Learning objectives

To review the spectrum of imaging appearances of immunoglobulin G4-related disease (IgG4-RD) in the pancreas, biliary tree, orbit, lacrimal glands, salivary glands, lung, kidney, aorta, retroperitoneum, lymph nodes, pachymeninges and the pituitary gland.

Background

IgG4-related disease (IgG4-RD) is a fibroinflammatory condition that was first recognised as a systemic disease in 2003 when patients with autoimmune pancreatitis were noted to have extrapancreatic manifestations (1). Since 2003 IgG4-RD has been described in a multitude of organs, including the orbit, salivary and lacrimal glands, lung, kidney, prostate, aorta and retroperitoneum, lymph nodes, biliary tree and visceral inflammatory pseudotumours. The disease frequently occurs in the absence of pancreatic disease.

Since it was first described, the nomenclature of IgG4-RD has evolved. It has been referred to as IgG4-related systemic disease, IgG4-related sclerosing disease, systemic IgG4 plasmacytic syndrome and IgG4-related multi-organ lymphoproliferative syndrome (2). However IgG4-related disease is now the term of choice (2, 3).

Pathologically IgG4-RD is characterised by multisite tumourfactive lesions comprising a dense lymphoplasmocytic infiltrate rich in IgG4 plasma cells; storiform fibrosis; often, but not invariably associated with elevated serum IgG4 concentrations (4). A wide variety of conditions are associated with elevations of serum IgG4 levels, and although high levels such as 1.35g/L have been proposed as a diagnostic criteria, these can still occur with infection, tumours, vasculitis and primary immune deficiencies (5). It is vital to have appropriate histopathological findings to diagnose IgG4-RD, as although elevated serum and tissue IgG4 are helpful, they are not diagnostic, and so reliance upon them may result in misdiagnosis (3).

The prevalence of IgG4-RD is uncertain and is difficult to determine, due to the lack of strict diagnostic criteria and limited awareness of this condition. Much of the literature is derived from Japan, and estimates of the incidence in that population is 0.28-1.08/100,000 with a median age of 58 years (2). Males are affected more often than females (2, 3). The symptoms of IgG4-RD are typically mild, with gradual onset and usually show a good response to steroid therapy. Specific symptoms relate to the organ that is involved, and specifics will be discussed later. It has also been postulated that
there is an association between IgG4-RD and malignancy(6) however no specific patient or disease factors have been identified and ongoing research is required(6).

### Imaging findings OR Procedure details

#### Autoimmune pancreatitis.

Autoimmune pancreatitis is the prototype disease of IgG4-RD. There are now two distinct subtypes of autoimmune pancreatitis each having overlapping clinical features, but different pathologic findings. Type 1 disease is a manifestation of IgG4-related disease, while type 2 is an idiopathic duct-centric pancreatitis with granulocytic epithelial lesions (7). Type 1 patients are typically older than patients with type 2 disease, and are also more likely to have extrapancreatic sites of disease and a response to systemic steroid therapy.

The classic description of autoimmune pancreatitis is of diffuse pancreatic enlargement with a capsule like rim, T1 hypointensity at MRI and delayed phase enhancement on both CT and MRI studies (8). More recent studies suggest that the late enhancement of involved pancreas is more frequently appreciated at MRI compared with CT examinations (9) and the gland is hypoenhancing in the arterial phase for both modalities (9). The rim sign is described in 25-40% of cases (9-11) and is seen as a periglandular halo comprising an inflammatory infiltrate that is hypodense on CT and hypointense on T1 and T2 weighted images (8). When diffusely involved the pancreas loses the normal fatty lobulations and has been described as a 'sausage pancreas' (Fig. 1 on page 7).

The reported rates of focal AIP vary between 30-71% of cases and these require differentiation from pancreatic adenocarcinoma (11, 12). Features that are suggestive of focal AIP include delayed homogenous enhancement, peripheral capsule like rim, irregular narrowing of the main pancreatic duct, and dilatation of the upstream main pancreatic duct by less than 5mm (13). Appreciating the pancreatic duct penetrating through the mass, the 'duct penetrating sign', rather than abruptly terminating, is also useful (14). The degree of enhancement in the arterial phase is similar for both adenocarcinoma and focal AIP, however focal AIP has greater enhancement in the portal venous phase (94 hounsfeld units) compared to adenocarcinoma (64 Hounsfield units) (15). The detection of extrapancreatic findings of IgG4 RD also help confirm a benign diagnosis. In appropriate diagnostic dilemma cases a steroid trial can be considered with short interval repeat imaging.
Biliary tree

Biliary involvement of the disease manifests as a sclerosing cholangitis. The disease may be radiologically indistinguishable from primary sclerosing cholangitis (PSC). It should be considered particularly in older patients and those with an acute onset of symptoms.

IgG4 related sclerosing biliary disease has four main patterns - a stricture of the distal CBD, diffuse intrahepatic and extrahepatic duct strictures (Fig. 2 on page 8), hilar and distal CBD strictures and solitary hilar strictures (16). The distal common bile duct stricture is the most common single location (17). The strictures are typically long continuous segments with prestenotic dilation and the contrast enhancement of the bile duct wall in active disease may be marked, but it declines following treatment (17). Cross sectional MRI demonstrates a thick symmetrical rind of enhancing soft tissue surrounding the strictures (18).

Single layer CBD wall thickness of greater than 2.5 mm, continuous biliary tree involvement, gallbladder wall thickening and the absence of liver parenchymal abnormalities have all been shown to be statistically significant at independently differentiating IgG4 related sclerosing cholangitis from PSC and other autoimmune diseases (19).

Salivary glands

The salivary glands are the most frequently involved organs in the head and neck (20). Involvement may be bilateral and diffuse with involved glands being enlarged (Fig. 3 on page 9 Fig. 4 on page 10) however less frequently it may be focal and unilateral (21). On MRI there is homogenous low to intermediate signal intensity on T1 and T2-weighted images with homogenous post contrast enhancement of the involved area. (20, 21) On ultrasound focal involvement is seen as a hypoechoic hypervascular area within the involved gland (21). Differentials include lymphoma, salivary gland tumours, mumps, acute phase Sjögren disease, sarcoidosis, Mikulicz disease and Kuttner tumour.

Lacrimal glands

Lacrimal involvement is typically bilateral and frequently seen in association with salivary involvement (5). The lacrimal glands generally demonstrate symmetric enlargement and homogenous enhancement on postcontrast CT and MRI (1, 21) (Fig. 5 on page 11 Fig. 6 on page 12). When compared to brain grey matter the involved lacrimal glands
are isoattenuative on noncontrast CT, isointense on T1-weighted MRI and hypointense on T2-weighted MRI (22). IgG4-related orbital disease may extend to involve adjacent structures, including perineural spread typically sparing the extraocular muscles (1). It can also involve the medial canthus and extraconal space, where lesions appear as focal nodules (22). Differentials include lymphoma, reactive hyperplasia, lacrimal gland tumours, sarcoidosis, Wegener’s granulomatosis and Mikulicz disease.

Aorta

Aortic involvement manifests radiologically as marked aortic wall thickening which is usually circumferential, but necessarily uniform, with homogenous enhancement on late arterial phase CT with no calcific or cystic areas with (14, 23). The mean wall thickness is 1.1 cm and mean length of involvement is 7.2 cm. Branching vessels pass through the thickened wall without occlusion (23). Most lesions are well circumscribed but periaortic inflammatory standing may be present (14, 23).

Aneurysmal dilatation and accelerated atherosclerotic changes can occur, but rupture is less common in IgG4-RD than other types of inflammatory aneurysm (14, 23, 24).

Involvement is not limited to the aorta and has been reported in the left common carotid, left subclavian, superior mesenteric, splenic, common iliac, internal iliac and coronary arteries (25). Differentials include isolated periaortis, inflammatory abdominal aortic aneurysm, chronic periaortitis, lymphoma and infection.

Retroperitoneum

IgG4 disease involving the retroperitoneum is characterised by infiltration IgG4 plasma cells to form soft tissue thickening. Typically in IgG4 disease there is preferential perivascular and periureteric involvement (Fig. 7 on page 13). IgG4 related retroperitoneal fibrosis is radiologically indistinguishable from the many other causes (26). Apart from the previously described aortic changes it can present as a periureteric mass or a plaquelike mass (14). MRI appearances depend on the degree of fibrosis and active inflammation, with a low-intermediate T1-weighted signal and a variable T2-weighted and postcontrast signal. (14). Ig-G4 related retroperitoneal fibrosis is radiologically indistinguishable from other causes of retroperineal fibrosis.

Renal
IgG4-related renal disease typically manifests as tubulointerstitial nephritis, with membranous glomerulonephritis and renal pyelitis less frequent (27). On imaging the renal lesions are typically bilateral (84% of cases), multiple (94%) and involve the renal parenchyma (87%), however the renal pelvis and perirenal space can also be involved (28).

Parenchymal involvement has four main subtypes - peripheral cortical nodules, round or wedge shaped regions, a large solitary mass or diffuse patchy involvement (29) (Fig. 8 on page 14). Cortical lesions are normally hypoattenuative on contrast enhanced CT in the early phases (30) and show mild enhancement on delayed images (29). On MRI lesions are normally isointense on T1-weighted images (94% of cases), hypointense T2 weighted images (77%) and show progressive enhancement following intravenous gadolinium administration (83%) (28). On diffusion weighted imaging (DWI) the signal characteristic depend on the b value, with all lesions hyperintense to renal parenchyma at a b value of 1000s/mm2 (28). Depending on the imaging appearances differentials include renal cell carcinoma, renal infarcts, pyelonephritis, transitional cell carcinoma and metastases.

**Lung**

IgG4 related lung disease have been divided into four categories based on its CT appearances (31). The solid nodular type has a solitary pulmonary mass or nodule greater than 1cm (Fig. 9 on page 15), however multiple masses have been described (32). The round shaped ground glass opacity type has well defined rounded ground glass opacities in multiple lobes. The alveolar interstitial type has changes within all lobes which include diffuse ground glass opacities, honeycombing and traction bronchiectasis. The bronchovascular type has thickening of the bronchovascular bundles and interlobular septae within all lobes. Further possible findings include centrilobular nodules, hilar and mediastinal lymphadenopathy, multiple thin walled cysts and bilateral pleural thickening (31, 33, 34). Depending on the imaging appearances differentials include primary lung cancer, alveolar carcinoma in situ, non-specific interstitial pneumonia, sarcoidosis and lymphoproliferative disorders.

**Pachymeningitis**

IgG4 related hypertrophic pachymeningitis is a rare manifestation of IgG4-RD, in which thickening of the dura may be diffuse (Fig. 10 on page 15)or focal (35). Localised changes may occur supratentorially, at the skull base or in the spinal canal. (36).
CT in focal disease demonstrates thickening of the dura which enhances following contrast administration (36). On T2 weighted MRI in focal disease the dura is thickened and hypointense with scattered foci of hyperintensity (36). Post gadolinium images demonstrate dural enhancement in 90% of cases of intracranial involvement and 85% of cases with spinal involvement (35).

When changes are focal and within the spinal canal they can result in mass effect with spinal canal stenosis (37). The main differential is of idiopathic hypertrophic pachymeningitis, lymphoma and post lumbar puncture.

**Hypophysitis**

IgG4 related disease may manifest rarely as pituitary hypophysitis with a focal mass or enlargement of the pituitary gland, its stalk or both (Fig. 11 on page 16). On postcontrast T1-weighted MRI homogenous enhancement is frequently seen (20), however it may also be heterogenous (38). Differentials include other causes of hypophysitis, adenoma, craniopharyngioma and metastasis.

**Lymph nodes**

Lymphadenopathy is commonly seen and may be the first disease manifestation in IgG4-RD. The involved lymph nodes enhance homogenously with no necrosis or calcification within (39) and are typically less than 2cm in short axis (40). Retroperitoneal, peripancreatic, mesenteric, mediastinal, hilar and cervical lymphadenopathy are described locations (14).

Mediastinal lymphadenopathy is seen in 78% of patients with autoimmune pancreatitis (26) and 46% of those with IgG4-related lung disease (31).

**Images for this section:**
Fig. 1: Axial portal venous phase CT demonstrates 'sausage' like diffuse pancreatic enlargement with loss of the normal fatty lobulations and a surrounding hypodense 'halo' like rim.
Fig. 2: MRCP MIP image shows multifocal intrahepatic and extrahepatic biliary strictures.
Fig. 3: Axial contrast enhanced CT demonstrates diffuse bilateral parotid enlargement.
**Fig. 4:** Axial contrast enhanced CT shows diffuse symmetrical bilateral submandibular gland enlargement.
Fig. 5: Axial post contrast CT and post contrast T1 MRI demonstrate bilateral lacrimal gland enlargement, left greater than right, with resultant left sided proptosis.
**Fig. 6:** Coronal post contrast CT and T1 weighted MRI demonstrate bilateral lacrimal gland enlargement, left greater than right.
**Fig. 7:** Non contrast axial CT shows extensive retroperitoneal fat stranding with loss of the normal para-aortic fat planes.
**Fig. 8:** Axial portal venous phase CT demonstrates nodular and wedge shaped regions of low attenuation within both kidneys.

**Fig. 9:** Axial non contrast CT demonstrates a solitary spiculated pulmonary nodule.
**Fig. 10:** Coronal post contrast T1 MRI shows smooth dural thickening and enhancement overlying the right frontal and parietal lobes.
**Fig. 11:** Sagittal and coronal post contrast T1 MRI show diffuse enlargement of the pituitary and infundibulum with resultant compression of the optic chiasm.
Conclusion

There are a large number of imaging manifestations of IgG4-RD. The majority of imaging appearances are non-specific and the distinction between IgG4-RD and potentially more serious conditions such as malignancy is usually not possible based on imaging findings alone. Increased awareness of the spectrum of the disease may lead to identification of other IgG4-RD manifestations and subsequent consideration of the condition. This may lead to more prompt corticosteroid therapy and potentially avoid invasive treatment.

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References


