History: Pancreas

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3.1 Introductory Remarks

IgG4-related disease (IgG4-RD) is a systemic disorder characterized by high serum IgG4 concentrations and abundant IgG4-positive plasma cell infiltration in affected organs. Autoimmune pancreatitis (AIP) and Mikulicz's disease are two major manifestations of this condition; lesions associated with IgG4-RD have been reported in the respiratory system, bile ducts, retroperitoneum, kidney, prostate, thyroid gland, and others. Many of the characteristic imaging and pathologic findings of these lesions in the respective organs have been documented in the literature, and in this book these findings are outlined and discussed in greater detail. In this chapter, we describe how the concept of IgG4-RD was elaborated, focusing on AIP and other pancreatic lesions, and consider separately events that occurred prior to and after recognition of the fact that IgG4 plays an important role in this condition [1].

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3.2 Prior to Recognition of the Involvement of IgG4

3.2.1 Pancreatitis in Which Autoimmune Mechanisms Are Suspected

A specific type of pancreatitis associated with autoimmune phenomena has long been suspected. In 1961, Sarles et al. in France noted hypergammaglobulinemia and local lymphoplasmacytic cell infiltrates in pancreatic lesions and implicated autoimmune mechanisms in the pathogenesis of pancreatitis [2]. In 1978, Nakano et al. reported for the first time the efficacy of glucocorticoid therapy in a disorder we now term AIP [3]. Nakano and colleagues observed the concomitant occurrence of Mikulicz's disease and hilar lymphadenopathy in their patient.

3.2.2 Lymphoplasmacytic Sclerosing Pancreatitis and Multifocal Idiopathic Fibrosclerosis

In 1991, Kawaguchi et al. outlined the characteristic pathologic findings of a pancreatic disorder they termed lymphoplasmacytic sclerosing pancreatitis (LPSP) [4]. These investigators reported widespread lymphoplasmacytic cell infiltrates, fibrosis, and obliterative phlebitis. Moreover, they observed that since the same histological findings could also be detected within lesions of the bile ducts and salivary glands in some of the same patients, there existed the possibility that this disorder was identical to the systemic disorder known as multifocal idiopathic fibrosclerosis (MIF), first proposed by Comings et al. in the 1960s [5].

MIF is known to be associated with conditions such as sclerosing cholangitis, retroperitoneal fibrosis, mediastinal fibrosis, Riedel's thyroiditis, sicca complex, and orbital pseudotumor. Many patients with these conditions are now recognized to have IgG4-RD. Although it is clear that IgG4-RD does not account

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for all cases of retroperitoneal fibrosis or mediastinal fibrosis, when one or more of these lesions occur in the same patient the probability of IgG4-RD as a unifying diagnosis is high.

3.2.3 Proposal of Chronic Pancreatitis with Diffuse Irregular Narrowing of the Main Pancreatic Duct

In 1992, Toki et al. drew attention to the narrowing of the main pancreatic duct that is now viewed as a cardinal feature of AIP. Toki and colleagues regarded their cases as having a new condition: "chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct" [6]. Today we identify the features of these four patients as being highly consistent with type 1 (IgG4-related) AIP: advanced age; male/female ratio of 3:1; mild abdominal pain and signs of obstructive jaundice, including serum elevations of biliary enzymes; diffuse pancreatic swelling on imaging; and histological findings of lymphoplasmacytic infiltrates and fibrosis. Gastroenterologists started to pay attention to these characteristic pancreatic duct and clinical findings, and many such cases were reported from Japan.

3.2.4 Proposal of Autoimmune Pancreatitis

In 1995, Yoshida, Toki, and colleagues summarized the clinical characteristics of chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct in a total of 11 cases derived from their own series, as well as cases reported by Nakano, Kawaguchi, and colleagues, and other reported cases in Japan (Table 3.1) [7]. The features they considered characteristic of "autoimmune pancreatitis" were hypergammaglobulinemia, the presence of various autoantibodies, lymphocytic infiltrates in the pancreatic parenchyma, any other coexistent "autoimmune diseases" (e.g., "Sjögren's syndrome"), and a favorable response to glucocorticoid therapy. These clinical characteristics have since been used by many clinicians as diagnostic guidelines [8], and many cases of AIP have subsequently been reported from Japan.

This report of Yoshida et al. became the basis for the preparation of "Diagnostic Criteria for Autoimmune Pancreatitis by the Japan Pancreas Society (2002)." The currently recognized clinical features of AIP are summarized in Table 3.2.

Table 3.1 Clinical characteristics of chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct (cited from [1])

1	Hypergammaglobulinemia (elevated blood IgG)
2	Presence of autoantibodies in serum
3	Diffuse pancreatic swelling
4	Diffuse irregular narrowing of main pancreatic duct
5	Pancreatic fibrosis associated with lymphocytic infiltrates
6	No or only mild abdominal symptoms (epigastralgia)
7	Constricting stenosis (jaundice) of the lower bile duct (intrapancreatic bile duct)
8	Not associated with pancreatic calcification
9	Not associated with pancreatic cysts
10	Associated with other autoimmune disorders
11	Steroid therapy very effective

Table 3.2 Characteristic clinical features of autoimmune pancreatitis (cited from [1])

1	Advanced age, male predominance
2	Often presents with obstructive jaundice; unlike usual pancreatitis seldom shows severe epigastralgia
3	Bilirubin and biliary enzymes are frequently elevated
4	IgG and IgG4 are frequently elevated. Especially IgG4 is useful in diagnosis and evaluation of disease activity
5	Abdominal US, CT, and MRI demonstrate pancreatic swelling
6	Pancreatic duct irregular narrowing and intrapancreatic bile duct stenosis are found
7	Gallium and FDG accumulation are seen in lesions focally
8	In pancreatic lesions focal marked lymphoplasmacytic infiltrates, fibrosis, obliterative phlebitis, and IgG4-positive plasma cell infiltrates are found
9	Steroid therapy is markedly effective, with clinical symptoms and signs and blood test and imaging findings all showing improvement
10	Repeated relapses promote pancreatic calcification

3.3 After Recognition of IgG4 Involvement

3.3.1 AIP and IgG4

Human IgG is composed of four subclasses numbered, in their order of identification, as IgG1 through IgG4. IgG4 comprises the smallest subclass under normal circumstances, usually accounting for no more than 7 % of the overall total IgG concentration and often even less. Elevated serum concentrations of IgG4 are reported in a number of conditions but are especially recognized to occur in allergic diseases, parasitic infections, and pemphigus.

Why and how, then, was the connection between elevated serum IgG4 concentrations and AIP recognized? The clue came from an observation pertaining to serum protein electrophoresis evaluations in these patients, namely, the finding of a slowly migrating "β–γ bridge" between the β-globulin and γ-globulin peaks. Immunofixation of this region revealed an elevated IgG4 fraction (Fig. 3.1) [9].

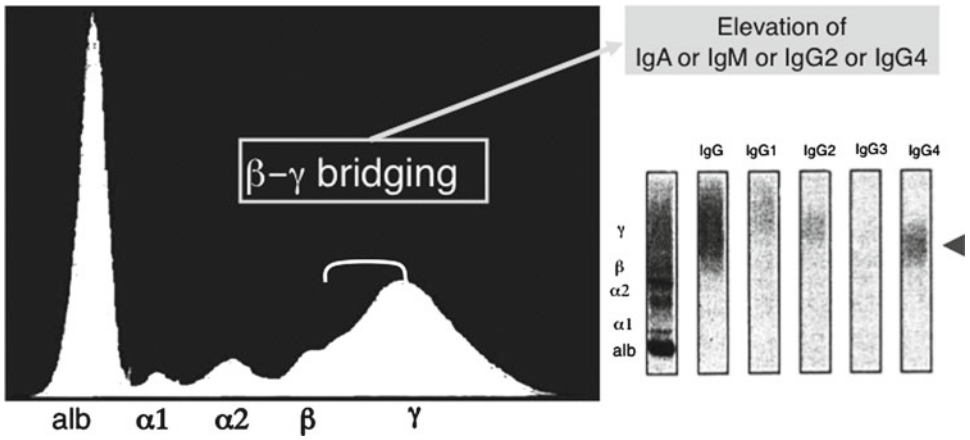

Fig. 3.1 Electrophoresis of the serum protein from a patient with autoimmune pancreatitis showing β–γ bridging and immunofixation study showing elevated IgG4 fraction

Subsequent analyses led to the realization that when serum IgG4 concentrations were compared between AIP patients and healthy persons, the values for the former group exceeded those of normal individuals by tenfold or more and that up to 90 % of AIP patients had elevated serum IgG4 concentrations. In contrast, elevated serum IgG4 concentrations of this magnitude were extremely rare among patients with conditions that often mimic AIP, to wit, pancreatic cancer, chronic pancreatitis of other etiologies, primary biliary cirrhosis, primary sclerosing cholangitis, and Sjögren's syndrome. In short, serum IgG4 concentrations were a useful factor in distinguishing AIP from these other conditions [9].

The finding of marked IgG4-positive plasma cell infiltrates within pancreatic lesions also proved in short order to be extremely helpful in establishing the histopathological diagnosis [10]. Moreover, these same IgG4-positive plasma cell infiltrates were also detected upon the histological examination of extrapancreatic lesions. It was therefore surmised that such pancreatic and extrapancreatic lesions share a common pathophysiology, and the underlying condition has come to be known as a systemic disorder related to IgG4, namely, "IgG4-related disease" [10–12].

3.3.2 Proposal of AIP from Countries Other than Japan (AIP Unrelated to IgG4)

Since 1995, AIP has been reported from countries other than Japan, as well. However, interesting differences have been observed in the nature of the AIP cases reported from Western countries, particularly from Europe, in comparison to the cases from Japan. The extent and explanation for these differences are the subject of ongoing investigations.

In 2002, discussions were held among researchers from the United States (Mayo Clinic), Italy, and Japan to clarify similarities and differences in AIP in the respective countries [13]. In the cases of AIP reported from Italy, the male/female ratio was approximately equal and the mean age at onset relatively young (42 years). However, the range in age of the patients affected was broad, and some patients presented with severe epigastric pain. No cases had elevated serum IgG4, and there was a frequent association with inflammatory bowel disease. All of these features differed substantially from the LPSP now known as type 1 (IgG4-related) AIP that is diagnosed most commonly in Japan, which is characterized by a male predominance, a tendency to affect older patients, mild abdominal symptoms, and generally striking elevations of the serum IgG4 concentration.

The cases of AIP reported from the Mayo Clinic differed histologically from LPSP in that destruction of the pancreatic duct epithelium associated with neutrophilic infiltrates was found and the existence of a histological subtype in which obliterative phlebitis is almost never present was reported. This variant, later named "idiopathic duct-centric chronic pancreatitis" (IDCP) by Notohara et al., is now regarded as being most compatible with type 2 AIP [14].

In 2004, Zamboni et al. reported a similar disease process from Italy that they termed "AIP with granulocytic epithelial lesions (GEL)" [15]. The clinicopathological pictures of IDCP and AIP with GEL, which are characterized by elevations in neither serum IgG4 concentration nor IgG4-positive plasma cell infiltrates within tissue, are identical. In summary, then, the LPSP variant of AIP that tends to predominate in Japan is recognized as being synonymous with type 1 (IgG4-related) AIP, and the IDCP/AIP with GEL variant—which has no relation to IgG4—is synonymous with type 2 AIP [16]. The frequency and clinical features of type 2 AIP in Japan remain largely obscure, because this entity is allegedly so rare in that country.

3.3.3 Diagnostic Criteria for AIP

In 2002, "Diagnostic Criteria for Autoimmune Pancreatitis by the Japan Pancreas Society (2002)" were presented. These included [1, 13, 17]:

- Narrowing of the main pancreatic duct that involves one third or more of the length of the pancreas, accompanied by pancreatic swelling.
- Hypergammaglobulinemia and/or positive autoantibodies such as antinuclear antibody and rheumatoid factor are noted.
- Pancreatic inflammation that consists primarily of a lymphoplasmacytic infiltrate and fibrosis.

AIP is diagnosed only if at least two of the items above are present, one of which must be the first item—narrowing of the main pancreatic duct and pancreatic swelling.

These diagnostic criteria were revised in 2006, with the essential changes being a discontinuation of the requirement that the pancreatic duct narrowing must affect ≥1/3 of the pancreatic duct length and the addition of serum IgG4 concentrations to the list of required blood test items [18].

With the generation of formal diagnostic criteria, AIP came to be internationally recognized as an independent disease entity. In 2006, investigators at the Mayo Clinic and South Korea proposed their own respective diagnostic criteria, and serum IgG4 was adopted as a diagnostic criterion [19, 20]. In order to unify the diagnostic criteria adopted in Japan and South Korea, researchers from the two countries held several meetings and in 2008 published a consensus statement on Asian diagnostic criteria for AIP [21]. In 2011, international consensus diagnostic criteria (ICDC) for AIP (both types 1 and 2) were proposed [22].

3.3.4 Extrapancreatic Lesions and IgG4

AIP can be complicated by diverse extrapancreatic lesions, most of which manifest the same histological features as those of pancreatic lesions, show marked IgG4-positive plasma cell infiltrates, and are responsive to glucocorticoid therapy [1, 23]. The realization that AIP and extrapancreatic lesions show the same underlying pathophysiology led to proposals that these entities be considered as part of a single systemic disorder related to IgG4 [11].

The lacrimal and salivary gland lesions of Mikulicz's disease were among the first to be linked to AIP and an underlying systemic disorder [24–26]. In 2010, the research group of the Japanese Ministry of Health reached a consensus on classifying these disorders together as a single disease entity to be called "IgG4-related disease" [11, 27]. An international symposium on IgG4-RD held in Boston in 2011 led to a consensus agreement on nomenclature for the diverse organ system manifestations of IgG4-RD and contributed further to the worldwide recognition of this disease [28, 29].

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