Other Organ Involvements

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Introduction

IgG4-related disease (IgG4-RD) is a fibroinflammatory disease that can involve essentially any organ simultaneously or metachronously [1]. It was first proposed as a systemic disease in 2003 by Kamisawa et al. following the recognition that a high percentage of patients with autoimmune pancreatitis (AIP) had extrapancreatic manifestations that shared similar histopathological features consisting of dense infiltration of IgG4-positive plasma cells and lymphocytes and fibrosis [2].

IgG4-related sclerosing cholangitis (IgG4-SC) is recognized as a biliary manifestation of IgG4-RD. Approximately 60% of IgG4-RD patients have IgG4-SC in the proximal and/or distal bile ducts [3]. Although there are diagnostic criteria for IgG4-SC, diagnosis of IgG4-SC remains a significant clinical challenge. Other organ involvements, such as AIP, might be helpful to diagnose IgG4-SC. In this chapter, we describe other organ involvements of IgG4-SC.

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Clinical Findings of IgG4-RD

IgG4-RD is a systematic disease that affects various organs, resulting in organomegaly or hypertrophy. Clinical symptoms depend on the pattern of each organ involvement and the severity of the disease activity. The course of IgG4-RD is varied. Some cases improve spontaneously, and the natural course of IgG4-RD is unknown [4]. IgG4-RD usually presents with a subacute onset, and a few cases of the disease lead to progressive organ failure. Although severe constitutional symptoms are rare, organomegaly or hypertrophy can sometimes cause serious complications of obstruction or compression including obstructive jaundice in AIP or IgG4-SC, visual disturbance in IgG4-related dacryoadenitis, and hydronephrosis in IgG4-related retroperitoneal fibrosis. Furthermore, persistent inflammation in affected organs has been shown to lead to fibrosis and permanent organ dysfunction or failure. Examples of such complications include exocrine and endocrine pancreatic dysfunction in AIP, liver fibrosis in IgG4-SC, and renal dysfunction in IgG4-related kidney disease [5].

Inoue et al. reported the incidence of IgG4-RD as follows. AIP is the leading manifestation of this systemic condition, being diagnosed in 60% of patients with IgG4-RD. The second most common manifestation is sialadenitis (34%), followed

T. Kamisawa, M.-H. Kim (eds.), *IgG4-Related Sclerosing Cholangitis*,
https://doi.org/10.1007/978-981-10-4548-6_15

by tubulointerstitial nephritis (TIN) (23%), dacryoadenitis (23%), and periaortitis (20%) [6]. Multiorgan disease is easier to identify at diagnosis; however, organ disease may evolve metachronously, with one organ at a time becoming involved over months to years.

Essentially, all IgG4-RDs respond dramatically to steroids. Additionally, it has recently been reported that IgG4-RD is successfully treated with rituximab.

Diagnosis of IgG4-RD

The current gold standard for diagnosis of IgG4-RD is its characteristic histology, which consists of abundant infiltration of IgG4-positive plasma cells and lymphocytes and storiform fibrosis together with obliterative phlebitis. Almost all IgG4-RDs show similar histopathological features regardless of the organs involved, although fibrosis is rare in IgG4-related dacryoadenitis and IgG4-related lymphadenopathy.

Clinically, diagnosis relies on the coexistence of various clinical, laboratory, radiological, and histopathological findings. Other organ involvements and response to steroids may aid in diagnosis, although none of these findings by themselves are pathognomonic. IgG4-RD occurs predominantly in older males. Serum IgG4 levels are frequently and significantly elevated in patients with IgG4-RD. Computed tomography (CT), magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) are common imaging methods used for diagnosis of other organ involvements of IgG4-RD. On enhanced CT images of IgG4-RD, diffuse or focal swelling of organs or soft tissue masses appears with soft tissue attenuation, well-defined margins, and homogeneous enhancement at the late stage. Accumulation of FDG is observed in almost all sites and organs affected by IgG4-RD.

Based on a combination of these findings, specific diagnostic criteria have been established for IgG4-RD in four organs: the bile duct (IgG4-SC) [7], pancreas (AIP) [8], kidney (IgG4-related kidney disease) [9], and lacrimal and salivary glands (IgG4-related sialadenitis and dacryoadenitis) [10]. In addition to these criteria, comprehensive diagnostic criteria for IgG4-RD have been proposed for practical use, which are independent of the predominant organ involvement (Table 15.1) [11].

Table 15.1 Comprehensive diagnostic criteria for IgG4-RD (2011) [11]

1. Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs
2. Hematological examination shows elevated serum IgG4 concentrations (≧135 mg/dl)
3. Histopathologic examination shows:
(a) Marked lymphocyte and plasmacyte infiltration and fibrosis
(b) Infiltration of IgG4 + plasma cells: ratio of IgG4+/IgG+ cells >40% and >10 IgG4 + plasma cells/HPF

1 + 2 + 3: definite
1 + 3: probable
1 + 2: possible

Other Organ Involvements of IgG4-SC

Autoimmune Pancreatitis

The pancreas was the first organ identified with IgG4-RD [2]. Of the two subtypes of AIP that are currently known, type 1 is the pancreatic manifestation of IgG4-RD, usually called AIP when referring to IgG4-RD. Type 2 AIP is characterized by granulocytic epithelial lesions [8].

On CT, typical AIP shows diffuse enlargement of the pancreas with delayed enhancement in association with a capsule-like low-density rim (Fig. 15.1). On endoscopic retrograde pancreatography, typical AIP shows diffuse irregular narrowing of the main pancreatic duct (Fig. 15.2). However, it is challenging to differentiate segmental-/focal-type AIP from pancreatic cancer. On pancreatography, long narrowing of the main pancreatic duct, skipped narrowed lesions, side branch derivation from the narrowed portion, and less upstream dilatation sug-

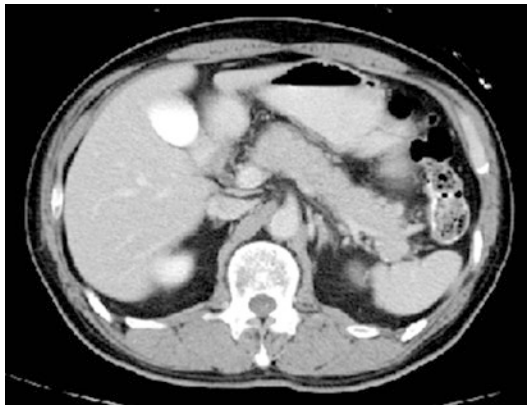

Fig. 15.1 Abdominal CT shows diffuse enlargement of the pancreas with delayed enhancement in association with a capsule-like low-density rim

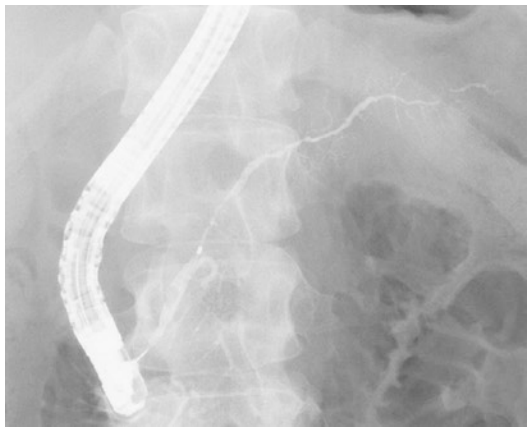

Fig. 15.2 ERCP shows diffuse irregular narrowing of the main pancreatic duct and stenosis of the lower bile duct

gest AIP rather than pancreatic cancer [12]. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is widely used to differentiate AIP from pancreatic cancer.

IgG4-SC develops in close association with AIP. In AIP patients, the lower bile duct is frequently stenotic; however, it remains under a debate whether stenosis of the lower bile duct associated with AIP is a primary disease or a direct extension of the inflammatory process from the pancreatic head. In the international consensus diagnostic criteria for AIP, only proximal IgG4-SC is recognized as IgG4-SC [8]. While proximal IgG4-SC frequently occurs in association with AIP, there are a few cases of isolated IgG4-SC that are quite difficult to differentiate from hilar cholangiocarcinoma.

IgG4-Related Sialadenitis and Dacryoadenitis

IgG4-related sialadenitis and dacryoadenitis, known as Mikulicz's disease which consists of bilateral symmetrical swelling of the lacrimal and salivary glands, are now recognized as a form of IgG4-RD.

There are some distinct findings between IgG4-related sialadenitis and Sjögren's syndrome as follows. Submandibular glands are more commonly affected in IgG4-related sialadenitis, while parotid gland enlargement predominates in Sjögren's syndrome. Xerostomia is less severe in IgG4-related sialadenitis than in Sjögren's syndrome, and IgG4-related sialadenitis improves with immunosuppression in contrast to Sjögren's syndrome.

In IgG4-related dacryoadenitis, in addition to (often bilateral) lacrimal glands, other tissues such as extraocular muscles, orbital fat tissues, eyelids, trigeminal nerve branches, and the nasolacrimal duct are sometimes involved. Thus, IgG4-related dacryoadenitis shows various ophthalmological symptoms due to extensive inflammation beyond the lacrimal gland such as eyelid swelling (Fig. 15.3), diplopia, ptosis, visual field disturbance, eye pain, decreased visual acuity, eye movement disturbance, dry eye, corneal ulcer, and epiphora [13].

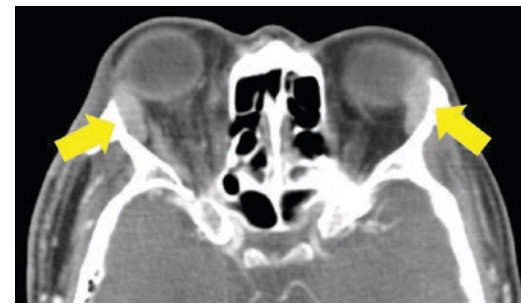

Fig. 15.3 MRI showing bilateral lacrimal gland swelling (arrows)

IgG4-Related Retroperitoneal Fibrosis

IgG4-related retroperitoneal fibrosis is characterized by inflammation and fibrosis of retroperitoneal tissues usually involving the anterior surface of the fourth and fifth lumbar vertebrae, with encasement and obstruction of retroperitoneal structures such as the ureter, aorta, and other abdominal organs. On CT, IgG4-related retroperitoneal fibrosis appears as a periaortic soft tissue density or a mass in the renal hilus with frequent medial deviation and obstruction of ureters, sometimes with hydronephrosis [14].

The management of IgG4-related retroperitoneal fibrosis involves urgent attention to obstructing organs, such as ureters, that require stenting. It should be kept in mind that IgG4-related retroperitoneal fibrosis is sometimes misdiagnosed as retroperitoneal visceral malignancy, resulting in surgery.

IgG4-Related Kidney Disease

A wide range of renal manifestations of IgG4-RD such as TIN, membranous glomerulonephritis and other glomerular lesions, and pyelitis are collectively referred to as IgG4-related kidney disease. More than 80% of patients with IgG4-related kidney disease have other organ involvements.

Contrast-enhanced CT is the most useful imaging system for delineating IgG4-TIN characteristics and distribution of renal lesions. The characteristic imaging findings on enhanced CT in IgG4-related kidney disease are multiple low-density lesions, diffuse kidney enlargement, hypovascular solitary mass in the kidney, and hypertrophic lesion of the renal pelvic wall without irregularity of the renal pelvic surface [9].

Histopathological findings are mandatory for definite diagnosis of IgG4-related kidney disease. However, in several situations such as inaccessible regional lesion distribution (e.g., lesions distributed only in the upper pole of the kidney) that hamper a histological approach, histopathological findings from other organs could support typical renal imaging findings and clinical features of IgG4-related kidney disease to allow diagnosis of IgG4-related kidney disease.

IgG4-Related Lymphadenopathy

Lymphadenopathy is one of the common manifestations in IgG4-RD, with enlarged lymph nodes. As it is usually asymptomatic, it is incidentally pointed out by imaging in many cases.

Generalized lymphadenopathy often clinically and/or histologically resembles lymphoma, Castleman disease, or disseminated malignancy and therefore needs to be distinguished from these diseases [15]. These diseases display fever, weight loss, and elevation of serum CRP, IL-6, and lactate dehydrogenase levels. An abundant infiltration of IgG4-positive plasma cells is a common feature of IgG4-related lymphadenopathy, including Castleman disease-like interfollicular plasmacytosis. Histological diagnosis by lymph node biopsy is required for differentiation from other diseases, especially when lymphadenopathy is not accompanied by other organ manifestations [16].

IgG4-Related Lung Disease

IgG4-related lung disease is reported as inflammatory pseudotumor of the lung with high IgG4 levels. Depending on the radiological findings, IgG4-related lung lesions can be divided into four groups: (1) solid nodular, (2) round-shaped ground-glass opacity, (3) alveolar interstitial, and (4) broncho-vascular [17]. Diagnosis of IgG4-related lung disease is sometimes difficult. Although CT-guided transthoracic core needle biopsy is convenient, it fails to yield a definitive diagnosis in about one-third of all patients. Thoracotomy or video-assisted thoracoscopic surgery (VATS) is therefore recommended to obtain more lung tissue so that a histopathological diagnosis of IgG4-related lung disease can be made.

IgG4-Related Thyroid Disease

IgG4-related thyroid disease is one of the newest identified organ involvement manifestations of IgG4-RD and is yet to be well characterized. To date, Riedel's thyroiditis and the fibrosing variant of Hashimoto's thyroiditis represent IgG4-related thyroid disease types. These disorders are frequently confused with malignancy due to intense sclerosis of the thyroid, which results in a hard texture on palpation, and is compounded by often-associated compressive symptoms [18].

IgG4-Related Cholecystitis

IgG4-related cholecystitis can occur with IgG4-SC. Thickening of the gallbladder wall was detected in 10 of 19 AIP patients on ultrasound and/or CT, and all of the 10 patients had stenosis of the extrahepatic bile duct [19]. There were no symptoms related to the gallbladder. IgG4-related cholecystitis consists of transmural fibrosis with dense infiltration of IgG4-positive plasma cells and lymphocytes [19]. Thickening of the gallbladder wall also improves after steroid therapy.

IgG4-Related Gastrointestinal Disease

While some reports have referred to IgG4-related gastrointestinal diseases, this concept is not well recognized because of insufficient observation. Nevertheless, two types of IgG4-related gastrointestinal disease have been reported. One type is a gastrointestinal lesion that shows marked thickening of the walls of the esophagus and stomach. This lesion consists of dense fibrosis with abundant infiltration of IgG4-positive plasma cells that usually shows submucosal spread. The other type is an IgG4-related pseudotumor that occurs in gastrointestinal lesions, such as the stomach, colon, and major duodenal papilla, and shows polypoid or mass-like lesions. Most solitary IgG4-related gastrointestinal lesions that are not associated with other IgG4-RDs appear to be difficult to diagnose, and it is of the utmost importance to rule out malignancy. However, as these lesions may respond to steroid therapy, IgG4-related gastrointestinal disease should be considered in the differential diagnosis to avoid unnecessary resection [20].

Summary

Diagnosis of IgG4-SC is still challenging, especially differentiation from primary sclerosing cholangitis and hilar cholangiocarcinoma in IgG4-SC involving the hilar bile duct. As it is difficult to obtain adequate biopsy material from the bile duct, association with other IgG4-RDs might aid in diagnosis of IgG4-SC.

Acknowledgment This work was supported in part by the Research Committee of IgG4 provided by the Ministry of Health, Labour, and Welfare of Japan.

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