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 extracranial 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.

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, Künntner 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. Künntner disease shows isolated involvement of the submandibular gland and biopsy may be needed to differentiate it from neoplasm.

Haman 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.
The intraorbital findings of the IgG4-RD may include orbital inflammatory pseudotumor, which may present as unilateral or bilateral intraconal, conal, or extraconal masses, 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-
corroborated by the fact that a subset of IgG4-RD elsewhere in the body. This is similar radiologic features with the features considered. Fibrosing mediastinitis has classical manifestations within the spectrum. Pansinusitis 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, Behçet 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...
magnetic resonance cholangiopancreatography (MRCP). It is important to identify autoimmune pancreatitis early in the course of management as it shows good response 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 (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 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 hypointense 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).
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.

References


