By the way, the case report was submitted to *Digestive Diseases and Sciences* in the summer of 1993 [1], and it had taken about two years since it had originally been submitted. There was a comment by a reviewer that since it was just a report of a single case, adding the subtitle "Proposal of the Concept of Autoimmune Pancreatitis" may have been an overstatement or an exaggeration. However, retaining the subtitle made a considerable impact, and it might have attracted a great deal attention in the age of the Internet. Obviously, it is difficult to propose anything new.

3. Treatment of AIP

AIP has recently been subclassified into type 1 and type 2 AIP [2, 3]. Type 1 AIP is a classical AIP that shows a histology of lymphoplasmacytic sclerosing pancreatitis and is considered the pancreatic manifestation of IgG4-related systemic disease [4, 5]. Type 2 AIP shows a histology of idiopathic duct-centric chronic pancreatitis and is not related to IgG4 [2, 3]. Although it is reported that type 2 AIP responds well to steroid therapy, similar to type 1 AIP [2], the precise clinical features of type 2 AIP have not been clarified. Only treatment of type 1 AIP is described in this paper.

3.1. Spontaneous Improvement. In some AIP patients, improvement of swelling of the pancreas or irregular narrowing of the main pancreatic duct improves without steroid therapy [6–8]. In our series [6], 3 of 12 AIP patients who were followed for more than 6 months without steroid therapy improved spontaneously, but 2 of them received steroid therapy later. Wakabayashi et al. [7] reported on 4 AIP patients who showed spontaneous regression; they had negative immunoserological tests and no biliary lesions. Kubota et al. [8] reported that seronegative findings for IgG4, no obstructive jaundice, and focal swelling of the pancreas were related to spontaneous remission. Considering that patients who are later treated with steroids due to AIP exacerbation also show steroid responsiveness, asymptomatic segmental AIP cases without biliary lesions may be followed without steroid therapy with periodic laboratory and imaging tests.

3.2. Indication. Because the fibroinflammatory process in AIP responds well to steroid therapy, administration of oral steroids has become standard therapy for AIP. However, it is important to differentiate pancreatic cancer from AIP before starting treatment with steroids in AIP patients. According to a recent international study of AIP [9], steroids are used for AIP patients in all countries. In the Japanese consensus guidelines for the management of AIP [10], indications for steroid therapy in AIP include symptoms such as obstructive jaundice due to associated sclerosing cholangitis and the presence of symptomatic extrapancreatic lesions such as hydronephrosis due to retroperitoneal fibrosis. Because diabetes mellitus (DM) seen in the acute presentation of AIP sometimes improves with steroid therapy, DM coincidental with AIP might be an indication for steroid therapy [10]. Although improvement in clinical findings with steroid therapy may be useful in the differential diagnosis of AIP from pancreatic cancer, facile diagnostic steroid trial should be avoided not to misdiagnose pancreatic cancer as AIP. Diagnostic steroid trials should be conducted carefully by pancreatologists only after a negative workup for cancer including endoscopic ultrasound-guided fine needle aspiration [11, 12]. Serological and imaging tests should be done 2 weeks after commencement of steroid therapy. Rapid response to steroids is reassuring and confirms the diagnosis of AIP. If steroid effectiveness is reduced, the patient should be reevaluated on suspicion of pancreatic cancer.

3.3. Steroid Regimen. In the Japanese guidelines [10], before starting steroid therapy, biliary drainage is usually done in cases with obstructive jaundice. However, as there are some patients whose jaundice is relieved by steroid therapy alone, it is unclear if biliary obstruction can be treated with steroid therapy alone without biliary drainage [13]. In cases with DM, glucose levels must be controlled. The recommended initial oral prednisolone dose is 0.6 mg/kg/day. Serological and imaging tests should be done periodically after commencement of steroid therapy [10]. Magnetic resonance cholangiopancreatography is useful to observe the response to steroids in the pancreaticobiliary ducts noninvasively [14]. Pancreatic size usually normalizes within a few weeks, and biliary drainage becomes unnecessary within about 1 month. Rapid response to steroids is reassuring and confirms the diagnosis of AIP. If steroid effectiveness is reduced, the patient should be reevaluated with a suspicion of pancreatic cancer. The initial dose of steroids should be administered for 2–4 weeks, and the dose should be gradually tapered to a maintenance dose of 2.5–5 mg/day over 2-3 months [10] (Figure 1).

In the Mayo Clinic [15], prednisolone is used at 40 mg/day for 4 weeks and is tapered by 5 mg/week for a total of 11 weeks of therapy. In Korea [16], remission is achieved on a regimen of prednisolone 0.5 mg/kg per day for 1-2 months followed by a gradual tapering of 5–10 mg per month to a maintenance dose of 2.5–7.5 mg/day.

3.4. Remission. Remission is defined as the disappearance of clinical symptoms and resolution of the pancreatic and/or extrapancreatic manifestations on imaging studies [17].

In a multicenter survey of steroid therapy for AIP [17], at remission, the enlarged pancreas returned to near-normal size in 239 of 300 patients (80%) and became atrophic in 58 patients (20%). Elevated serum IgG4 levels decreased in all patients after the start of steroid therapy but failed to normalize (<135 mg/dL) in 115 of 182 patients (63%). At remission, irregularity of the pancreatic ducts and/or some degree of bile duct stenosis remained in 67 of 115 patients (58%) with persistent elevation of serum IgG4 levels, but only 18 of 67 patients (27%) with normalized serum IgG4 levels.

In our other study [18], HbA1c decreased by more than 0.5% in 8 of 21 AIP patients (38%) with DM after 3 months of steroid therapy. One year after the start of therapy, HbA1c decreased compared with levels before steroid therapy in 13 of 15 DM patients (87%). Impaired pancreatic exocrine function improved in all AIP patients and normalized in half of them [19].

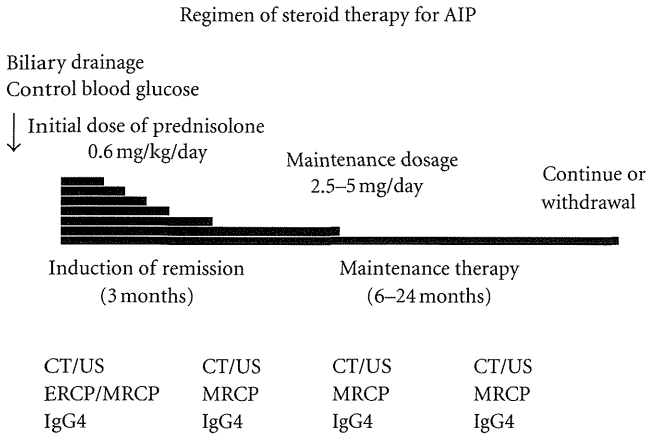

FIGURE 1: Regimen of oral steroid therapy for AIP.

3.5. Relapse and Maintenance Therapy. Relapse of AIP is defined as reappearance of symptoms with the reappearance of pancreatic and/or extrapancreatic (including bile duct, salivary gland, and retroperitoneum) abnormalities on imaging and/or elevation of serum IgG4 levels [17].

In a multicenter survey [17], the relapse rate of AIP patients was significantly lower in those who received steroid therapy (24%, 110/451) than in those not given steroid therapy (42%, 32/77). There was no correlation between the relapse rate and the initial prednisolone dose (40 mg/day, 19% (31/160) versus 30 mg/day, 23% (65/283)). In patients who received steroid therapy, relapse occurred in the pancreas (n = 57, 52%), bile duct (n = 37, 34%), and extrapancreatic lesions (n = 19; salivary gland swelling (n = 10), interstitial pneumonia (n = 4), and others (n = 5)).

Maintenance steroid therapy (oral prednisolone dose: 2.5 mg–5 mg/day) was given after remission in 377 of 459 patients (82%) treated with steroids. The relapse rate with maintenance therapy was 23% (63/273), which was significantly lower than that of patients who stopped maintenance therapy (34%, 35/104) [17]. In the United States and United Kingdom, where no maintenance therapy was given, relapse rates of patients treated with steroids were reportedly 38–60% [20–22]. In Korea, where maintenance therapy was stopped completely after about 6 months, the relapse rate of AIP patients treated with steroids was 33% (13/40) [16]. In consideration of these findings, maintenance therapy with low-dose prednisolone may prevent relapse. In Japan, maintenance therapy is used for about 1–3 years. However, the optimal duration of maintenance therapy is an issue requiring further investigation, as continued steroid therapy may increase the risk of steroid-induced adverse events. AIP often occurs in the elderly, who are already at heightened risk for osteoporosis and complications of glucose intolerance.

For relapsed AIP, readministration or increasing the dose of steroids is effective. In the United States and United Kingdom, immunomodulatory drugs such as azathioprine were used for maintenance of remission in patients with relapse after steroid withdrawal although azathioprine also has adverse effects such as allergic reactions, bone marrow suppression, and increased risk of infection [20–22]. Recently, it was reported that an AIP patient refractory to steroids and 6 mercaptopurine was successfully treated with rituximab, a monoclonal antibody directed against the CD20 antigen on B lymphocytes [23].

3.6. Predictive Factors for Relapse. For patients with relapsed AIP, maintenance therapy with steroids should be given with longer duration and higher dose than that of the initial maintenance therapy. Furthermore, pancreatic stones may form in some relapsing AIP patients, which might be induced by pancreatic juice stasis from incomplete obstruction of an irreversibly damaged pancreatic duct system [24]. Therefore, relapse of AIP should be avoided as much as possible. Identification of risk factors for relapse may help to identify high-risk patients who would benefit from maintenance therapy up front, and allow short-term therapy in lower-risk patients who may not need long-term therapy.

Hirano et al. [25] reported that obstructive jaundice is a predictive factor for unfavorable events. Kubota et al. [8] reported that diffuse pancreatic swelling independently predicted a relapse of AIP. Raina et al. described that relapse occurred in 7 of 9 patients (78%) with extrapancreatic biliary stenosis after withdrawal of immunosuppressive therapy [21]. Ghazale et al. reported that the relapse rate (64%) of patients with proximal biliary stenosis was significantly higher than that of patients with distal biliary stenosis alone (32%) [22]. In Korean data, relapse rate in patients with intrahepatic or proximal biliary stenosis was 65% compared with 25% in those without proximal biliary disease [26]. In a multicenter study [17], the relapse rate of AIP was significantly higher in patients with persistent elevation of serum IgG4 levels (30%, 34/115) than in those with normalized serum IgG4 levels (10%, 7/69). Although serum IgG4 levels fluctuated by more than 30 mg/dL in 94 of 172 patients (55%) during maintenance therapy, reelevation of serum IgG4 levels was detected in 37 of 54 patients (69%) who relapsed during maintenance therapy. The presence of proximal bile duct stenosis and elevated serum IgG4 levels may be predictive factors of relapse of AIP. Changes in serum IgG4 levels during serial checkups may provide clinically useful information to detect relapse of AIP earlier.

In the future, it will be necessary to verify the validity of the Japanese regimen of steroid therapy for AIP. The necessity, drugs, and duration of maintenance therapy need to be clarified by prospective studies.

As recent interesting reports have shown that pancreatic cancer was complicated with AIP [27, 28], we have to pay attention not only AIP but also pancreatic cancer even in a follow-up period.

4. Conclusion

It is important to differentiate AIP from pancreatic cancer before starting therapy. Steroids are the standard therapy for AIP, but this regimen should be evaluated in prospective studies.

Conflict of Interests

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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ORIGINAL ARTICLE

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Short and Long-Term Outcomes of Diabetes Mellitus in Patients with Autoimmune Pancreatitis after Steroid Therapy

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Background/Aims: Autoimmune pancreatitis (AIP) is frequently associated with diabetes mellitus (DM). This study evaluated the effect of steroid therapy on the course of DM in AIP. **Methods:** Glucose tolerance was examined in 69 patients with AIP. DM onset was classified as either a simultaneous onset with AIP or an exacerbation of pre-existing DM. Based on the changes in the HbA1c levels and insulin dose, the responses of DM to steroids were classified as improved, no change, or worsened. **Results:** Thirty (46%) patients were diagnosed as having DM (simultaneous onset, n=17; pre-existing, n=13). Three months after starting the steroid treatment, the DM improved in 13 (54%) of 24 DM patients. The DM improved in 55%, had no change in 36%, and worsened in 9% of the 11 simultaneous onset DM patients, and it improved in 54%, had no change in 31%, and worsened in 15% of the 13 pre-existing DM patients. At approximately 3 years after starting the steroid treatment, the DM improved in 10 (63%) of 16 patients. The pancreatic exocrine function improved in parallel with the changes in the DM in seven patients. **Conclusions:** Because approximately 60% of DM associated with AIP is responsive to steroids in the short- and long-terms, marked DM associated with AIP appears to be an indication for steroid therapy. **(Gut Liver 2012;6:501-504)**

Key Words: Autoimmune pancreatitis; Diabetes mellitus; Steroids

INTRODUCTION

Autoimmune pancreatitis (AIP) is a particular type of pancreatitis that is thought to have an autoimmune etiology. It is characterized radiologically by enlargement of the pancreas and irregular narrowing of the main pancreatic duct; serologically by elevation of serum IgG4 levels; pathologically by lymphoplasmacytic sclerosing pancreatitis; and clinically by responsiveness to steroid.[1,2]

Diabetes mellitus (DM) is sometimes associated with AIP. DM is diagnosed simultaneously with onset of AIP in some cases, and pre-existing DM is exacerbated in some cases. DM also improves after steroid therapy in some cases. Although there are some published reports on the short-term effect of steroid therapy on the course of DM,[3-9] the long-term outcome of DM after steroid therapy in AIP patients remains unknown. This study aimed to compare the course of the two different onset types of DM in AIP patients after steroid therapy and clarify its long-term outcome.

MATERIALS AND METHODS

A total of 69 patients with AIP in the Tokyo Metropolitan Komagome Hospital from 1992 to 2011 were retrospectively examined. The diagnosis of AIP was made according to the Asian diagnostic criteria for AIP.[10] To make the diagnosis of AIP, the imaging criterion, consisting of enlargement of the pancreas and irregular narrowing of the main pancreatic duct, must be present, together with the serological criterion (elevated serum IgG or IgG4 levels, or detection of autoantibodies) and/or the histopathological criterion (lymphoplasmacytic sclerosing pancreatitis). AIP can also be diagnosed with fulfillment of both the imaging criterion and a good response to steroid treatment.

DM was diagnosed according to the following criteria:[11] 1) early-morning fasting serum glucose ≥126 mg/dL; 2) serum glucose 2 hours after the oral glucose tolerance test ≥200 mg/dL; 3) casual serum glucose ≥200 mg/dL; and 4) glycosylated

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hemoglobin values (HbA1c) ≥6.5%. One of the first three items and item 4 lead to the diagnosis of diabetes. DM onset was divided into simultaneous onset with AIP and exacerbation of pre-existing DM. Clinical findings, including age at diagnosis, sex, body mass index (BMI), alcohol intake, and obstructive jaundice as an initial symptom, and pancreatic imaging findings (diffuse or segmental enlargement) on computed tomography were compared between AIP patients with and without DM.

Before steroid therapy, blood glucose levels were usually controlled using insulin in patients with DM. Steroid therapy was started at 0.6 mg/kg/day of prednisolone and gradually tapered to a maintenance dose over a period of about 3 months. Biochemical and serological blood tests, such as liver enzymes and IgG4 levels, and imaging tests, such as CT, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiopancreatography, were performed periodically after steroid therapy was started. To prevent relapse, maintenance therapy, usually with 5 mg/day of prednisolone, was performed for 1 to 3 years.[12,13] Changes in DM patients' glucose tolerance were examined at 3 months, 1 year, and about 3 years after starting steroid therapy. A decreased dose of insulin with a decrease of HbA1c by more than 0.5% in patients treated with insulin or a decrease of HbA1c by more than 0.5% in patients treated with diet therapy or oral antidiabetic agents was judged as improvement of glucose tolerance after steroid therapy. An increased dose of insulin or an increased HbA1c level by more than 0.5% percentage points in patients treated without insulin was considered an exacerbation. The other patterns were judged as no change.

N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) excretion tests were performed to assess pancreatic exocrine function before and 3 months after steroid therapy in 11 AIP patients with DM. The normal limit of BT-PABA was ≥70%, and an increase >10% points on the BT-PABA test after steroid therapy was considered improvement. This study was approved by the Institutional Review Board of Tokyo Metropolitan Komagome Hospital.

Statistical analysis used Fisher's exact test and Mann-Whitney U test. A $p<0.05$ was considered a significant difference.

RESULTS

Thirty (46%) of 69 AIP patients were diagnosed as having DM. In 17 patients, the diagnoses of DM and AIP were made simultaneously, whereas the other 13 showed exacerbation of pre-existing DM with onset of AIP. Anti-gultamic acid decarboxylase antibody was negative in the 12 patients with DM in whom this test was performed. There were no significant differences in the age at diagnosis of AIP, male-to-female ratio, BMI, alcohol intake, and presence of obstructive jaundice between patients with and without DM (Table 1).

Twenty-four AIP patients with DM were treated with steroid, and all of them responded well to steroid radiologically and serologically. Three months after starting steroid therapy, DM improved in 13 (54%) of 24 DM patients. DM was improved in six (55%), no change in four (36%) and worse in one (9%) of 11

Table 1. Clinical Characteristics and Radiological Findings of the Study Population

Characteristic	All patients	Diabetes (+)	Diabetes (-)	p-value
No.	69	30	39	
Age, median, yr	64.7	65.5	62.7	NS
Male/Female	50/19	22/8	28/11	NS
BMI, median, kg/m^2	22.3	22.5	21.9	NS
Alcohol intake, +, n (%)		4 (13)	7 (18)	NS
Jaundice, +, n (%)		22 (73)	22 (56)	NS
Type, diffuse/segmental (%)	35/34 (51)	14/16 (47)	21/18 (54)	NS

Data are presented as median or number (%).
NS, not significant.

Table 2. The Effect of Steroid Therapy on the Clinical Course of Diabetes by the Type of Onset in the Patients with at Least 3 Months of Treatment (n=24)

Onset of diabetes	Course of diabetes		
	Improved	No change	Worse
Simultaneous onset (n=11)	6 (55)	4 (36)	1 (9)
Pre-existing (n=13)	7 (54)	4 (31)	2 (15)

Data are presented as number (%).

Table 3. Effect of Steroid Therapy in the Patients with at Least 3 Years of Treatment on the Clinical Course of Diabetes by Type of Onset (n=16)

Onset of diabetes	Course of diabetes		
	Improved	No change	Worse
Simultaneous onset (n=6)	4 (66)	2 (34)	0
Pre-existing (n=10)	6 (60)	4 (40)	0

Data are presented as number (%).

Table 4. Comparison of Pancreatic Endocrine and Exocrine Functions before and after the Steroid Therapy (n=11)

Course of diabetes	Pancreatic exocrine function		
	Improved	No change	Worse
Improved	7	0	0
No change	0	2	1
Worse	1	0	0

Data are presented as number.

simultaneous onset DM patients, and it was improved in seven (54%), no change in four (31%), and worse in two (15%) of 13 pre-existing DM patients (Table 2).

At about 3 years after starting steroid therapy, DM improved in 10 (63%) of 16 DM patients. DM was improved in four (66%), including two patients in whom insulin became unnecessary, and no change was seen in two (34%) of six simultaneous onset DM patients, and it was improved in six (60%), with no change in four (40%) of 10 pre-existing DM patients (Table 3). Each simultaneous onset and pre-existing DM patients who was worse after 3 months of steroid therapy was improved 3 years later.

Pancreatic exocrine function was reduced in 10 (91%) of 11 AIP patients with DM. In all seven patients whose glucose tolerance improved after steroid therapy, pancreatic exocrine function also improved. In three patients whose glucose tolerance was not changed after steroid therapy, pancreatic exocrine function was not changed in two and worse in one. In one patient whose glucose tolerance was worse after steroid therapy, pancreatic exocrine function improved (Table 4).

DISCUSSION

DM was seen in 30 (46%) of 69 AIP patients in this series. Of the 30 DM patients, 57% were diagnosed as having DM simultaneously with the onset of AIP, and the remaining 43% showed exacerbation of pre-existing DM with onset of AIP. According to a nationwide survey in Japan,[8] DM was present in 67% of 167 AIP patients, and about half of the patients started DM simultaneously with AIP, and one-third of the patients had DM before AIP. A lower incidence of DM in AIP patients in the present study might be due to the fact that DM was diagnosed strictly according to the diagnostic criteria of DM. Onset of DM during the course of AIP was similar to that reported in the nationwide survey.

AIP responds well to steroid therapy symptomatically, radiologically, and serologically. Pancreatic enlargement began to improve 1 to 2 weeks after the start of steroid therapy, and the pancreas returned to almost normal size after 3 to 4 weeks. If a biliary stent is placed when biliary strictures are present, the stent can be removed 1 to 2 months after starting steroid. Serum IgG4 levels decreased in all cases after steroid administration.[12,14]

It has been reported that DM associated with AIP sometimes improved after steroid therapy. Nishino *et al.*[7] reported that the HbA1c level improved in 30% of 10 AIP patients with DM after steroid therapy. According to the report of Ito *et al.*,[6] in seven AIP patients with simultaneous onset DM, five (71%) showed improvement of DM control, and two (29%) showed no change after steroid therapy; and in four AIP patients with early-onset DM, three (75%) showed aggravation of DM, and one (25%) showed no change. According to the National survey,[8] in the 31 AIP patients with simultaneous onset DM, 17 (55%) showed improvement of DM, nine (29%) showed no change, and five (16%) showed worsening after steroid therapy; and in 22 AIP patients with early-onset DM, eight (36%) showed improvement, 10 (45%) showed no change, and four (18%) showed worsening. In the present study, at 3 months after starting steroid, 55% showed improvement, 36% showed no change, and 9% showed worsening of the 11 simultaneous onset DM patients, whereas it was improved in 54%, no change in 31%, and worse in 15% of 13 pre-existing DM patients. From these data, it can be seen that more than half of simultaneous onset DM patients improved after steroid therapy. Although pre-existing DM showed less responsiveness to steroid than simultaneous onset DM, some patients with steroid-responsive pre-existing DM might have had subclinical AIP.

There are few data about long-term changes in DM associated with AIP, and the present study may be the first reporting such changes. At about 3 years after starting steroid therapy, DM improved in 63% of 16 DM patients, although the incidence of improvement was 54% at 3 months. A fair number of DM associated with AIP appears to respond well to steroid over the short- and long-terms, although 13% showed worsening of DM control at 3 months after starting steroid. Each simultaneous onset and pre-existing DM patients who showed worsening at 3 months after steroid improved 3 years later. Even though the negative effect of steroid to counter the effect of insulin may be greater in some cases in the short-term, the long-term positive effect of steroid therapy on glucose tolerance and pancreatic inflammation might be greater in such cases.

The mechanism of pancreatic endocrine dysfunction and its recovery are undefined at present. Histopathologically, dense infiltration of lymphocytes and IgG4-positive plasma cells with fibrosis is seen in the pancreas, and ectopic expression of the MHC class II molecule is seen in pancreatic cells. Rapid inflammation and fibrosis may induce reduction in blood flow in the exocrine pancreas, resulting in ischemia of islet cells, which causes dysfunction of hormone secretion. It is also estimated that elevated cytokine production and fibroblast proliferation occurs in the pancreas. The steroid therapy inactivates inflammatory cells and fibroblast function, and it is estimated that the functional disorder is improved by control of a series of autoimmune mechanisms, including cytokine production.[15]

Nishino *et al.*[7] reported that the BT-PABA test showed reduced pancreatic exocrine function in six (67%) of nine AIP pa-

tients, and it improved in three (50%) after steroid therapy. According to a study of Ito *et al.*[5] of pancreatic exocrine function in AIP using the secretin test, 92% of 12 AIP patients showed reduction in volume and amylase output, but a reduction in bicarbonate secretion was observed in only 42%, whereas a reduction in bicarbonate secretion was observed in all 25 patients with ordinary chronic pancreatitis. They explained this discrepancy based on the fact that most of the basement membrane where pancreas progenitor cells exist was preserved in AIP patients, whereas the basement membrane was destroyed in chronic pancreatitis. In the present series, pancreatic exocrine function was reduced in 91% of 11 AIP patients with DM, and in all seven patients whose glucose tolerance improved after steroid therapy, pancreatic exocrine function also improved. Given that pancreatic exocrine and endocrine function improved in parallel, initiation of steroid therapy in the early stage when pancreatic islets and the basement membrane are preserved appears to be important. Although the major indication for steroid therapy for AIP is clinical symptoms such as obstructive jaundice,[12,13] marked DM requiring insulin associated with AIP also appears to be an indication for steroid therapy.

In conclusion, about half of AIP patients had DM. Since around 60% of DM associated with AIP is responsive to steroid in the short- and long-terms, marked DM associated with AIP appears to be an additional indication for steroid therapy.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Risk factors for pancreatic stone formation in autoimmune pancreatitis over a long-term course

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Abstract
Background Autoimmune pancreatitis (AIP) has the potential to progress to a chronic state that forms pancreatic stones. The aim of this study was to clarify the risk factors underlying pancreatic stone formation in AIP.
Methods Sixty-nine patients with AIP who had been followed for at least 3 years were enrolled for evaluation of clinical and laboratory factors as well as computed tomography and endoscopic retrograde cholangiopancreatography findings.
Results During the course of this study, increased or de novo stone formation was seen in 28 patients, who were defined as the stone-forming group. No stones were observed in 32 patients, who were defined as the non-stone-forming group. Nine patients who had stones at diagnosis but showed no change during the course of this study were excluded from our cohort. Univariate analysis revealed no significant differences in clinical or laboratory factors associated with AIP-specific inflammation between the two groups. However, pancreatic head swelling ($P = 0.006$) and narrowing of both Wirsung's and Santorini's ducts in the pancreatic head region ($P = 0.010$) were significantly more frequent in the stone-forming group. Furthermore, multivariate analysis identified Wirsung and Santorini duct narrowing at diagnosis as a significant independent risk factor for pancreatic stone formation (OR 4.4, $P = 0.019$).
Conclusions A primary risk factor for pancreatic stone formation in AIP was narrowing of both Wirsung's and Santorini's ducts, which most presumably led to pancreatic juice stasis and stone development.

Keywords Autoimmune pancreatitis · Pancreatic stone · Wirsung duct · Santorini duct

Abbreviations

AIP	Autoimmune pancreatitis
CT	Computed tomography
ERCP	Endoscopic retrograde cholangiopancreatography

Introduction

Autoimmune pancreatitis (AIP) is a specific type of chronic pancreatitis possibly caused by autoimmune mechanisms that is characterized by pancreatic swelling and irregular narrowing of the main pancreatic duct, both of which mimic pancreatic cancer [1]. Other characteristic features of AIP are high serum IgG4 concentration and IgG4-positive plasma cell infiltration in affected pancreatic tissue that also aid in serological and pathological AIP diagnosis [2, 3]. As patients with AIP respond favorably to corticosteroid therapy, the disease was previously believed to be a non-progressive condition which did not progress to an advanced stage of chronic pancreatitis or pancreatic stone formation [4]. However, the short-lived pancreatic swelling and severe lymphoplasmacytic infiltration in acute AIP are now believed to manifest as different clinical features in a chronic state; earlier studies have

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shown that AIP progresses to a chronic stage showing pancreatic stone formation and atrophy resembling ordinary chronic pancreatitis that is closely associated with relapse [5–12]. Moreover, we found that patients with seemingly typical chronic pancreatitis also included several cases with elevated serum IgG4 concentration, which may have been due to chronic stage AIP [6].

Two major mechanisms attempt to explain the formation of pancreatic stones in AIP: severe inflammation specific to AIP and stasis of pancreatic juice due to narrowing of the pancreatic duct [13, 14]. In general, AIP rarely results in severe inflammation or tissue necrosis. Corticosteroid therapy ameliorates irregular narrowing of the pancreatic duct in the majority of patients, although residual stenosis may persist [15]. Additionally, some patients not undergoing corticosteroid therapy show progression of duct changes [16]. On the basis of these findings, we hypothesized that the formation of pancreatic stones in AIP is associated with stasis of pancreatic juice due to stenosis of the pancreatic duct. The aim of the present study was to clarify the risk factors underlying pancreatic stone formation in AIP by comparing the clinical features and frequency of pancreatic stone formation in a long-term follow-up cohort of AIP patients.

Patients and methods

Study subjects

Ninety-three patients with AIP were examined and treated at Shinshu University Hospital between August 1992 and July 2011. Among them, we enrolled 69 patients who had been followed for at least 3 years (median follow-up 91 months, range 36–230 months), which included 54 men and 15 women (median age 64 years, range 38–84 years). Diagnosis of AIP was based on the Asian diagnostic criteria for AIP [17].

Clinical features and laboratory tests

We reviewed the medical charts of our cohort for observation period, age at diagnosis, gender, alcohol consumption, corticosteroid treatment, and relapse. We also compared serum values representative of AIP activity from blood tests at diagnosis, including those for IgG, IgG4, C3, C4, soluble interleukin 2 receptor (sIL2-R), circulating immune complex (CIC), and amylase.

Evaluation of pancreatic stone formation

The presence of pancreatic stones was assessed by using CT images. We evaluated the location of stones with respect to pancreatic region (head, body, or tail), as well as with respect to the pancreatic duct (in the main pancreatic duct or in parenchyma). We also assessed the size and number of stones during the study period. CT scanning was performed using different protocols during the course of this study. At our institute, CT testing was changed to multidetector computed tomography (MDCT) in 2003, which resulted in clearer CT images.

Evaluation of pancreatic swelling

Swelling of the pancreas in CT images was assessed by three pancreatology experts. Pancreatic swelling was determined using the Haaga criteria [18] or a marked decrease in size after corticosteroid therapy and was classified by its location in the pancreas (head, body, or tail). Swelling restricted to either one area or spanning two or three areas was considered to be focal or segmental-diffuse swelling, respectively.

Evaluation of pancreatic duct narrowing

Narrowing of the pancreatic duct seen in endoscopic retrograde pancreatocholangiography (ERCP) was assessed by three expert endoscopists. Pancreatic duct narrowing was classified by its location in the pancreas (head, body, or tail), and narrowing in the head region was further divided into narrowing of Wirsung's duct and narrowing of Santorini's duct. Narrowing restricted to either one area or spanning two or three areas was considered to be focal or segmental-diffuse narrowing, respectively.

Statistical analysis

The Fisher's exact and Pearson's chi-square tests were adopted to test for differences between subgroups of patients. The Mann–Whitney U test was employed to compare continuous data. Multivariate analyses were performed using a logistic regression model. Variables associated with a P value of less than 0.2 in univariate analyses were included in a stepwise logistic regression analysis to identify independent risk factors associated with the formation of pancreatic stones. All tests were performed using the IBM SPSS Statistics Desktop for Japan ver. 19.0 (IBM Japan Inc, Tokyo, Japan). P values of less than 0.05 were considered to be statistically significant.

Ethics

This study was approved by the ethics committee of Shinshu University (approval number 1805).

Results

Pancreatic stone formation

At diagnosis, pancreatic stones were found in 17 of 69 patients and increased in size and number in 8 patients. De novo stone formation was observed in 20 of the remaining 52 patients. In total, increased or de novo stones were seen in 28 patients during the study period, who were collectively defined as the stone-forming group. The 32 patients in whom no stones were found during the course of the study were defined as the non-stone-forming group (Fig. 1). Nine patients who had stones at diagnosis but showed no change during the course of this study were excluded from our cohort.

There were no significant differences in the frequency of pancreatic stone formation among pancreatic areas between the stone increase and de novo stone cases. However, stone formation in the main pancreatic duct was more frequently seen in de novo cases, but not significantly ($P = 0.151$) (Table 1). Thus, there were no fundamental differences in the manner of new stone formation. For de novo stone patients, the median and range of the study period between diagnosis of AIP and stone formation were 57 and 8–138 months, respectively.

Correlation between pancreatic stone formation and clinical and laboratory features associated with AIP-specific inflammation

We next searched for risk factors of pancreatic stone formation by comparing several parameters between the stone-forming and non-stone-forming groups. Univariate analysis revealed no significant differences in observation period, age, gender, alcohol consumption, or corticosteroid treatment between the stone-forming group and the non-stone-forming group. Relapse was more frequently seen in the stone-forming group, but not significantly ($P = 0.093$). We also found no significant differences in serum values of disease activity markers, such as IgG, IgG4, C3, C4, sIL2-R, and CIC, between the two groups (Table 2).

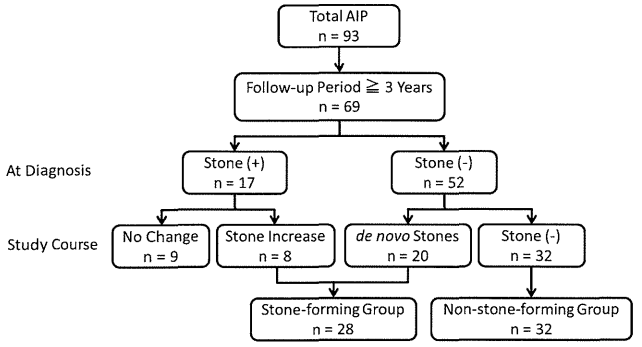

Fig. 1 Study participation flowchart and outcome of 69 patients with AIP who were followed for at least 3 years (mean 91 months, range 36–230 months)

Table 1 Location of pancreatic stone formation

	Stone increase cases ($n = 8$)	De novo stone cases ($n = 20$)	*P* value
Head/body/tail	6/8/5	17/20/15	NS
In MPD/in parenchyma	3/16	18/34	0.151

MPD main pancreatic duct, *NS* not significant

Correlation between pancreatic stone formation and pancreatic swelling

We examined whether pancreatic stone formation was associated with the extent or location of pancreatic swelling. Univariate analysis showed no significant differences in the extent of pancreatic swelling in the focal area versus in the segmental-diffuse area between the stone-forming group and the non-stone-forming group. However, pancreatic head swelling was significantly more frequent in the stone-forming group ($P = 0.006$). No significant differences were seen for pancreatic body or tail swelling (Table 3, Fig. 2).

Table 2 Clinical features and laboratory tests at diagnosis

	Stone-forming group ($n = 28$)[a]	Non-stone-forming group ($n = 32$)[a]	*P* value
Clinical features			
Observation period[b]	100 (36–165)	90 (36–230)	0.524
Age	67 (47–84)	64.5 (38–81)	0.543
Sex (M/F)	24/4	22/10	0.140
Alcohol (+/−)	20/8	19/12	0.582
Prednisolone (+/−)	25/3	28/4	1.000
Relapse (+/−)	11/17	6/26	0.093
Laboratory tests			
Amylase	94 (17–431)	86 (22–478)	0.678
IgG	2,187 (892–7,236)	2,183 (1,194–5,545)	0.686
IgG4	640 (154–2,855)	424 (4–2,970)	0.916
C3	91 (33–157)	87 (29–199)	0.538
C4	20.1 (7.7–39.7)	21.3 (1.1–38.7)	0.627
sIL2-R	738 (132–2,260)	940 (257–4,695)	0.130
CIC	5.1 (1.9–40)	5.5 (1.9–27.5)	0.392

sIL2-R soluble interleukin 2 receptor, *CIC* circulating immune complex

[a] Values are expressed as median (range)

[b] Period from diagnosis of AIP to the most recent observation (months)

Correlation between pancreatic stone formation and pancreatic duct narrowing

We next examined whether pancreatic stone formation was associated with the extent or location of pancreatic duct narrowing. Univariate analysis revealed no significant differences in the extent of pancreatic duct narrowing in the focal area versus in the segmental-diffuse area between the stone-forming group and the non-stone-forming group, nor were there significant differences in the location of pancreatic duct narrowing between the two groups. However, among cases with narrowing of the head region, patients with narrowing of both Wirsung's and Santorini's ducts were significantly more frequent in the stone-forming group ($P = 0.010$) (Table 3, Fig. 3).

In the stone-forming group, 4 patients showed duct narrowing in the body and tail regions, but 2 of them showed parenchymal pancreatic stones in the downstream pancreatic region.

Table 3 Pancreatic morphology at diagnosis

	Stone-forming group ($n = 28$)	Non-stone-forming group ($n = 32$)	P value
Swelling (by CT)			
Head (+/−)	26/2	20/12	0.006*
Body (+/−)	20/8	19/13	0.419
Tail (+/−)	17/11	19/13	1.000
Focal/segmental-diffuse	7/21	12/20	0.406
Ductal narrowing (by ERCP)			
Head (+/−)	24/4	22/10	0.140
Wirsung + Santorini (+/−)	21/7	13/19	0.010*
Body (+/−)	15/13	19/13	0.795
Tail (+/−)	22/6	24/8	0.770
Focal/segmental-diffuse	6/22	11/21	0.390

* $P < 0.05$

Multivariate analysis of pancreatic stone formation in AIP at diagnosis

Multivariate analysis was performed for gender, relapse, sIL2-R, pancreatic head swelling, and Wirsung and Santorini duct narrowing, all of which had P values of less than 0.2 in univariate studies. We identified that narrowing of both Wirsung's and Santorini's ducts at diagnosis was a significant determinant of pancreatic stone formation in AIP (odds ratio 4.4, 95% confidence interval 1.3–15.5, $P = 0.019$).

Correlation between pancreatic stone formation and residual pancreatic swelling or residual pancreatic duct narrowing after prednisolone (PSL) therapy

We further assessed whether pancreatic stone formation was associated with the extent or location of residual pancreatic swelling or residual pancreatic duct narrowing 4 weeks after PSL therapy between stone-forming patients and non-stone-forming patients. Univariate analysis showed that residual pancreatic head swelling was more

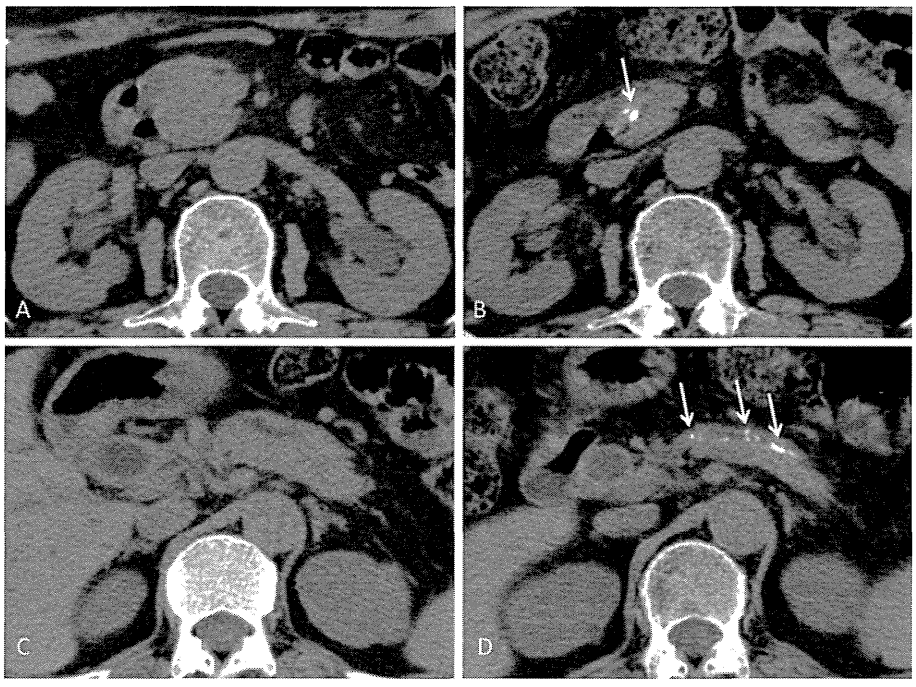

Fig. 2 CT findings in a 67-year-old female with pancreatic head swelling. **a**, **c** CT at diagnosis in May 2005 showing pancreatic head swelling. **b**, **d** CT 27 months later in August 2007 showing pancreatic stone formation (*arrows*) and pancreatic atrophy

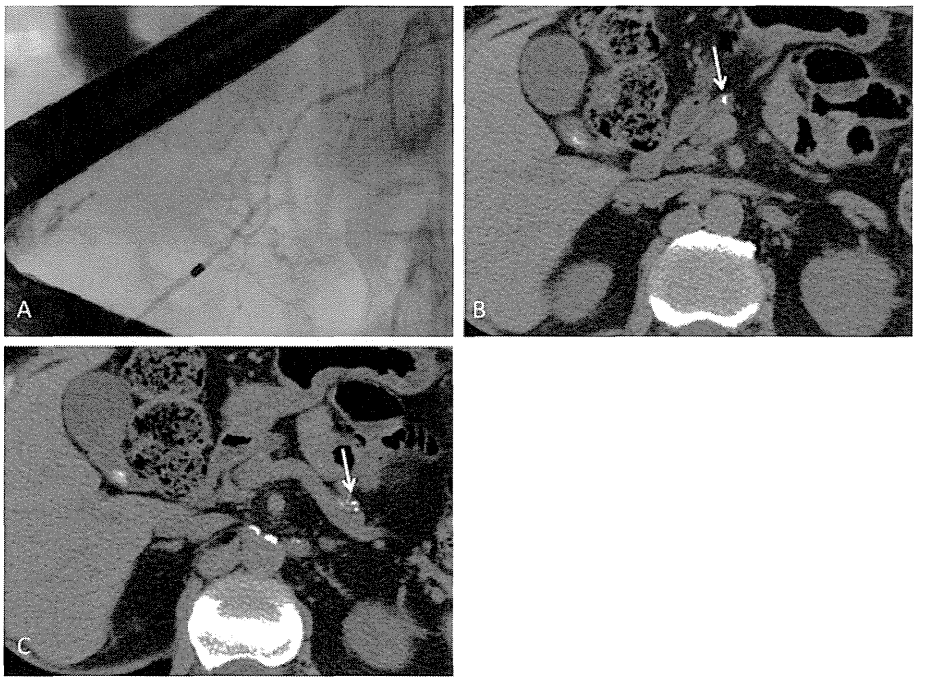

Fig. 3 ERCP and CT findings in a 69-year-old male with narrowing of both Wirsung's and Santorini's ducts. **a** ERCP at diagnosis in April 2001 showing Wirsung's and Santorini's duct narrowing. **b**, **c** CT 105 months later in December 2009 showing pancreatic stone formation (*arrows*) and pancreatic atrophy

Table 4 Pancreatic morphology after corticosteroid therapy

	Stone-forming patients ($n = 24$)	Non-stone-forming patients ($n = 26$)	P value
Swelling (by CT)			
Head (+/−)	7/17	2/24	0.069
Body (+/−)	3/21	3/23	1.000
Tail (+/−)	7/17	6/20	0.866
Focal/segmental-diffuse	7/4	2/4	0.334
	Stone-forming patients ($n = 22$)	Non-stone-forming patients ($n = 20$)	
Ductal narrowing (by ERCP)			
Head (+/−)	17/5	11/9	0.229
Wirsung + Santorini (+/−)	11/11	4/16	0.088
Body (+/−)	4/18	2/18	0.665
Tail (+/−)	7/15	10/10	0.376
Focal/segmental-diffuse	10/8	3/10	0.139

frequently seen in stone-forming patients, but not significantly ($P = 0.069$). In addition, cases with residual narrowing of both Wirsung's and Santorini's ducts in the pancreatic head region tended to be more frequently seen among stone-forming patients ($P = 0.088$) (Table 4).

Correlation between pancreatic stone formation and pancreatic function during the course of the study

We compared serum levels of amylase and HbA1c at diagnosis, at 5 years, and at 8 years among non-stone-forming patients, stone-forming patients, and intraductal stone-forming patients, who seemed to be at a more advanced stage of stone formation. Although we found no significant differences among the groups, both enzyme and HbA1c values tended to be at abnormal levels in intraductal stone-forming patients compared with non-stone-forming patients (Table 5).

Discussion

Autoimmune pancreatitis and pancreatic stone formation

An early study reported that AIP was characterized by the absence of pancreatic stones [5, 6]. Later, hallmark histological findings of marked lymphoplasmacytic infiltration representing acute AIP inflammation were found to give way to other features in the chronic stage; we reported that several patients with AIP formed pancreatic stones during the disease course [5, 6], which has been confirmed by other studies [7]. Since pancreatic stones are a major characteristic of ordinary chronic pancreatitis, such as alcoholic pancreatitis, it appears that chronic stage AIP

Table 5 Pancreatic function during the course of the study

	Non-stone-forming patients[a]	Stone-forming patients[a]	*P* value[b]	Intraductal stone-forming patients ($n = 9$)[a]	*P* value[c]
Amylase					
At diagnosis	86 (22–478)	94 (17–431)	0.678	102 (62–323)	0.490
5 years later	85 (45–160)	80 (42–136)	0.497	92 (46–134)	0.569
8 years later	83 (59–130)	75 (37–128)	0.230	75 (48–98)	0.313
HbA1c					
At diagnosis	5.7 (4.1–11.2)	5.7 (4.5–9.5)	0.536	6.0 (4.5–9.5)	0.549
5 years later	5.8 (5.1–10.4)	6.0 (4.6–10.2)	0.366	6.0 (5.4–10.2)	0.289
8 years later	5.8 (5.1–9.8)	6.0 (5.1–10.3)	0.504	6.8 (5.1–10.3)	0.293

[a] Values are expressed as median (range)

[b] Non-stone-forming patients versus stone-forming patients

[c] Non-stone-forming patients versus intraductal stone-forming patients

may present symptoms resembling those of ordinary chronic pancreatitis. Indeed, elevation of serum IgG4 was found in 7% of ordinary chronic pancreatitis in one study, which may have in fact represented chronic stage AIP [6]. Similarly to alcoholic pancreatitis in which recurrent attacks facilitate pancreatic stone formation, stone formation in AIP is preferentially seen in relapsed cases [5].

For de novo stone cases, the median and range of the study period between diagnosis of AIP and stone formation were 57 and 8–138 months, respectively. However, since we had no prospective protocol for CT testing, the duration of pancreatic stone formation may have been affected by the timing of CT tests.

Risk factors for pancreatic stone formation

Pancreatic stone formation implies the progression of pancreatic tissue damage. Accordingly, identification of the direct risk factors of stone formation is expected to disclose the mechanism of tissue injury in order to develop treatments that suppress this progressive damage. We postulated two mechanisms for pancreatic stone formation in AIP in this study, namely severe tissue injury attributed to the specific inflammatory process of AIP and pancreatic juice stasis due to pancreatic duct narrowing, and sought to clarify the risk factors responsible for stone development.

Correlation between pancreatic stone formation and clinical and laboratory features associated with AIP-specific inflammation

There were no significant differences in observation period, age, gender, alcohol consumption, or corticosteroid treatment between the stone-forming group and the non-stone-forming group, nor were there any notable changes in serum amylase concentration at diagnosis. Therefore, acute attacks seemed not to contribute to stone formation.

In a highly active stage of AIP, serum concentrations of various markers vary in parallel with disease activity; serum IgG, IgG4, sIL2-R, and CIC increase at relapse and decrease after corticosteroid therapy, while serum C3 and C4 show reciprocal changes [19]. To determine whether the specific inflammatory process of AIP was associated with pancreatic stone formation, we investigated the correlation between stone formation and published activity markers, but found no significant differences between the two groups. However, although we could not confirm a correlation between the intensity of the inflammatory process in AIP and pancreatic stone formation, we could not completely exclude a relationship since we did not check the values of these markers throughout the patients' clinical course. In addition, serum IgG4 concentration remained slightly elevated in 60% of patients in a clinically inactive state after corticosteroid therapy, which suggested that active inflammatory processes may have persisted even when the patients were in apparent remission [20]. On the other hand, it was reported that the histology of characteristic inflammatory changes in AIP normalized after corticosteroid therapy [21, 22], and so it appears unlikely that the inflammatory process in AIP progresses to an advanced stage of severe necrosis and fibrosis like the one found in ordinary chronic pancreatitis, which also induces pancreatic stone formation.

Correlations between pancreatic stone formation and pancreatic swelling and pancreatic duct narrowing

Univariate analysis disclosed that the factors of pancreatic head swelling and narrowing of both Wirsung's and Santorini's ducts were significantly associated with pancreatic stone formation, and multivariate analysis confirmed the latter as a significant independent risk factor for pancreatic stone formation in AIP. Severe inflammation in the pancreatic head region results in swelling and Wirsung and Santorini duct narrowing, and therefore these two findings may be considered to represent the same pathophysiological feature. Diffuse irregular narrowing is a typical duct finding in AIP [4], but some cases showed duct stenosis in an area other than the head region [16]. With progression of the disease, restricted duct stenosis may

progress to diffuse lesions [15, 16]. Residual pancreatic head swelling and residual narrowing of both Wirsung's and Santorini's ducts after corticosteroid therapy were also more frequently found in stone-forming patients compared to non-stone-forming patients in our cohort, strengthening the notion that Wirsung and Santorini duct narrowing in the pancreatic head region caused pancreatic juice stasis in the pancreas and eventual stone formation. In the stone-forming group, 4 patients showed duct narrowing in the body and tail region, but 2 of them showed parenchymal pancreatic stones in the downstream pancreatic region. Accordingly, some stone formation may be due to factors other than pancreatic juice stasis.

There is a lack of consensus as to what causative factors lead to chronic pancreatitis. Hypotheses include the oxidative stress theory, toxic-metabolic theory, stone and duct obstruction theory, necrosis-fibrosis theory, primary duct hypothesis, and sentinel acute pancreatitis event hypothesis [23, 24]. With respect to pancreatic stone formation, the stone and duct obstruction theory postulates that alcohol modulates exocrine function to increase the lithogenicity of pancreatic juice, leading to the formation of protein plugs and stones in the duct. This concept presupposes that alcohol must primarily modulate the properties of pancreatic fluid to promote stone formation [25]. On the other hand, partial outflow obstruction of the pancreatic duct was also proved to induce stone formation. This condition was found in cases with Vater ampulla carcinoma and pancreatic mucin-producing adenocarcinoma [now recognized as intraductal papillary-mucinous carcinoma (IPMC)] [26, 27], and was used in experimental dog models to demonstrate that incomplete ligation of the main pancreatic duct resulted in the formation of calculi [13, 14]. The present study showed that many AIP patients with stone formation had Wirsung and Santorini duct narrowing, which supported the condition of incomplete ligation of the main pancreatic duct seen in the dog model.

Correlation between pancreatic stone formation and pancreatic function during the course of the study

In comparisons among non-stone-forming patients, stone-forming patients, and intraductal stone-forming patients at diagnosis and 5 and 8 years afterwards, both serum amylase and HbA1c values tended to be at abnormal levels in intraductal stone-forming patients compared with non-stone-forming patients, but not significantly. We believe that further observation may disclose a significant deterioration of pancreatic function in stone-forming patients despite the notion that stone-forming AIP might have a different pathophysiology from that of ordinary chronic pancreatitis.

Prevention and management of pancreatic stone formation

Our findings imply that prophylactic measures for reduction of pancreatic head swelling and duct narrowing would prevent increased or de novo stone formation. For patients presenting with narrowing of both Wirsung's and Santorini's ducts, intensive therapy that includes corticosteroids may be needed from an early stage, even when clinical symptoms, such as obstructive jaundice or abdominal pain, have not yet manifested. Furthermore, it is advisable to check for residual changes in pancreatic head swelling and Wirsung and Santorini duct narrowing after corticosteroid therapy.

Limitation of the present study

At our institute, CT has been done by MDCT since 2003, which results in improved images. Accordingly, pancreatic stone detection was likely biased by CT imaging as scans were obtained using different CT protocols during the course of this study.

In conclusion, the main risk factor for pancreatic stone formation in AIP was narrowing of both Wirsung's and Santorini's ducts at diagnosis, which most presumably led to pancreatic juice stasis in the pancreas and stone development.

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Conflict of interest None of the authors have any conflicts of interest associated with this study.

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Review Article

The Utility of Serum IgG4 Concentrations as a Biomarker

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IgG4-related disease is a new disease entity involving IgG4 in its clinical presentation and having 6 characteristic features: (1) systemic involvement; (2) solitary or multiple lesions showing diffuse or localized swelling, masses, nodules, and/or wall thickening on imaging; (3) high serum IgG4 concentration >135 mg/dL; (4) abundant infiltration of lymphoplasmacytes and IgG4-bearing plasma cells; (5) a positive response to corticosteroid therapy; and (6) complications of other IgG4-related diseases. To date, most IgG4-related diseases have been recognized as extrapancreatic lesions of autoimmune pancreatitis. This paper will discuss the utility of IgG4 as a biomarker of IgG4-related diseases, including in the diagnosis of autoimmune pancreatitis and its differentiation from pancreatic cancer, in the prediction of relapse, in the long-term follow-up of patients with autoimmune pancreatitis and normal or elevated IgG4 concentrations, and in patients with autoimmune pancreatitis and extrapancreatic lesions, as well as the role of IgG4 in the pathogenesis of IgG4-related disease.

1. Introduction

IgG4-related disease is a new disease entity involving IgG4 in its clinical presentation. To date, 6 characteristic features of IgG4-related disease have been identified: (1) systemic involvement; (2) solitary or multiple lesions showing diffuse or localized swelling, masses, nodules, and/or wall thickening on imaging; (3) high serum IgG4 concentrations >135 mg/dL; (4) abundant infiltration of lymphoplasmacytes and IgG4-bearing plasma cells; (5) a positive response to corticosteroid therapy; (6) complications of other IgG4-related diseases [1–4].

IgG4-related disease involves organs throughout the entire body. The major manifestations of IgG4-related disease include autoimmune pancreatitis, lacrimal and salivary gland lesions known as Mikulicz's disease, sclerosing cholangitis, retroperitoneal fibrosis, lung disease, and tubulointerstitial nephritis. In addition, many minor lesions have been reported in patients with IgG4-related disease, including hypophysitis, thyroiditis, hepatopathy, and prostatitis. At present, it is not clear whether these lesions are caused by the same etiology or merely show clinical and pathological findings associated with IgG4. Imaging modalities have shown diffuse or localized swelling in the pancreas and the lacrimal and salivary glands, masses in patients with retroperitoneal fibrosis, nodules in patients with lung pseudotumors, and wall thickening in the bronchi and bile ducts.

Most patients with IgG4-related disease have high serum IgG4 concentrations, over 135 mg/dL, [5] a finding both sensitive and specific for this disease, as well as useful for its diagnosis. Characteristic pathological findings include the infiltration of large numbers of lymphoplasmacytes and IgG4 bearing plasma cells [6]. Although storiform or swirling fibrosis and obstructive phlebitis are also characteristics of IgG4-related disease, they are rarely observed in specific lesions, such as those of the salivary glands. Most lesions, except for those that are predominantly fibrotic, respond positively to corticosteroid therapy. For example, patients with autoimmune pancreatitis show reduced swelling, products with lung pseudotumors show the disappearance of nodules, and patients with sclerosing cholangitis show the

disappearance of bile duct strictures after corticosteroid treatment. At present, most IgG4-related diseases have been recognized as extrapancreatic lesions of autoimmune pancreatitis [2, 7, 8].

This paper will discuss the utility of serum IgG4 concentrations as a biomarker of the major IgG4-related disease, autoimmune pancreatitis. Topics will include IgG4 concentration and the diagnosis of autoimmune pancreatitis, as well as its differentiation from pancreatic cancer; IgG4 and the prediction of relapse; long-term followup of patients with autoimmune pancreatitis and either normal or elevated IgG4 concentration; IgG4 and extrapancreatic lesions in patients with autoimmune pancreatitis; and the role of IgG4 in the pathogenesis of IgG4-related disease.

2. IgG4 and the Diagnosis of Autoimmune Pancreatitis

The sera of patients with autoimmune pancreatitis have a polyclonal band in the rapidly migrating fraction of γ-globulins, resulting in β–γ bridging. Immunoprecipitation assays have confirmed that this band is always due to elevation of IgG4 concentration [5]. IgG is composed of 4 subclasses, IgG1, IgG2, IgG3, and IgG4. In normal subjects, IgG4 constitutes only 3–7% of total serum IgG. However, serum IgG4 concentrations are over 10-fold higher in patients with autoimmune pancreatitis. Elevated serum IgG4 has also been observed in individuals with allergic disorders, parasite infestations, and pemphigus. High serum IgG4 concentrations have been observed in 90% of patients with autoimmune pancreatitis, but rarely in patients with pancreatic cancer, chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and Sjögren's syndrome, suggesting that IgG4 is a sensitive and specific marker of autoimmune pancreatitis and may be diagnostic for this disease [5]. Corticosteroid therapy significantly reduces serum IgG4 concentration and the IgG4/IgG ratio [5]. The utility of IgG4 for the diagnosis of autoimmune pancreatitis has been evaluated worldwide, with a sensitivity ranging from 50% to 92% and a specificity over 90%. Serum IgG4 concentration is therefore considered a reliable marker for the diagnosis of autoimmune pancreatitis and has been included in various diagnostic criteria [9–12]. Differences in sensitivity and specificity may be partly due to the use of different assays to measure serum IgG4 and different cut-offs for the upper limit of normal around the world, as well as variations in diagnostic criteria used in individual countries, which may be associated with histological differences between lymphoplasmacytic sclerosing pancreatitis (LPSP) [13] and idiopathic duct-centric chronic pancreatitis (IDCP) [14].

Clinical features of autoimmune pancreatitis have been reported to differ based on the serum concentration of IgG4. Compared with patients having normal serum IgG4 levels, those with elevated IgG4 are regarded as being in a highly active state, with a higher incidence of jaundice at onset, more frequent diffuse pancreatic enlargement on imaging, significantly higher 18F-2-fluoro-2-deoxy-d-glucose uptake by pancreatic lesions, more frequent extrapancreatic lesions, and more frequent requirement for maintenance therapy [15].

In addition, infiltration of IgG4 bearing plasma cells is a histological hallmark of autoimmune pancreatitis and is used in pathologic diagnoses [6].

3. IgG4 and the Differentiation of Autoimmune Pancreatitis from Pancreatic Cancer

Lymphoplasmacytic sclerosing pancreatitis (LPSP), which is similar pathologically to autoimmune pancreatitis, has been observed in 2.5% of patients undergoing the Whipple resection [16]. Therefore, it is necessary to differentiate autoimmune pancreatitis from pancreatic cancer. We reported that IgG4 had a sensitivity of 90%, a specificity of 98%, and an accuracy of 95% in differentiating between these conditions, [5] indicating that IgG4 is useful both for the diagnosis of autoimmune pancreatitis and for differentiating it from pancreatic cancer. Other reports have also shown the usefulness of IgG4 in differential diagnosis [17–19]. The sensitivity and specificity of IgG4 were superior to those of IgG, ANA, and RF, although the additional measurement of ANA and RF further increased the sensitivity and negative predictive value of IgG4 [8].

4. IgG4 and Prediction of Relapse

Some patients with autoimmune pancreatitis experience relapse during their clinical course. For effective management, it is necessary to determine the frequency of relapse and its prevention. During the period from 1992 to 2011, a total of 93 patients with autoimmune pancreatitis were examined and treated at Shinshu University Hospital. Of the 84 patients followed up for more than 1 year, 28 (33%) experienced relapse. In Japanese patients, the relapse rate has been estimated to vary from 30 to 50%, [20–22] although corticosteroid therapy significantly reduced relapse rates [22]. Japanese consensus guidelines for the management of autoimmune pancreatitis have stated that the indications for corticosteroid therapy include symptoms such as obstructive jaundice, abdominal pain, and back pain, and the presence of symptomatic extrapancreatic lesions. The major lesions at relapse included autoimmune pancreatitis ($n = 26$), sclerosing cholangitis ($n = 18$), lachrymal and salivary gland lesions ($n = 5$), and retroperitoneal fibrosis ($n = 4$). In addition, the involvement of other organs and symptoms were seen at relapse. We failed to identify any serum markers at diagnosis that could predict relapse, although we observed elevated concentrations of IgG and immune complex in the relapse compared with the nonrelapse group, although these differences were not significant. Serial changes in IgG4 and immune complexes in a 69-year-old woman with autoimmune pancreatitis who experienced 3 relapses showed that these markers were elevated in serum several months before clinically evident relapse, suggesting that regular measurements of these markers in an out-patient clinic may predict relapse [23].

Table 1: IgG4 concentrations, age and complications of more than 3 extrapancreatic lesions in patients with autoimmune pancreatitis and major extrapancreatic lesions.

	n (male/female)	Age, yr Median (range)	IgG4, mg/dL Median (range)	Complications of more than 3 extrapancreatic lesions, *n* (%)
Autoimmune pancreatitis	92 (72/20)	66 (38–85)	545 (4–2970)	11(12%)
Mikulicz's disease	41 (31/10)	65 (43–82)	697 (18–2970)	13 (32%)
Sclerosing cholangitis	71 (53/18)	67 (38–84)	500 (4–2970)	13 (18%)
Retroperitoneal fibrosis	27 (23/4)	66 (50–80)	1110 (247–2970)	12 (44%)
Kidney lesion	18 (14/4)	67 (56–82)	1313 (156–2970)	9 (50%)

5. Long-Term Followup of Patients with Autoimmune Pancreatitis and Normal or Elevated IgG4

We followed 2 patients with autoimmune pancreatitis for 10 years each, a 55-year-old man with a serum IgG4 concentration of 1135 mg/dL and a 65-year-old woman with a serum IgG4 concentration of 42 mg/dL [24]. The first patient experienced several recurrences, developing a pancreatic stone and pancreatic duct stenosis, whereas the latter patient showed no duct changes over time. These findings suggest that autoimmune pancreatitis accompanied by normal IgG4 concentrations may represent lower activity and a nonprogressive state [24].

6. IgG4 and Extrapancreatic Lesions in Autoimmune Pancreatitis

Extrapancreatic lesions in patients with autoimmune pancreatitis may involve organs throughout the entire body [7, 8]. Serum IgG4 concentrations were well correlated with the number of extrapancreatic organs involved, indicating a correlation between increased serum IgG4 and extrapancreatic involvement. Among the 5 types of extrapancreatic involvement, lachrymal and salivary gland lesions and hilar lymph adenopathy have been significantly associated with high serum IgG4 concentrations, suggesting that patients with high serum IgG4 should be assessed for the occurrence of these lesions [7]. However, a recent study of large numbers of patients with autoimmune pancreatitis and extrapancreatic lesions showed different results, as shown in Table 1. Patients with IgG4-related retroperitoneal fibrosis and kidney lesions had higher IgG4 concentrations than other patients, probably because these lesions were complications of many other IgG4-related diseases (Table 1).

7. Role of IgG4

IgG4 in these patients may be (1) pathogenic, (2) anti-inflammatory, or (3) as a rheumatoid factor. For example, anti-desmoglein3 IgG4 autoantibody has been reported pathogenic for pemphigus vulgaris [25]. Transfer of an anti-desmoglein3 IgG4 autoantibody from a pemphigus vulgaris patient to BALB/C mice resulted in a pemphigus vulgaris like lesion, suggesting the involvement of an IgG4 autoantibody directed against an unknown target antigen. Similarly, IgG4 deposits have been detected in tissues of patients with autoimmune pancreatitis [26]. In contrast, IgG4 was found to have anti-inflammatory effects against allergic reactions. IgG4 antibodies can bind to soluble antigens, blocking the interaction between these antigens and IgE on mast cells and inhibiting allergic reactions. A dynamic Fab arm exchange of IgG4 can occur, resulting in bispecific activity, loss of monospecific cross-linking activity, and loss of the ability to form immune complexes, resulting in anti-inflammatory effects [27].

IgG4 may act as an autoantibody against IgG or have rheumatoid factor activity. Western blotting has shown that IgG4 from the sera of patients with autoimmune pancreatitis can bind to IgG1, IgG2, IgG3, and IgG Fc [28]. Furthermore, IgG4 Fc, but not IgG4 Fab, was found to bind to IgG Fc [28], indicating that IgG4 binding to IgG Fc is via an Fc-Fc interaction, not via rheumatoid activity. ELISA showed that IgG4 from the serum of each patient with autoimmune pancreatitis could bind to IgG1 coated onto microplates, a binding well correlated with serum IgG4, but not rheumatoid factor, concentration [28]. The role of IgG4 Fc-IgG Fc is unclear, but it may have physiological and/or pathological effects, suggesting the need for further studies.

8. Conclusion

The utility of serum IgG4 concentration as a biomarker of the major IgG4-related disease, autoimmune pancreatitis, includes its ability to diagnose autoimmune pancreatitis as well as to differentiate this disease from pancreatic cancer. Moreover, serum IgG4 concentration may be a marker for predicting relapse and for the evaluation of extrapancreatic lesions. It remains unclear, however, whether IgG4 and its rheumatoid factor-like activity may be beneficial or pathogenic in these patients.

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ARTICLE

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Mst1 regulates integrin-dependent thymocyte trafficking and antigen recognition in the thymus

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Thymocyte trafficking has an important role in thymic selection. Here we show that the Hippo homologue Mst1 is required for thymocyte migration and antigen recognition by LFA-1 and ICAM-1 within the medulla. Using two-photon imaging of thymic tissues, we found that highly motile mature thymocytes arrest and are activated in the vicinity of rare populations of Aire^{+} ICAM-1^{hi} medullary thymic epithelia in a negatively selecting environment. Notably, Mst1 deficiency or blocking the cell adhesion molecules LFA-1 and ICAM-1 results in inefficient migration and antigen recognition of CD4^{+} thymocytes within the medulla. Consistent with these defects, thymocyte selection is impaired in *Mst1*$^{-/-}$ mice, which display T cell-dependent inflammatory infiltrates in multiple organs and develop autoantibodies. Our results suggest that Mst1 has a key role in regulating thymocyte self-antigen recognition in the medulla.

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