Serial Changes of Elevated Serum IgG4 Levels in IgG4-related Systemic Disease

Taku Tabata¹, Terumi Kamisawa¹, Kensuke Takuma¹, Naoto Egawa¹, Keigo Setoguchi¹, Koji Tsuruta², Taminori Obayashi¹ and Tsuneo Sasaki⁴

Abstract

Objective Autoimmune pancreatitis (AIP) and Mikulicz’s disease have recently been recognized as pancreatic or salivary gland lesions of IgG4-related systemic disease. These are frequently associated with elevated serum IgG4 levels. This study aimed to clarify clinical implications of serial changes of elevated serum IgG4 levels in IgG4-related systemic diseases.

Methods Serial changes of elevated serum IgG4 levels were examined in patients with IgG4-related systemic diseases.

Patients Serial changes of elevated serum IgG4 levels were examined in 44 patients: AIP (n=24), Mikulicz’s disease (n=8), pancreatic cancer (n=5), bile duct cancer (n=1), sclerosing cholangitis (n=1), hypereosinophilic syndrome (n=1), chronic thyroiditis (n=1), hypophysitis (n=1), idiopathic pancreatitis (n=1), and Behcet’s disease (n=1).

Results The serum IgG4 levels decreased in all patients with AIP and Mikulicz’s disease after steroid therapy. The serum IgG4 levels were normalized in 46% of AIP patients and 38% of Mikulicz’s disease patients. The serum IgG4 levels were not normalized at remission in 3 of 4 relapsed AIP patients, and re-elevation of serum IgG4 levels was detected in all relapsed patients. Elevated serum IgG4 levels decreased in 3 patients with pancreatic cancer after resection or chemotherapy, and decreased in patients with hypereosinophilic syndrome, sclerosing cholangitis, and hypophysitis after steroid therapy.

Conclusion Measurement of serial serum IgG4 levels is useful to determine the disease activity of IgG4-related systemic diseases.

Key words: IgG4, autoimmune pancreatitis, Mikulicz’s disease, pancreatic cancer

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Introduction

Autoimmune pancreatitis (AIP) is a particular type of pancreatitis with a presumed autoimmune etiology. Serum IgG4 levels are frequently and significantly elevated in AIP patients (1, 2). AIP responds well to steroid therapy, but some AIP cases recur (3). Serum IgG4 levels decrease after steroid therapy in AIP patients, but the precise serial changes are unknown. It is not known when and what percentage of serum IgG4 levels are normalized in AIP patients after steroid therapy. Furthermore, whether changes in serum IgG4 levels can predict or detect early recurrence of AIP is also not known.

Since abundant infiltration of IgG4-positive cells and T lymphocytes with fibrosis has been detected in various organs of AIP patients, we proposed the existence of a novel clinicopathological entity, an IgG4-related systemic (sclerosing) disease, and suggested that AIP is a pancreatic lesion of this systemic disease. Serum IgG4 levels are most frequently elevated in IgG4-related systemic disease (4-6). Mikulicz’s disease is a unique condition that involves bi-
lateral enlargement of the salivary and lacrimal glands (7). It has recently been clarified that Mikulicz’s disease is also a manifestation of IgG4-related systemic disease (8). Mikulicz’s disease responds well to steroid therapy, but the changes in serum IgG4 levels after steroid therapy are unknown.

Although it is still equivocal, IgG4-related systemic disease may include some cases of interstitial pneumonia, interstitial nephritis, hypothyroidism, and pseudotumor, since they are occasionally associated with AIP (6, 9). On the other hand, it has been reported that serum IgG4 levels are elevated in a few patients with pancreatic cancer, ordinary chronic pancreatitis, idiopathic pancreatitis, bile duct cancer, and sclerosing cholangitis (10, 11).

In this study, to clarify the clinical implications of serial changes of elevated serum IgG4 levels in IgG4-related systemic diseases, serial changes of elevated serum IgG4 levels were examined in patients with AIP, Mikulicz’s disease, and other IgG4-related diseases after steroid therapy.

### Patients and Methods

Serum IgG4 levels were prospectively examined at the time of initial evaluation in 554 patients who were suspected of having pancreatobiliary, allergic, or immunological diseases based on their clinical findings at Tokyo Metropolitan Komagome Hospital from July 2002 to September 2009. Serum IgG4 levels were measured by nephelometry using IgG subclass (BS-NIA) kits. A cutoff value of 135 mg/dL, which is widely accepted (12), was used. Eighty-four (15%) of 554 patients showed elevated serum IgG4 levels before any treatment. Elevated serum IgG4 levels were found in 72% (34/47) of AIP patients and 100% (19/19) of Mikulicz’s disease patients. The mean serum IgG4 level was 437.8 mg/dL in AIP patients and 602.6 mg/dL in Mikulicz’s disease patients (Table 1).

Serum IgG4 levels were examined more than once, at intervals of more than one month, in 44 of the 84 patients with elevated serum IgG4 levels. They had AIP (n=24), Mikulicz’s disease (n=8), pancreatic cancer (n=5), and other diseases (n=7). The 7 other diseases were: bile duct cancer (n=1), sclerosing cholangitis (n=1), hypereosinophilic syndrome (n=1), chronic thyroiditis (n=1), hypophysitis (n=1), idiopathic pancreatitis (n=1), and Behcet’s disease (n=1).

AIP was diagnosed according to the Asian diagnostic criteria for AIP (13). Mikulicz’s disease was diagnosed according to two criteria: persistent symmetrical swelling of the major salivary glands and/or lacrimal glands, and exclusion of other diseases presenting as glandular swelling, such as sarcoidosis and lymphoproliferative disease (14). Pancreatic cancer and bile duct cancer were diagnosed based on histology and/or cytology, in addition to a compatible clinical course and radiological findings.

In AIP patients including those associated with Mikulicz’s disease, steroid therapy was started at 30–40 mg/day of prednisolone and gradually tapered to a maintenance dose over a period of 3-6 months. To prevent relapse, in general steroid maintenance therapy (5 mg/day) is continued for 1-3

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### Table 1. Patients with Elevated Serum IgG4 Levels

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total cases</th>
<th>Elevated IgG4</th>
<th>Rate</th>
<th>Mean value, mg/dL (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune pancreatitis</td>
<td>47</td>
<td>34</td>
<td>72.3%</td>
<td>437.8 (11-2490)</td>
</tr>
<tr>
<td>Mikulicz’s disease</td>
<td>19</td>
<td>19</td>
<td>100%</td>
<td>602.6 (21-1910)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>136</td>
<td>8</td>
<td>5.9%</td>
<td>57.4 (&lt;3-1170)</td>
</tr>
<tr>
<td>Interstitial pneumonia</td>
<td>6</td>
<td>4</td>
<td>66.7%</td>
<td>187.6 (&lt;3.0-389)</td>
</tr>
<tr>
<td>Bile duct cancer</td>
<td>41</td>
<td>3</td>
<td>7.3%</td>
<td>47.6 (&lt;3.0-206)</td>
</tr>
<tr>
<td>Idiopathic pancreatitis</td>
<td>4</td>
<td>2</td>
<td>50.0%</td>
<td>103.5 (23-174)</td>
</tr>
<tr>
<td>Hypereosinophilic syndrome</td>
<td>16</td>
<td>2</td>
<td>12.5%</td>
<td>74.6 (4.3-327)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>8</td>
<td>2</td>
<td>25%</td>
<td>78.5 (17-286)</td>
</tr>
<tr>
<td>Chronic pancreatic</td>
<td>21</td>
<td>1</td>
<td>4.8%</td>
<td>33.2 (4-137)</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
<td>8</td>
<td>1</td>
<td>12.5%</td>
<td>96.8 (16-473)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>166</td>
</tr>
<tr>
<td>Chronic thyroiditis</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>159</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>335</td>
</tr>
<tr>
<td>ANCA-related vasculitis</td>
<td>2</td>
<td>1</td>
<td>50%</td>
<td>137 (88-186)</td>
</tr>
<tr>
<td>Drug-induced liver dysfunction</td>
<td>2</td>
<td>1</td>
<td>50%</td>
<td>89.0 (23-155)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>5</td>
<td>1</td>
<td>20%</td>
<td>113.1 (20-329)</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm</td>
<td>14</td>
<td>1</td>
<td>7.1%</td>
<td>41.3 (4-141)</td>
</tr>
<tr>
<td>Behcet’s disease</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>137</td>
</tr>
<tr>
<td>Others</td>
<td>221</td>
<td>0</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>554</td>
<td>84</td>
<td>15.2%</td>
<td></td>
</tr>
</tbody>
</table>

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Figure 1. The serial changes of elevated serum IgG4 levels in AIP patients. Dashed lines show changes of relapsed patients.

Table 2. Profile of Relapsed AIP Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period from onset to relapse</th>
<th>Oral prednisolone dose at relapse</th>
<th>Serum IgG4 levels (mg/dL) Onset</th>
<th>Remission</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 months</td>
<td>10 mg/day</td>
<td>2490</td>
<td>250</td>
<td>298</td>
</tr>
<tr>
<td>2</td>
<td>13 months</td>
<td>5 mg/day</td>
<td>1160</td>
<td>177</td>
<td>379</td>
</tr>
<tr>
<td>3</td>
<td>25 months</td>
<td>5 mg/day</td>
<td>450</td>
<td>273</td>
<td>430</td>
</tr>
<tr>
<td>4</td>
<td>60 months</td>
<td>0 mg/day</td>
<td>395</td>
<td>89</td>
<td>780</td>
</tr>
</tbody>
</table>

years (3). Relapse of AIP was defined as the reappearance of symptoms with the development or reappearance of pancreatic and/or extrapancreatic abnormalities on imaging studies.

In independent Mikulicz’s disease patients, steroid therapy was started at 0.4-0.5 mg/kg/day of prednisolone and gradually tapered based on their symptoms. The initial dose of prednisolone for Mikulicz’s disease was different from that for AIP. Five patients with pancreatic cancer were treated with distal pancreatectomy (n=2), pancreatoduodenectomy (n=1), chemo-radiotherapy (n=1), and chemotherapy with gemcitabine (n=1). The 3 pancreatic cancers were resected curatively, and chemotherapy was effective in reduction of the mass of the patient. The resected specimens of the 3 pancreatic cancer patients were examined with IgG4-immunostaining.

In most patients with AIP or Mikulicz’s disease, serum IgG4 levels were measured before treatment, and at 1, 3, 6, and 12 months after steroid therapy. In patients who were followed-up for more than 1 year, serum IgG4 levels were measured periodically with intervals of 3-6 months. In other patients, serum IgG4 levels were measured twice; before treatment and after treatment or during conservative follow-up. A significant change in the serum IgG4 level was defined as an increase or decrease of more than 30 mg/dL based on the previous study (15).

All patients provided written informed consent. The study protocols were in accordance with the current revision of the Helsinki Declaration, and were approved by the ethics committee of Tokyo Metropolitan Komagome Hospital.

Differences between groups were analyzed using Mann-Whitney’s U-test. In all tests, corrected p values of less than 0.05 were considered statistically significant.

Results

Serial changes of serum IgG4 levels in AIP and Mikulicz’s disease

In all patients with AIP or Mikulicz’s disease, the serum IgG4 levels decreased after steroid therapy. In AIP patients, the serum IgG4 levels normalized (<135 mg/dL) in 17% at 1 month, 46% at 3 months, 46% at 12 months, and 50% at 24 months after starting therapy (Fig. 1). Four AIP patients relapsed during maintenance therapy (n=3) or after cessation of steroid (n=1), and serum IgG4 levels were not normalized at remission in the 3 relapsed patients. In all relapsed patients, re-elevation of serum IgG4 levels was detected (Table 2), and the elevated IgG4 levels decreased after dose increase or re-administration of steroid, along with ameliora-
tion of the imaging findings. Fluctuation of serum IgG4 levels of >30 mg/dL was detected in 50% of cases during follow-up.

In Mikulicz’s disease patients, the serum IgG4 levels normalized in 25% at 1 month, and 38% at 12 months after starting steroid therapy (Fig. 2). No Mikulicz’s disease patients relapsed during follow-up.

**Serial changes of serum IgG4 levels in pancreatic cancer**

Although the serum IgG4 levels decreased in 3 patients after treatment (distal pancreatectomy, pancreatoduodenectomy, and chemotherapy), the serum IgG4 levels normalized in no patients with pancreatic cancer. In 2 patients, the serum IgG4 levels did not change after treatment (Table 3). In the resected specimens, there was no evidence of AIP. Pancreatic cancer cells were not immunoreactive for IgG4. In 2 patients whose serum IgG4 levels decreased after resection, abundant IgG4-positive plasma cells (>20/high power field) had infiltrated the cancerous areas of the pancreas, but only a few IgG4-positive plasma cells were detected in the non-cancerous areas, and they were also detected in the duodenal mucosa and swollen peripancreatic regional lymph nodes (16). In another patient whose serum IgG4 levels did not change after resection, infiltration of IgG4-positive plasma cells was detected only in the peripancreatic lymph nodes.

**Serial changes of serum IgG4 levels in the other diseases**

The elevated serum IgG4 levels were decreased after steroid therapy in a patient with hypereosinophilic syndrome, in a patient with sclerosing cholangitis, and in a patient with hypophysitis. In one patient with chronic thyroiditis, ele-
vated serum IgG4 levels decreased spontaneously without any medication.

In a patient with advanced bile duct cancer, the serum IgG4 levels increased 1 year later without any therapy. In patients with Behcet’s disease and idiopathic pancreatitis, the serum IgG4 levels did not change (Table 4).

### Discussion

IgG4 is a subtype of immunoglobulin G (IgG), which accounts for 3-6% of total IgG. It is unique among the IgG subclass in its inability to bind C1q complement, and in its low affinity for target antigen (17). Hamano et al. reported the frequent and significant elevation of serum IgG4 levels in AIP patients and reported that an IgG4 cutoff value of 135 mg/dL resulted in high accuracy (97%), sensitivity (95%), and specificity (97%) in distinguishing AIP from pancreatic cancer (12). Based on histological and immunohistochemical examination of various organs of AIP patients, we proposed the existence of a novel clinicopathological entity, an “IgG4-related systemic (sclerosing) disease”; we suggested that AIP is a pancreatic lesion of this systemic disease, and that the extrapancreatic lesions of AIP are clinically manifested of organs involved in this disease (4-6).

AIP responds well to steroid therapy, and serum IgG4 levels decrease along with amelioration of pancreatic imaging findings. However, although recurrence occurs in about 30-40% of AIP patients during steroid tapering, maintenance therapy, or after cessation of steroid therapy, there are no definite markers to predict or detect relapse early (18).

In this study, elevated serum IgG4 levels decreased in all AIP patients after steroid therapy. Elevated serum IgG4 levels became normalized in 17% at 1 month, and in 46% at 3 months after starting steroid, but they failed to be normalized in 54% at 12 months later. Elevated serum IgG4 levels were not normalized in 3 of 4 relapsed patients. In the other relapsed patient, normalized serum IgG4 levels began to increase gradually after cessation of steroid therapy. Although serum IgG4 levels were not associated with an increased risk of relapse on multivariate analysis in the study of Kubota et al (19), persistent elevation of serum IgG4 levels may be one predictor of AIP relapse. Although serum IgG4 levels fluctuated by more than 30 mg/dL in 30% of the present cases, significant re-elevation of serum IgG4 levels was detected in all relapsed AIP patients. Accordingly, serum IgG4 levels at remission and during follow-up may be useful to predict or detect relapse earlier in AIP patients.

Mikulicz’s disease was recently reported to be associated with prominent infiltration of IgG4-positive plasma cells into the swollen salivary and lacrimal glands, and it is suggested to be a salivary or lacrimal gland lesion of IgG4-related systemic disease (8). In all patients with Mikulicz’s disease, the serum IgG4 levels decreased after steroid therapy. Although serum IgG4 levels were not normalized in 5 (63%) Mikulicz’s disease patients, no patients relapsed during follow-up. Yamamoto et al (8) reported that all 16 patients with Mikulicz’s disease had elevated serum IgG4 levels (average 1111.0 mg/dL). Steroid therapy for 2 months decreased the serum IgG4 levels from 1556.4 mg/dL to 234.7 mg/dL in 8 of the 16 patients, but serum IgG4 levels increased with relapse of salivary and lacrimal gland swelling (8).

Elevated serum IgG4 levels in patients with pancreatic cancer were detected in 6% (8/136) in the present series, and in 7% (5/71) in the University of Pittsburgh Medical Center series (20). Ghazale et al. reported that serum IgG4 levels were elevated (>140 mg/dL) in 13/135 (10%) pancreatic cancer patients, but only 1% had IgG4 levels >280 mg/dL, compared with 53% of AIP patients (11). In this series, elevated serum IgG4 levels decreased in 2 patients with pancreatic cancer after pancrætoduodenectomy or distal pancretectomy and in 1 patient with advanced pancreatic cancer after chemotheraphy. These patients had no serological, radiological, or histological evidence of AIP. Abundant infiltration of IgG4-positive plasma cells was detected in the cancerous areas of the pancreas, duodenal mucosa, and the swollen regional lymph nodes in the 2 patients whose serum IgG4 levels decreased after resection, but it was detected only in the peripancreatic lymph nodes in another patient whose serum IgG4 levels did not change after resection. Raina et al. re-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Serum IgG4 levels (mg/dL) Before</th>
<th>Serum IgG4 levels (mg/dL) After</th>
<th>Observation period (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hypersinusitis syndrome</td>
<td>Steroid spray</td>
<td>327</td>
<td>71.3</td>
<td>decreased</td>
</tr>
<tr>
<td>2</td>
<td>Sclerosing cholangitis</td>
<td>Steroid</td>
<td>209</td>
<td>108</td>
<td>decreased</td>
</tr>
<tr>
<td>3</td>
<td>Hypophysitis</td>
<td>Steroid</td>
<td>335</td>
<td>249</td>
<td>decreased</td>
</tr>
<tr>
<td>4</td>
<td>Chronic thyroiditis</td>
<td>Steroid</td>
<td>159</td>
<td>122</td>
<td>decreased</td>
</tr>
<tr>
<td>5</td>
<td>Bile duct cancer</td>
<td>None</td>
<td>206</td>
<td>391</td>
<td>increased</td>
</tr>
<tr>
<td>6</td>
<td>Behcet’s disease</td>
<td>Ibuprofen</td>
<td>137</td>
<td>160</td>
<td>no change</td>
</tr>
<tr>
<td>7</td>
<td>Idiopathic pancreatitis</td>
<td>None</td>
<td>174</td>
<td>170</td>
<td>no change</td>
</tr>
</tbody>
</table>

*Table 4. Serial Change of Elevated Serum IgG4 Levels in Patients with Other Diseases*
ported that abundant infiltration of IgG4-positive plasma cells was detected in the common bile duct of one patient, in the lymph nodes of one patient, and in the duodenal mucosa of one patient with pancreatic cancer and elevated serum IgG4 levels (20). It is unknown whether pancreatic cancer can initiate an immunological response with subsequent infiltration of IgG4-positive plasma cells in the pancreatic and peripancreatic area, or whether pancreatic cancer occurs independently in patients with subclinical IgG4-related systemic disease who had infiltration of IgG4-positive plasma cells in various organs but did not show symptoms. However, it is true that elevated serum IgG4 levels decreased with remission of pancreatic cancer with IgG4-related manifestations. The reduction of the organs or tissues involved in IgG4-related disease may contribute to the decrease of the serum IgG4 levels.

The elevated serum IgG4 levels decreased after steroid therapy in a patient with hypereosinophilic syndrome, in a patient with sclerosing cholangitis, and in a patient with hypophysitis. Some cases of sclerosing cholangitis (6, 9, 21) and hypophysitis (22) have been reported to be associated with AIP, and they appear to be part of IgG4-related systemic disease.

Although the relationship between hypereosinophilic syndrome and IgG4-related sclerosing disease is unclear, AIP patients sometimes show peripheral blood eosinophilia (23). Zen et al. reported that IgG4-related disease is characterized by an immune reaction predominantly mediated by T helper (Th) 2 cells producing interleukin (IL)-5 or IL-13 (24). IL-5 is important for eosinophilic infiltration and activation, and IL-13 is another T-cell-derived cytokine involved in the eosinophilic infiltration (25).

Elevated serum IgG4 levels in a patient with chronic thyroiditis decreased spontaneously. The relationship between chronic thyroiditis and IgG4 is unknown, but hypothyroidism has been reported in 22% of AIP patients (9). Considering that some AIP cases improve spontaneously (18), chronic thyroiditis in this case may be associated with IgG4-related systemic disease. Elevated serum IgG4 levels also decreased in patients with IgG4-related systemic disease other than AIP and Mikulicz’s disease, with or without steroid therapy.

In summary, the present study demonstrated the following: 1) elevated serum IgG4 levels decreased after steroid therapy in all patients with IgG4-related systemic disease, but about half of them were not normalized; 2) persistent elevated serum IgG4 levels may be a predictor for relapse, and re-elevation of serum IgG4 levels suggests relapse; and 3) serum IgG4 levels may decrease with reduction of lesions involved in IgG4-related disease.

The biggest weakness of this study is small number of cases which might not render it sufficient to generalize the results, especially with regard to the findings based on only one patient. However, most IgG4-related systemic diseases are relatively rare, and follow-up measurement of serum IgG4 levels is sometimes difficult. Further prospective study should be undertaken on the serial changes of serum IgG4 levels.

In conclusion, the measurement of serial serum IgG4 levels is useful to determine disease activity of IgG4-related systemic diseases.

The authors state that they have no Conflict of Interest (COI).

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