Serology

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Introduction

Serum markers associated with autoimmune pancreatitis (AIP) are roughly classified as immunoglobulins, autoantibodies, complement, and activity markers for lymphoid cells. These markers have been used for the diagnosis of AIP, differentiation of AIP from pancreatic cancer, prediction of AIP recurrence, and estimation of AIP disease activity in clinical follow-up assessments [1]. Among these markers, IgG4 is recognized to be specifically associated with AIP; thus, it is a characteristic indicator with high clinical utility [2]. Many studies have focused on the association between AIP and IgG4. However, other markers also represent useful tools in the various clinical aspects of AIP. In the following sections, we describe the clinical significance of these markers.

Diagnosis

Marker Sensitivities

Many serum markers have been assessed for their utility in diagnosing AIP, and many are included in diagnostic criteria for AIP. The first diagnostic criteria for AIP were published by the Japanese Pancreas Society (2002). Those criteria included laboratory data that demonstrated abnormally elevated levels of serum γ-globulin and/or IgG or the presence of autoantibodies [3]. After the clinical usefulness of IgG4 was discovered [2], most diagnostic criteria for AIP in Japan and other countries included only IgG4 as a diagnostic serum marker [4–10].

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We compared the rates of positive detection for each marker (Table 9.1) and found that IgG4 provided the best result.

Immunoglobulins

IgG4

The sera of patients with AIP exhibited a polyclonal band in the rapidly migrating fraction of gel electrophoresis that contained γ-globulins; this resulted in the finding that β–γ globulin bridging was a characteristic of AIP. Immunoprecipitation assays revealed that this polyclonal band was the result of high serum concentrations of IgG4 [2]. IgG4 is typically a minor component in IgG

Table 9.1 Rates of detection for each serum marker in autoimmune pancreatitis

Marker	Positive/total (*n*)	%
Immunoglobulins		
IgG4	80/88	90.9
IgG	59/88	67.0
IgE	33/83	39.8
IgA	7/88	8.0
IgM	4/88	4.5
Autoantibodies		
Antinuclear antibody (ANA)	39/74	52.7
Rheumatoid factor (RF)	18/67	23.9
Anti-SSA(Ro) antibody	0/56	0.0
Anti-SSB(La) antibody	0/56	0.0
Antimitochondrial antibody (AMA)	2/47	4.3
Complement components and immune complex		
C3	29/84	34.5
C4	27/84	32.1
Circulating immune complex (CIC)	68/82	82.9
Activity markers for lymphoid cells		
Soluble interleukin-2 receptor (sIL-2R)	68/81	84.0
β2 microglobulin (β2-m)	62/82	75.6

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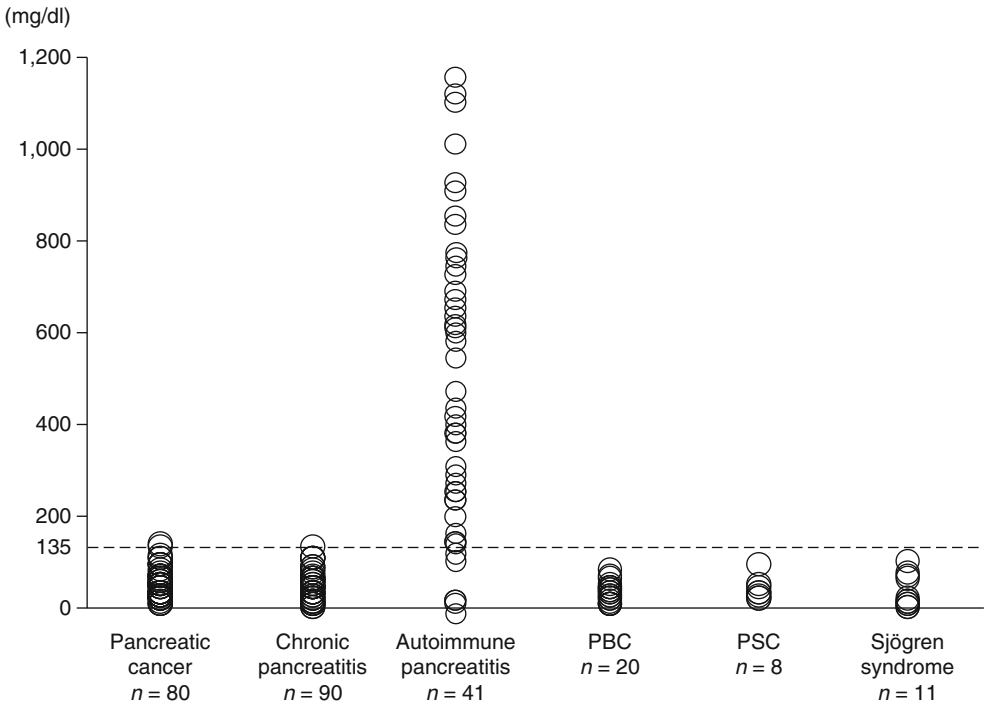

Fig. 9.1 IgG4 levels measured in patients with autoimmune pancreatitis and various other related diseases. The horizontal *dotted line* shows the maximum IgG4 level (135 mg/dl) observed in the related diseases. *PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis (Data are reprinted from Hamano et al. [2] with modification and from Kawa and Hamano [11] with permission from the *Journal of Gastroenterology*)

fractions; it constitutes only 3–7 % of total serum IgG. However, the serum IgG4 concentrations in patients with AIP were over tenfold higher than those in healthy subjects. In addition, we found elevated serum IgG4 concentrations in 90 % of patients with AIP, but rarely in patients with other conditions, including pancreatic cancer, chronic pancreatitis, primary biliary cirrhosis (PBC), primary sclerosing cholangitis, and Sjögren's syndrome (Fig. 9.1) [2, 11]. It has been reported that elevated serum IgG4 was found in a restricted number of conditions, including allergic disorders, parasite infestations, and pemphigus. Those results suggested that IgG4 represents a sensitive and specific marker for AIP, and it promised to be useful for the diagnosis of this disease [2]. The serum IgG4 concentration and the IgG4/IgG ratio were significantly reduced after corticosteroid therapy; this finding indicated that IgG4 might be a useful disease activity marker. Later, the clinical usefulness of IgG4 was assessed worldwide. Currently, serum IgG4 is considered a reliable marker for the diagnosis of AIP, and it has been included in various diagnostic criteria [4–10].

Patients with elevated IgG4 are considered to be in a highly active AIP disease state. Compared to patients with normal serum IgG4 levels, those with elevated IgG4 more frequently exhibit jaundice at AIP onset, diffuse pancreatic enlargement on imaging, significantly higher 18F-2-fluoro-2-deoxy-d-glucose uptake in pancreatic lesions, multiple extrapancreatic lesions, and a requirement for maintenance therapy [12, 13]. In addition, infiltration of IgG4-bearing plasma cells is a histological hallmark of AIP, and it is used in pathological diagnoses [14].

IgG

When the concept of AIP was first proposed, a high serum IgG concentration was listed as a characteristic laboratory finding [15]. Thus, IgG was considered a serological marker in the first diagnostic criteria proposed by the Japanese Pancreatic Society in 2002 [3]. However, the sensitivity and specificity of IgG are inferior for diagnosing AIP compared to IgG4. Therefore, IgG is currently used mainly as an activity marker to predict recurrence and estimate disease activity in clinical follow-ups of patients with AIP.

IgE

High serum IgE concentrations were detected in 30–40 % of patients with AIP, and the positive detection rate was also very high (86 %) [16, 17]. These findings suggested that an allergic mechanism may be contributing to the pathogenesis of AIP; thus, in some patients, AIP is complicated with an allergic response [16, 17]. However, the exact role or clinical significance of serum IgE elevation in AIP has not been fully elucidated. Although IgE does not necessarily reflect disease activity, the detection of elevated IgE might be a useful marker for the diagnosis of AIP in an inactive stage [17].

IgA and IgM

Interestingly, reduced IgA and IgM concentrations were detected in patients with AIP, in addition to increased IgG4 levels. It was reported that IgM was negatively correlated to IgG or IgG4 in patients with AIP. Moreover, the ratios of IgG:IgM and IgG:IgA in patients with AIP were significantly increased compared to those in patients with other

diseases; thus, these ratios provided excellent diagnostic sensitivity and specificity in differentiating AIP from the other diseases. Those results suggested that IgG:IgM and IgG:IgA ratios may serve as novel diagnostic markers for differentiating AIP from other hepatopancreatic diseases [18].

Autoantibodies

When the concept of AIP was first proposed, serum autoantibodies, like antinuclear antibody (ANA) and rheumatoid factor (RF), were listed as a characteristic laboratory finding [15]. Thus, the presence of serum autoantibodies was considered a serological marker in the first diagnostic criteria proposed by the Japanese Pancreatic Society in 2002 [3]. To date, many autoantibodies have been studied, and below, we describe those proposed as candidates for autoantibody markers of AIP pathogenesis.

ANA and RF

ANA and RF are detectable in a wide range of autoimmune diseases, but their production may not be specifically related to those conditions. ANA and RF are typically detected in 30–50 % of AIP samples. However, this detection may represent a nonspecific, active disease state in immunological conditions [1]. After corticosteroid therapy, these autoantibodies promptly returned to undetectable levels.

Anti-SSA/Ro and Anti-SSB/La Autoantibodies and Antimitochondrial Antibody

Anti-SSA/Ro and anti-SSB/La autoantibodies are specific markers for Sjögren's syndrome. Antimitochondrial antibody (AMA) is a specific marker for PBC. These disease-specific autoantibodies are seldom detected in patients with AIP [1, 19].

Candidate Pathogenic Autoantibodies

Carbonic anhydrase II (CA II) and lactoferrin are distributed in the ductal cells of the pancreas. Both proteins have been proposed as candidate target antigens in the pathogenesis of AIP, but the presence of autoantibodies to these antigens is not sufficiently specific or sensitive for an AIP diagnosis [20, 21].

Helicobacter pylori (*H. pylori*) infections may also trigger the occurrence of AIP, possibly as a result of molecular mimicry. There is substantial structural homology between the human CA II and the *H. pylori* alpha-carbonic anhydrase; the homologous segments contain the binding motif for the HLA molecule, *DRB1*04:05*, which is closely associated with AIP [22]. Those data led to the hypothesis that the *DRB1*04:05*-restricted peptide of CA II might be presented in genetically predisposed subjects; then, when reactive T cells and autoantibodies interact with the CA II of pancreatic ductal cells, they cause injury to pancreatic tissue [23]. Similarly, selected peptides from the plasminogen-binding protein (PBP) of *H. pylori* exhibited structural homology with the ubiquitin-protein ligase E3 component, n-recognin 2 (UBR2), which is highly expressed in pancreatic acinar cells. Antibodies against the PBP peptide were detected at high levels in patients with AIP, but they were barely detectable in patients with pancreatic cancer. It seems likely that the UBR2 in pancreatic acinar cells may be targeted by an autoantibody against the PBP of *H. pylori* in patients with AIP [24].

Complement and Circulating Immune Complex

AIP is associated with reduced levels of complement in 30–40 % of cases and elevated levels of circulating immune complex (CIC; determined by C1q assay). High serum CIC levels were significantly associated with increased serum levels of IgG1, reduced levels of C4, and a tendency toward reduced levels of C3. There were no significant elevations in serum mannose-binding lectin. These results suggested that AIP was associated with high serum CIC in the active state, which then links to a complement activation system and the classical pathway, rather than the mannose-binding lectin or alternative pathways [25]. In patients with AIP, complement C3c, IgG4, and IgG were deposited in collagen IV-positive basement membranes of pancreatic ducts, bile ducts, and acini. That finding suggested that CIC-mediated destruction of ducts and acini might play a role in the pathogenesis of AIP [26]. Decreased serum complement levels have also been detected in the active stage of the IgG4-related kidney disease, tubulointerstitial nephritis [27].

Activity Markers for Lymphoid Cells

A characteristic pathological finding of AIP is abundant lymphocyte infiltration. This infiltration represents an elevation in serum markers for active lymphoid cells, such as soluble interleukin-2 receptor (sIL-2R) and β-2 microglobulin (β2-m). Thus, high elevations in serum sIL-2R and β2-m may well correlate with AIP activity [1, 28]. It is reported that the sensitivity of sIL-2R was equal to that of IgG4 and higher than that of IgG. A significant reduction in sIL-2R was associated with administration of steroid therapy; this suggested that sIL-2R may serve as an indicator of the need for maintenance therapy. Serum sIL-2R is also strongly correlated to the number of systemic lesions associated with AIP; thus, sIL-2R is thought to be a potent serological marker for assessing autoimmune activity in AIP [28].

Table 9.2 Comparison of various markers in identical sera for differentiation between autoimmune pancreatitis (AIP) and pancreatic cancer (PC)

	Sensitivity (AIP $n=100$)	Specificity (vs. PC $n=80$)	Accuracy (vs. PC)
IgG4	86 %	96 %	91 %
IgG	69 %	75 %	72 %
ANA	58 %	79 %	67 %
RF	23 %	94 %	54 %
IgG4 + ANA	95 %	76 %	87 %
IgG + ANA	85 %	63 %	75 %
IgG4 + IgG + ANA	95 %	63 %	81 %
IgG4 + RF	90 %	90 %	90 %
IgG + RF	78 %	73 %	76 %
IgG4 + IgG + RF	91 %	71 %	82 %
ANA + RF	69 %	60 %	78 %
IgG4 + ANA + RF	97 %	73 %	86 %
IgG + ANA + RF	91 %	61 %	78 %
IgG4 + IgG + ANA + RF	97 %	61 %	81 %

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ANA antinuclear antibody, *RF* rheumatoid factor

Differentiation from Pancreatic Cancer

Lymphoplasmacytic sclerosing pancreatitis (LPSP), which is pathologically similar to AIP, was observed in 2.5 % of patients that underwent the Whipple resection [29]. Therefore, it is necessary to differentiate AIP from pancreatic cancer. In differentiating between AIP and pancreatic cancer, IgG4 showed the best results among several markers measured in identical sera; IgG4 exhibited 86 % sensitivity, 96 % specificity, and 91 % accuracy (Table 9.2) [2, 30]. IgG4 was therefore adopted in various diagnostic criteria for AIP [4–10]. The sensitivity and specificity of IgG4 were superior to those of IgG, ANA, and RF, but the additional measurements of ANA and RF further increased the sensitivity and negative predictive value of IgG4 [30]. However, elevated serum IgG4 and numerous IgG4 bearing plasma cell infiltrations have also been found in a few patients with pancreatic cancer [31]. Thus, a high serum IgG4 concentration and numerous IgG4-positive plasma cell infiltrations in pancreatic tissue are not completely specific to AIP. These markers cannot exclude the presence of pancreatic cancer.

Estimation of AIP Activity

Prediction of Recurrence

Some patients with AIP experience recurrence during the clinical course. The recurrence rate has been estimated to vary from 30 to 50 %, but corticosteroid therapy can significantly reduce the recurrence rate [32–35]. We aimed to clarify the validity of various serum markers measured at disease onset for predicting recurrences. We found that the CIC level, determined at disease onset with the monoclonal rheumatoid method (IC-mRF), was significantly higher in the recurrence group than in the nonrecurrence group [36]. We used an IC-mRF cutoff value of 10 μg/dl to test the prediction of recurrence. The probability of recurrence was 60 % in cases where IC-mRF was >10 μg/dl, and it was 30 % in cases where IC-mRF was <10 μg/dl. We also compared the serum levels of complement components in groups with either a high or normal serum level of CIC. We found that serum C4 was significantly lower and serum C3 tended to be lower in the high-CIC group compared to levels in the normal-CIC group [25]. These results suggested that a classical pathway of complement activation system may be operating in some patients with AIP that have high serum CIC; thus, high serum CIC may predict both tissue damage and the probability of recurrence. Previous studies have shown that various factors measured at diagnosis, including diffuse pancreatic swelling, low bile duct stenosis with obstructive jaundice, IgG, CIC, sIL-2R, and complement, were highly predictive of relapse [34, 36–39].

Other studies have shown that specific HLA antigens could predict the recurrence of AIP. Furthermore, a substitution of aspartic acid at position 57 in the HLA DQβ1 was reported to affect the recurrence of AIP [40]. Another predictor of AIP recurrence is the cytotoxic T-lymphocyte antigen 4 (CTLA4) polymorphism. One study found that the +49A/A and +6230A/A polymorphic genotypes were associated with an enhanced risk of AIP recurrence [41].

In patients with AIP, extrapancreatic lesions may involve organs throughout the body and sometimes appears as recurrence lesions. Patients with AIP that had multiple extrapancreatic lesions were found to have significantly higher IgG4 levels than those with AIP, but no extrapancreatic lesion [12]. Among various extrapancreatic lesions, lachrymal and salivary gland lesions and hilar lymph adenopathy have been significantly associated with high serum IgG4 concentrations; this association suggested that patients with high serum IgG4 should be assessed for the presence of these lesions and abundant cell infiltration [12].

Follow-Up

We followed the clinical course of a 69-year-old woman that presented with two AIP recurrences. In this case, serum elevations of CIC and IgG4 were detected several months before the overt appearance of clinical recurrence. This finding indicated that CIC could represent disease activity with a sensitivity similar to that of IgG4 (Fig. 9.2) [11]. In clinical follow-ups of AIP, we currently use IgG and complement components, which are routinely measured

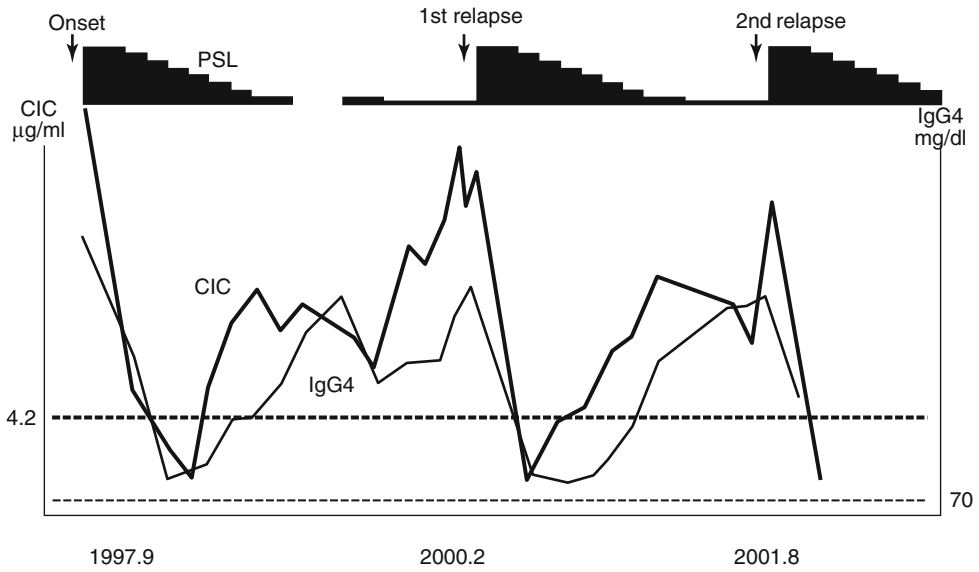

Fig. 9.2 Clinical course of autoimmune pancreatitis (AIP) in a 69-year-old female patient. After the onset of AIP and prednisolone (PSL) administration in 1997, the patient experienced two relapses in 2000 and 2001. The *black steps* indicate PSL dose reductions over time. The *horizontal dotted lines* show the typical IgG4 (light line; 70 mg/dl) and CIC (heavy line; 4.2 μg/ml) levels in healthy individuals. All three AIP occurrences were correlated with elevations in both IgG4 (*light line*) and CIC (*heavy line*). *CIC* circulating immune complex (Data are reprinted from Kawa and Hamano [11] with permission from the *Journal of Gastroenterology*)

in laboratory tests, to estimate AIP activity and predict the recurrence of AIP.

We followed two patients with AIP for 10 years each. One was a 55-year-old man with a high serum IgG4 concentration (1,135 mg/dl), and the other was a 65-year-old woman with a normal serum IgG4 concentration (42 mg/dl). The first patient experienced several recurrences, and he developed a pancreatic stone and pancreatic duct stenosis. The second patient showed no duct changes over time. These results suggested that when AIP is accompanied by normal IgG4 concentrations, it may have low activity, and it may represent a nonprogressive state [36]. Accordingly, serum IgG4 values may be useful in determining when maintenance therapy can be discontinued.

Role of IgG4

IgG4 may act in either a pathogenic or antiinflammatory role. For example, in a pathogenic role, an IgG4-type, anti-desmoglein 3 autoantibody was reported to provoke the lesions of pemphigus vulgaris [42]. Transfer of an anti-desmoglein 3 IgG4 autoantibody from a patient with pemphigus vulgaris to healthy BALB/C mice resulted in a pemphigus vulgaris-like lesion. Those studies suggested that an IgG4 autoantibody was directed against an unknown target antigen in AIP. In accordance with that hypothesis, IgG4 deposits have been detected in tissues of patients with AIP [26, 43].

In contrast, IgG4 was also found to have antiinflammatory effects against allergic reactions. IgG4 antibodies can bind to soluble antigens and block the interaction between these antigens and IgE on mast cells. This IgG4 activity resulted in the inhibition of allergic reactions.

For example, in an antiinflammatory role, it was reported that IgG4 underwent a Fab arm exchange [44]. It has been recognized that a characteristic feature of the IgG4 molecule is that it can undergo a dynamic Fab arm exchange; this exchange resulted in a Fab with bispecific activity, a loss of monospecific cross-linking activity, and a loss of the ability to form immune complexes. These findings suggested that IgG4 may primarily be an antiinflammatory agent [44].

IgG4 has been shown to act as an autoantibody against IgG, and it exhibited rheumatoid factor activity. Western blotting has shown that IgG4 from the sera of patients with AIP could bind to IgG1, IgG2, IgG3, and IgG Fc. Furthermore, IgG4 Fc, but not IgG4 Fab, was found to bind to IgG Fc; this indicated that the binding between IgG4 and IgG Fc occurred via an Fc-Fc interaction, not via rheumatoid activity [45]. The role of IgG4Fc-IgGFc is unclear, but it may have physiological and/or pathological effects. Further studies are needed to clarify this issue.

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