, reflecting fibrosis.⁴

Pituitary gland

IgG4-RD represents one type of hypophysitis, based on histopathologic appearance.² The most common symptoms are hypopituitarism (e.g., weight loss, fatigue and appetite loss), diabetes insipidus and headache.⁵ A typical MR imaging finding is pituitary gland enlargement, especially pituitary stalk thickening or a mass (Fig. 1b).⁵ Loss of T1-weighted (T1-W) high signal intensity in the posterior pituitary gland can be observed.

Fig. 1 (a) Immunoglobulin G4 (IgG4)-related hypertrophic pachymeningitis in a 49-year-old man with a history of autoimmune pancreatitis who presented with diplopia and abducens nerve palsy. Contrast-enhanced coronal MR image shows linear dural thickening with homogeneous enhancement (white arrows). (b) IgG4-related hypophysitis in a 61-year-old man with a history of autoimmune pancreatitis who presented with thirst, polydipsia and polyuria. Unenhanced sagittal T1-W image shows an enlarged pituitary stalk (black arrow) with no swelling of the anterior pituitary gland. A loss of high signal intensity in the posterior pituitary gland is also observed.

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HEAD AND NECK
Perineural disease
IgG4-RD can involve the peripheral nervous system, especially the branches of the trigeminal nerve; therefore, careful evaluation along the course of the cranial nerves is crucial. Symptoms are related to other organ lesions or mass effects of peripheral nerve lesions. On MR imaging, perineural disease is characterised by distinct masses along the affected nerve fascicles or enlarged nerves. These lesions show hypointense signal on T2-W imaging, reflecting fibrosis (Fig. 2).

Salivary and lacrimal glands
The salivary glands are the most frequently involved organs in IgG4-RD of the head and neck area. Involvement of the lacrimal glands often accompanies salivary gland lesions. Mikulicz’s disease and Küttner’s tumour, both of which are well-known in this area, are now considered a part of the spectrum of IgG4-RD. Mikulicz’s disease is characterised by bilateral painless swelling of at least two of the lacrimal, submandibular and parotid glands. Küttner’s tumour, also known as chronic sclerosing sialadenitis, was originally described as unilateral or bilateral hard swelling of the submandibular glands. It is challenging to distinguish Mikulicz’s disease and Küttner’s tumour owing to their similar imaging findings. IgG4-related salivary and lacrimal gland lesions demonstrate bilateral gland swelling with relatively low signal intensity on T2-W imaging and homogeneous enhancement due to fibrosis (Fig. 3).

Thyroid
An association between IgG4-RD and thyroid diseases, including Hashimoto’s thyroiditis, Riedel’s thyroiditis and Graves’ disease, has recently been described. Hashimoto’s thyroiditis is thought to consist of two subtypes: IgG4-related thyroiditis and non-IgG4 thyroiditis. Riedel’s thyroiditis is commonly considered to be IgG4-RD with extensive fibrosis, resulting in a hard, painless mass that involves the thyroid parenchyma and surrounding tissues. Compressive symptoms are the most common, including dyspnoea, hoarseness of voice and dysphagia. CT reveals either focal or diffuse low attenuation of the thyroid, with minimal contrast enhancement relative to the surrounding thyroid tissue. These lesions can have a hypointense signal on T2-W imaging, resulting from fibrosis (Fig. 4).
CHEST
Various conditions have been identified at several sites in the thoracic area, including the lungs, mediastinal lymph nodes, bronchial walls and pleura. These have been comprehensively classified as IgG4-related respiratory disease. Generally, patients have non-specific symptoms that include cough, dyspnoea or chest pain, and they can also be asymptomatic. Common CT findings include thickening of the bronchial wall (Fig. 5a), bronchovascular bundles and/or interlobular septa (Fig. 5b), and hilar and mediastinal lymphadenopathy (Fig. 5a). These characteristics are due to a high affinity of the disease for the lymphatic tract. Solid nodules (Fig. 5c), consolidation (Fig. 5b), ground-glass opacities and alveolar interstitial disease can be found in the lung parenchyma. Visceral or parietal pleural thickening and pleural effusion have also been reported. Although these findings are not specific for IgG4-RD, it should be included in the differential diagnoses when these findings are observed. A systematic survey should be undertaken as the next step. Paravertebral soft tissue masses are rarely observed, but are a characteristic finding in IgG4-RD. They occur mainly on the right side of the lower thoracic vertebrae and present as a homogeneously enhanced mass or paravertebral thickening (Fig. 6). This remarkable trend may suggest that IgG4-related paravertebral lesions develop along the thoracic duct.

BREAST
Breast involvement in IgG4-RD (IgG4-related sclerosing mastitis) is uncommon. Most patients are asymptomatic, but some may have a painless palpable lesion. On imaging, it presents as a non-specific lesion with contrast enhancement (Fig. 7). Therefore, it is challenging to distinguish IgG4-related sclerosing mastitis from breast cancer.

PANCREAS
Autoimmune pancreatitis (AIP) is the most common lesion in IgG4-RD, because the concept of IgG4-RD was originally established based on intense study of AIP. There are two subtypes of AIP based on pathological findings: Type 1, lymphoplasmacytic sclerosing pancreatitis and Type 2, idiopathic duct-centric chronic pancreatitis. Type 1 is the pancreatic manifestation of IgG4-RD, whereas Type 2 has distinctly different histologic and clinical features without elevation of serum IgG4 or autoantibodies. Patients may have abdominal pain, obstructive jaundice, weight loss or new-onset diabetes mellitus, and some patients have no symptoms. There are two imaging patterns of AIP: diffuse and focal. Diffuse type is the more common pattern that is characterised by a diffusely enlarged pancreas with the absence of normal lobulated contours, giving it a sausage-like appearance. The affected area has a hypovascular appearance on arterial phase CT and delayed enhancement. Another characteristic finding is a capsule-like rim, which shows hypointense signal on T2-W imaging and delayed enhancement owing to fibrosis. Approximately 25%–40% of AIP cases are the focal type, which can have imaging findings similar to those of pancreatic adenocarcinoma. Focal AIP shows hypointense signal on T1-W images, hyperintense signal on T2-W and diffusion-weighted imaging.
Specific findings of AIP are multifocal lesions (Fig. 8b), speckled or dotted hyperintense areas on fat-saturated T1-W imaging (Fig. 8c) and penetration of the pancreatic duct through the mass on magnetic resonance cholangiopancreatography (MRCP) (duct penetrating sign, Fig. 8d).

BILIARY SYSTEM

The structures of the biliary system are commonly involved in IgG4-RD. IgG4-related sclerosing cholangitis (IgG4-SC) can affect both the intrahepatic and extrahepatic bile ducts, and the main differential diagnoses are primary sclerosing cholangitis and cholangiocarcinoma. Biliary involvement is observed in 60%–80% cases of Type 1 AIP, and Type 1 AIP is frequently associated with cholangiopathy and biliary tree involvement.

The most common presentation of IgG4-SC is obstructive jaundice. On CT and MR imaging, IgG4-SC shows circumferential symmetric wall thickening of the bile ducts, with smooth outer and inner margins (Fig. 9a). The involved bile ducts show luminal narrowing; however, the lumen is often visible (Fig. 9b). The thickened wall shows hypointense signal on T2-W imaging and homogeneous delayed enhancement (Fig. 9a).

IgG4-SC is classified into four types based on the part of the bile duct involved, and MRCP is useful for assessing the entire biliary system (Fig. 9b). Gallbladder involvement can occur, and it presents as diffuse wall thickening with hypointensity on T2-W imaging and homogeneous delayed enhancement.

LIVER

Hepatic involvement in IgG4-RD is rare. There are two types of hepatic involvement: IgG4-related autoimmune hepatitis and inflammatory pseudotumour. The symptoms are non-specific and include fever, abdominal pain and general malaise, or patients may be asymptomatic. IgG4-related inflammatory pseudotumour demonstrates variable enhancement patterns, including delayed homogenous enhancement or peripheral enhancement (Fig. 10).

KIDNEY

IgG4-related renal disease is found in approximately one third of patients with AIP and can present as acute or chronic renal failure. Five imaging patterns have been described: bilateral
round or wedge-shaped lesions (Fig. 11a), diffuse patchy involvement (Fig. 11b), rim-like soft tissue around the kidney (Fig. 11c), a solitary round lesion (Fig. 11d) and diffuse wall thickening of the renal pelvis (Fig. 11e). It is challenging to detect these patterns on unenhanced CT owing to the isoattenuation of the lesions with the renal parenchyma. On postcontrast CT and MR imaging, they show a hypoattenuating/hypointense signal on arterial phase images with delayed enhancement. When the lesions appear as bilateral round or wedge-shaped lesions, the differential diagnosis includes pyelonephritis and lymphoma. When the disease manifests as a solitary round lesion or diffuse wall thickening of the renal pelvis, differentiation from renal cell carcinoma or renal pelvis cancer may be difficult.

**PROSTATE**

IgG4-related prostatitis is rare and is associated with approximately 8% of AIP cases. Patients may be asymptomatic or may present with lower urinary tract symptoms such as benign prostatic hypertrophy. On imaging, IgG4-related retroperitoneal fibrosis shows homogeneous delayed enhancement (Figs. 12 & 13). On MR imaging, lesions can show a hypointense signal on T2-W images owing to fibrosis.

**GASTROINTESTINAL TRACT AND MESENTERY**

Gastrointestinal tract lesions in IgG4-RD have been reported sporadically in the stomach and duodenum, and small bowel lesions are extremely rare. The lesions can cause wall thickening and ulcer formation; therefore, they often mimic malignancy (Fig. 15a). IgG4-related gastritis causes epigastric pain, anorexia, nausea or abdominal discomfort, while IgG4-related enteritis may cause small bowel obstruction.

IgG4-related sclerosing mesenteritis is a rare entity characterised by focal or diffuse fibrosis and inflammation in the small bowel mesentery that can appear as a soft tissue mass. On
imaging, it appears as a soft tissue mass enveloping the mesenteric vessels (Fig. 15b).

**LYMPH NODES**

Lymphadenopathy is often observed in patients with IgG4-RD. IgG4-related lymphadenopathy is common in the porta hepatis, cervical, mediastinal (Fig. 5a), axillary, peripancreatic, para-aortic and mesenteric regions. On imaging, non-specific swelling of the lymph nodes with homogeneous enhancement is observed.

It is challenging to differentiate lymphadenopathy from other pathologic conditions; however, IgG4-related lymph nodes are generally smaller than 2 cm and the patients do not have fever or weight loss.

**CONCLUSION**

IgG4-RD is sometimes challenging to differentiate from other inflammatory or neoplastic diseases. However, characteristic imaging features can aid in the diagnosis of IgG4-RD. Moreover,
multiorgan involvement can be a helpful clue to the possibility of IgG4-RD, especially in cases in which the multitude of findings initially seem unrelated. Radiologists should be familiar with the imaging presentations of IgG4-RD to avoid delayed diagnosis and unnecessary invasive interventions. This article illustrates the many characteristic CT and MR imaging findings of IgG4-RD across the whole body and is a useful compilation to aid in the diagnosis of IgG4-RD.

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**SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME**  
*(Code SMJ 202111B)*

**Question 1.** Regarding immunoglobulin G4 (IgG4)-related disease:  
(a) The most commonly involved organ is the pancreas.  
(b) The thyroid cannot be affected.  
(c) Most of the lesions show high signal intensity on T2-weighted images.  
(d) The prostate can be affected.

**Question 2.** Regarding autoimmune pancreatitis (AIP):  
(a) There are three subtypes of AIP.  
(b) Type 2 AIP is the pancreatic manifestation of IgG4-related disease.  
(c) Focal AIP shows a hypervascular appearance on arterial phase imaging.  
(d) Penetration of the pancreatic duct through the mass can be observed on magnetic resonance cholangiopancreatography.

**Question 3.** Regarding IgG4-related respiratory disease:  
(a) Imaging findings of IgG4-related respiratory disease are highly specific.  
(b) Paravertebral soft tissue masses are frequently observed.  
(c) Paravertebral soft tissue masses occur mainly on the right side of the lower thoracic vertebrae.  
(d) Hilar and mediastinal lymphadenopathy are common findings.

**Question 4.** Regarding IgG4-related sclerosing cholangitis (IgG4-SC):  
(a) It can affect both the intrahepatic and extrahepatic bile ducts.  
(b) IgG4-SC shows circumferential symmetric wall thickening of the bile ducts with a smooth margin.  
(c) Gallbladder involvement cannot occur.  
(d) The main differential diagnosis is primary sclerosing cholangitis.

**Question 5.** Regarding IgG4-related disease:  
(a) IgG4-related periaortitis occurs only in the abdominal aorta.  
(b) Approximately 50% of patients with AIP have retroperitoneal fibrosis.  
(c) IgG4-related renal disease can show a solitary lesion.  
(d) Hepatic involvement in IgG4-related disease is common.

| True | False |
|------|-------|
| ☐    | ☐     |
| ☐    | ☐     |
| ☐    | ☐     |
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**RESULTS:**

(1) Answers will be published online in the SMJ January 2022 issue. (2) The MCR numbers of successful candidates will be posted online at the SMJ website by 31 January 2022. (3) Passing mark is 60%. No mark will be deducted for incorrect answers. (4) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council. (5) One CME point is awarded for successful candidates. (6) SMA credits CME points according to the month of publication of the CME article (i.e. points awarded for a quiz published in the November 2021 issue will be credited for the month of November 2021, even if the deadline is in January 2022).  

Deadline for submission (November 2021 SMJ 3B CME programme): 12 noon, 24 January 2022.