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Review

Diagnosis and classification of autoimmune pancreatitis

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ABSTRACT

Recent studies suggested the existence of two subtypes of autoimmune pancreatitis (AIP): type 1 related with IgG4 as the pancreatic manifestation of IgG4-related disease (IgG4-RD), and type 2 related with a granulocytic epithelial lesion. Apart from type 2 AIP, the characteristic features of type 1 AIP are increased serum IgG4 levels, lymphoplasmacytic sclerosing pancreatitis (abundant infiltration of IgG4+ plasmacytes and lymphocytes, storiform fibrosis, and obliterative phlebitis), extra-pancreatic manifestations of IgG4-RD (e.g. sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis), and steroid responsiveness. Although the way how to diagnose IgG4-RD has not been established yet, the Comprehensive Diagnostic Criteria (CDC) for IgG4-RD for general use, and several organ specific criteria for AIP have been proposed; the International Consensus Diagnostic Criteria (ICDC) and the revised clinical diagnostic criteria in 2011 by Japan Pancreas Society (JPS-2011) for type1 AIP. In cases of probable or possible IgG4-RD diagnosed by the CDC, organ specific diagnostic criteria should be concurrently used according to an algorithm of diagnosis for IgG4-RD with reference to the specialist.

Contents

1. The history of autoimmune pancreatitis (AIP): before and after discovery of IgG4 (Table 1)

In 1961, Sarles et al. [1] observed a case of particular pancreatitis with hypergammaglobulinemia, which is supposed to be a prototype of AIP. In 1995, Yoshida et al. [2] proposed a novel concept of autoimmune pancreatitis (AIP), nowadays recognized as type 1 AIP (IgG4-related pancreatitis), the pancreatic manifestation of IgG4-related disease (IgG4-RD) [3], which has been recognized as a novel clinical entity following the epoch-making evidence of increased serum levels of IgG4 in the history of AIP [4]. The histopathological findings are characterized by the periductal localization of predominantly CD4 positive T-cells,

Abbreviations: AIP, autoimmune pancreatitis; ANA, anti-nuclear antibody; ERCP, endoscopic retrograde cholangio-pancreatography; LPSP, lymphoplasmacytic sclerosing pancreatitis; MD, Mikulicz disease; MOLPS, multiorgan lymphoproliferative disease; SjS, Sjögren's syndrome; PSC, primary sclerosing cholangitis; RF, rheumatoid factor; SIPS, IgG4-systemic plasmacytic syndrome; SLE, systemic lupus erythematosus.

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Table 1
History of autoimmune pancreatitis and IgG4-related disease.

Year	Authors	Ref	Evidences/contents
1892	Mikulicz J. et al.	[12]	Mikulicz's disease (*Z. Chir. Fesrschr*)
1961	Sarles H. et al.	[1]	Hyper-gammaglobulinemia in CP (*Am J Dig Di*)
1967	Comings DE. et al.	[9]	Familial multifocal fibrosclerosis (*Ann Intern Med*)
1972	Kuttner	[13]	Kuttner tumor (*Acta Otolaryngol*)
1991	Kawaguchi K. et al.	[7]	Lymphoplasmacytic sclerosing pancreatitis (*Human Pathol*)
1995	Yoshida et al.	[2]	Autoimmune pancreatitis (*Dig Dis Sci*)
2001	Hamano et al.	[4]	High IgG4 levels in sclerosing pancreatitis (*N Eng J Med*)
2002	Japan Pancreas Society	[43]	Clinical diagnostic criteria for AIP 2002 (*Suizo*)
2006	Okazaki K, et al.	[44]	Clinical diagnostic criteria for AIP 2006 (*J Gastroenterol*)
2006	Chari ST et al.	[47]	Mayo criteria (*Clin Gastroenterol Hepatol*)
2006	Kamisawa T. et al.	[14]	IgG4-related sclerosing disease (*J Gastroenterol*)
2006	Yamamoto M. et al.	[15]	IgG4-related plasmacytic disease (*Mod Rheumatol*)
2008	Masaki Y et al.	[16]	IgG4-multiorgan lymphoproliferative syndrome (MOLPS) (*Ann Rheum Dis*)
2011	Shimosegawa T. et al.	[25]	International Consensus Diagnostic Criteria (ICDC) for AIP (*Pancreas*)
2012	Umehara, Okazaki et al.	[17,18]	Concept and comprehensive Diagnostic Criteria for IgG4-related disease (*Mod Rheumatol*)
2012	Deshpande et al.	[19]	International Pathological Consensus for IgG4-RD (*Mod Pathol*)
2012	Stone, J et al.	[20]	Nomenclatures of individual organ manifestation of IgG4-RD (*Arthritis Rheum*)
2012	Japan Pancreas Society	[43,4444]	Clinical diagnostic criteria for AIP 2011 (*Suizo*)

IgG4-positive plasma cells, storiform fibrosis with acinar cell atrophy frequently resulting in stenosis of the main pancreatic duct, and obliterative fibrosis [5,6], which is also called lymphoplasmacytic sclerosing pancreatitis (LPSP) [7]. On the other hand, mainly in the western countries, histological analyses using resected pancreatic samples in patients with chronic nonalcoholic pancreatitis demonstrated a different histological pattern of pancreatitis from LPSP, so called idiopathic duct-centric pancreatitis (IDCP) or AIP with GEL. In 2003, Kamisawa et al. [8] first suggested that AIP showing LPSP is a systemic sclerosing disease based on the concept of multifocal fibrosclerosis proposed by Comings et al. [9], because the pancreas and other involved organs have fibrosis with abundant infiltration of IgG4-positive plasma cells. On the other hand, patients with IDCP, extremely rarely observed in Japan, are not associated with either serum IgG4 elevation or with other organ involvement (OOI) typically seen in LPSP. AIP is subclassified according to the International Consensus of Diagnostic Criteria (ICDC) for Autoimmune Pancreatitis as either type 1 (IgG4-related) or type 2 (granulocytic epithelial lesions; GEL) [10]. Different from type 1, type 2 AIP is supposed to be a specific pancreatic disease with occasional coexistence with ulcerative colitis [10,11].

On the other hand, in 1892, Mikulicz first observed a patient with symmetrical swelling of the lachrymal, parotid and submandibular glands, with massive infiltration of mononuclear cells [12]. The condition was called Mikulicz's disease (MD); however, it has since been classified as an atypical type of Sjögren's syndrome, which also presents with bilateral, painless, and symmetrical swelling of the lachrymal, parotid, and submandibular glands. Kuttner reported a tumor-like enlargement of the submandibular gland that was sometimes a result of stones in the Wharton duct [13], which indicated that the underlying cause had not been identified. These patients, lacking anti-SS-A/Ro or anti-SS-B/La antibodies, often show other systemic organ involvement with elevated serum levels of IgG4, infiltration of IgG4-positive plasma cells into the glands, and recovery of secretion with steroid treatment similar to AIP [4–6]. About 60 to 80% of patients with AIP show obstructive jaundice with sclerosing cholangitis (IgG4-related sclerosing cholangitis; IgG4-SC) and other organ involvement (OOI), in which cholangiographic features are similar to those of primary sclerosing cholangitis (PSC), pancreatic cancer, and cholangiocarcinoma. The steroid responses and the prognoses of sclerosing cholangitis associated with AIP differ from patients with PSC, which suggests different pathological conditions. In addition to the original concept of multifocal idiopathic fibrosclerosis, recent studies led us to develop a novel concept of a systemic disease such as IgG4-related systemic sclerosing disease [14], systemic IgG4-related plasmacytic syndrome (SIPS) [15], or IgG4-positive multiorgan lymphoproliferative syndrome (IgG4-MOLPS) [16], all of which may refer to the same conditions. Based on these findings, although it is unclear whether the pathogenetic mechanisms in individual organs are same or not [17,18], the comprehensive term "IgG4-related disease IgG4-RD", which was internationally endorsed with the proposal of nomenclatures for individual organ lesions as well as pathological consensus, and diagnostic criteria have been proposed from the Japanese investigators [18].

2. Current concepts of IgG4-RD

Patients with IgG4-RD show diffuse or focal organ enlargement and mass-forming or nodular/thickened lesions in various organs, either synchronously or metachronously. This is due to the prominent infiltration of lymphocytes and plasmacytes with fibrosis [5,14,17]. The causes of the disease are still not clear; however, some abnormal immunological mechanisms are involved. The organs known to be affected include the pancreas, biliary duct, lacrimal/salivary glands, retroperitoneum, central nervous system, thyroid gland, lungs, liver, gastrointestinal tracts, kidneys, prostate gland, and lymph nodes [5,14–20]. These suggest that type 1 AIP related with IgG4 is defined as a pancreatic manifestation and other organ involvements (OOIs) as extrapancreatic of IgG4-RD. IgG4-RD mainly affects middle-aged to elderly men, and clinical symptoms vary depending on the organ in which the lesions are located. Many cases are treated effectively by steroid therapy [5,17,18]; however, the prognosis is not clear. Some patients develop serious complications such as obstructive jaundice due to hepatic, gallbladder, or pancreatic lesions; hydronephrosis due to retroperitoneal fibrosis; or respiratory symptoms due to pulmonary lesions [1–10,13–23]. Although the infiltration of IgG4-positive cells and increased serum levels of IgG4 are characteristic in IgG4-RD, the severity of fibrosis seems to be different among the individual organs involved. These conditions are quite similar to multifocal idiopathic fibrosclerosis [9]. Storiform fibrosis and obliterative phlebitis are characteristic in pancreatic and biliary tract lesions, but the degree varies depending on the individual organs. For example, very seldom do lesions appear in the lachrymal/salivary gland or lymph node. The previous nomenclature of "IgG4-related sclerosing disease" is mainly based on the fibrous swollen organs, whereas those of "IgG4-SIPS" and "IgG4+MOLPS" have been based on lymphoplasmacytic proliferation and swollen lymph nodes without fibrosis [14–17]. Although most patients have multiorgan lesions synchronously or metachronously, about 10 to 20% of the patients do not have confirmed OOI. Therefore, it is unclear whether the pathogenetic mechanism is same among individual organs or not.

3. The clinical diagnostic criteria for IgG4-related disease

The patients with IgG4-related disease show diffuse/focal organ enlargement, mass-forming, or nodular/thickened lesions in various

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