Corticosteroids prevent the progression of autoimmune pancreatitis to chronic pancreatitis

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Short title: Long-term effect of steroids in AIP

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Abstract

Background/Objectives: Patients with autoimmune pancreatitis (AIP) sometimes progress to chronic pancreatitis (CP). We evaluated the ability of corticosteroids to prevent the progression to CP.

Methods: We defined patients with definitive findings of CP (stones in the main pancreatic duct [MPD] or multiple pancreatic calcifications) as having severe calcification (SC). A total of 145 AIP patients were enrolled. We measured the duration between AIP diagnosis and SC development and retrospectively compared the time to SC development between patients with and without steroids. Multivariate analysis for factors associated with SC were performed.

Results: Nineteen (13%) patients progressed to SC. Since 95 patients had pancreatic head swelling and SC was found in these patients only, our analysis focused mainly on these at-risk populations. In Kaplan-Meier analysis limited to patients with pancreatic head swelling, the incidence of SC was significantly lower in patients with steroids than in those without (hazard ratio [HR] 0.18, 95% confidence interval [CI] 0.07–0.52; p<0.001). Multivariate testing of patients with pancreatic head swelling confirmed that steroid therapy was significantly associated with a lower incidence of SC (HR 0.11, 95% CI 0.03–0.34; p<0.001), while MPD dilation at AIP diagnosis was related to a higher incidence of SC (HR 4.02, 95% CI 1.43–11.7; p=0.009).

Conclusions: Corticosteroids appeared to prevent progression to CP in AIP patients, especially in those with pancreatic head swelling. Patients with both pancreatic head swelling and MPD dilation at diagnosis have a higher incidence of progression to CP. Steroid therapy is suggested for these high-risk cases.

Key words: autoimmune pancreatitis; chronic pancreatitis; pancreatic calcification; steroid therapy

Introduction

Type 1 autoimmune pancreatitis (AIP in the present paper) is a distinct type of pancreatitis displaying elevated serum IgG4 levels and characteristic image findings of pancreatic enlargement and irregular narrowing of the main pancreatic duct (MPD) that responds well to steroid therapy[1-3]. The pancreatic duct narrowing in AIP stems from dense lymphoplasmacytic infiltration with extensive fibrosis mainly composed of IgG4-positive plasma cells around the pancreatic duct[4], which are improved both morphologically and histologically by steroid treatment[5].

Patients with ordinary chronic pancreatitis (CP), such as alcoholic pancreatitis, frequently exhibit the most common and characteristic complication of pancreatic stones. Pancreatic stone formation is caused by the hypersecretion of protein from acinar cells and pancreatic juice stasis[6]. In CP, pancreatic stones and MPD stricture induce pancreatic juice stasis in the upstream pancreatic duct and increase pancreatic intraductal pressure, which worsens the morphological and functional disease state[7]. On the other hand, AIP was earlier believed as free from pancreatic stones and transformation into confirmed CP resembling alcoholic pancreatitis because it was considered a reversible and acute disorder due to histologically dense lymphoplasmacytic infiltration and a favorable response to steroid therapy[3]. However, it has become apparent that some AIP patients experience pancreatic stone formation and pancreatic atrophy over a long-term course[8-11], suggesting that AIP can also progress to a state similar to ordinary CP. A prior study on serum IgG4 levels in 175 CP patients who had been diagnosed before 1995, when the concept of AIP was first proposed, showed elevated IgG4 in 7.4% patients[12], which indicated that some cases may have been attributable to AIP.

The frequency of pancreatic calcification in AIP reportedly ranges from 5% to 40%[11, 13-16]. We previously described that

pancreatic stone formation was significantly associated with pancreatic head swelling and narrowing of both Wirsung's and Santorini's ducts in the pancreatic head region at diagnosis[15]. Moreover, we investigated the risk factors of progression to CP fulfilling the Japanese clinical diagnostic criteria, including stones in the pancreatic duct and multiple calcifications distributed throughout the entire pancreas, in AIP patients who underwent long-term follow-up[10]. Multivariate analysis revealed that pancreatic head swelling and MPD non-narrowing in the pancreatic body were significant independent risk factors for the development of confirmed CP. This close association of pancreatic head swelling with pancreatic stone formation was confirmed in a Japanese multicenter study[14]. In experimental canine models of MPD stenosis from incomplete MPD ligation, partial outflow obstruction of the pancreatic duct induced the formation of pancreatic stones[17, 18]. Collectively, the above findings indicate the underlying mechanism of AIP progression to CP to be pancreatic juice stasis induced by pancreatic head swelling over a long-term period[10, 11, 15]. MPD narrowing accompanied by pancreatic head swelling causes the upstream stasis of pancreatic juice, which leads to the formation of pancreatic stones and ultimately CP.

Alcoholic and other forms of ordinary CP are irreversible conditions that result in pancreatic exocrine and endocrine insufficiency and often display severe complications, such as pancreatic cancer and pseudocysts[19]. AIP patients with pancreatic calcification and atrophy have also been reported to suffer from pancreatic exocrine and endocrine abnormalities[8, 9, 20]. Moreover, some AIP patients exhibit pseudocysts[21] or pancreatic cancer[22, 23] similar to those in ordinary CP.

AIP patients respond well to corticosteroid therapy in the short term, with pancreatic exocrine and endocrine function being improved somewhat by the treatment[16, 24-26]. However, the long-term influence of steroids on AIP progression to CP

remains unclear. Considering the favorable response to steroid therapy for improving MPD narrowing, pancreatic swelling, and presumably pancreatic juice stasis in AIP patients, steroids are also suspected to prevent the progression to CP. We herein aimed to clarify the efficacy of corticosteroid treatment for preventing AIP progression to CP and the appropriate indications for steroid therapy towards effective long-term AIP management.

Methods

This study adhered to the current ethical guidelines of the Declaration of Helsinki and was conducted in accordance with the requirements of the Institutional Review Board of Shinshu University School of Medicine (approval number: 4019).

Patients

The medical records of AIP patients who were treated between January 1996 and November 2018 at Shinshu University Hospital in Matsumoto, Japan, were reviewed retrospectively. Of them, a total of 145 AIP patients (107 men and 38 women, median age: 67 years [range: 38-92 years]) who had been followed for at least 1 year were enrolled. Median follow-up duration was 78 months (range: 14-284 months). All patients had type 1 AIP. The diagnosis of AIP was conducted according to the International Consensus Diagnostic Criteria[27].

Among the 145 AIP patients, 102 (70%) had received steroid therapy based on the Japanese consensus guidelines for AIP[28]. The initial oral prednisolone dose for remission induction was 0.6 mg/kg/day for approximately 4 weeks, which was then tapered by 5 mg every 1-2 weeks until a daily dose of 5 mg/day. In 74 of 85 patients (87%) who had been followed for at least 3 years, maintenance steroid therapy of 5 mg/day was conducted for more than 3 years.

Evaluation for transformation into CP

We examined AIP patients for progression to CP based on the revised Japanese clinical diagnostic criteria for CP[29]. Cases with image findings of stones in the MPD or multiple calcifications distributed throughout the pancreas, which were definite findings of CP in the clinical diagnostic criteria, were defined as severe calcification (SC) in this study. Accordingly, the development of SC indicated progression to CP in terms of image findings. We evaluated the presence of SC retrospectively using cross-sectional computed tomography (CT) images for each patient. CT-based follow-up was performed at least once a year for almost all subjects.

The following clinicodemographic factors potentially associated with pancreatic calcification were assessed: sex, age, drinking and smoking habits, abdominal/back pain, obstructive jaundice, pancreatic swelling, other organ involvements found in IgG4-related disease, elevations in serological IgG, IgG4, or amylase, relapse, and MPD dilation. All factors apart from relapse were analyzed at the time of AIP diagnosis. Other organ involvements were limited to multiple biliary strictures, salivary/lachrymal gland enlargement, retroperitoneal fibrosis, tubulointerstitial nephritis, and interstitial pneumonitis. Similarly to past reports[10, 15], pancreatic swelling was evaluated based on the Haaga criteria[30] or a marked reduction in size after steroid therapy. Serological values of IgG $\geq$1800 mg/dL, IgG4 $\geq$135 mg/dL, and amylase $\geq$130 IU/L were regarded as positive for serum elevation. Relapse was defined as pancreatic lesion recurrence after remission during the study course. The presence of MPD dilation ($\geq$3 mm) at 1 or more pancreatic areas, mainly in the pancreatic body and tail, was evaluated using endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography.

We measured the duration between AIP diagnosis and SC development and compared the time to SC development between patients with and without steroid therapy to evaluate the effectiveness of corticosteroid treatment for preventing the progression to CP.

Statistical analysis

For clinicodemographic characteristics, the variables for each patient were expressed as the number and percentage. Pearson's chi-squared tests were adopted to test for differences between subgroups of patients. The time to SC development in AIP patients was calculated using the Kaplan-Meier method, and the difference in those rates was compared by the log-rank test. Univariate and multivariate analyses for factors associated with SC were performed using a Cox proportional hazard regression model. Variables that reached a p-value of 0.2 in univariate analysis were further considered in multivariate analysis. A p-value of <0.05 was regarded as statistically significant. All statistical analyses were performed using JMP Statistics software version 13 (JMP, Tokyo, Japan).

Results

Characteristics of AIP patients with severe pancreatic calcification

Of the 145 patients, diffuse pancreatic swelling and pancreatic head swelling were observed in 85 patients (59%) and 96 patients (66%), respectively. Diffuse pancreatic swelling was defined as swelling in more than two thirds of the pancreas. Patients with pancreatic head swelling included not only cases of pancreatic head swelling, but also those of body or tail swelling in addition to head swelling. Respective median serum IgG and IgG4 levels were 1976 mg/dL (range: 379-7142

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mg/dL) and 459 mg/dL (range: 4-3660 mg/dL). Thirty-four patients (23%) experienced at least 1 pancreatic lesion relapse.

MPD dilation at diagnosis was observed in 44 patients (30%).

Nineteen of 145 recruited patients (13%) exhibited SC displaying the characteristic image findings that fulfilled the clinical diagnostic criteria for CP. SC was detected at the initial diagnosis of AIP in 2 patients and during subsequent follow-up in 17 patients (Figure 1a). Specifically, pancreatic duct stones were seen in 12 patients and multiple calcifications distributed throughout the pancreas were found in 15 patients, with overlap in some patients (Figure 1b). Pancreatic head swelling and MPD dilation at AIP diagnosis were observed in 18 patients (95%) and 10 patients (53%), respectively.

To assess pancreatic exocrine function in AIP with SC, we measured fecal elastase-1 concentration (FEC)[31] in 11 of 19 patients experiencing SC during follow-up. Exocrine insufficiency was defined as FEC <200 μg/g. Median FEC level was 68 μg/g (range: 5-520 μg/g) and the rate of patients with exocrine insufficiency was 73% (8/11). Regarding endocrine function in patients with SC, 17 patients (90%) suffered from diabetes mellitus, 7 of which required insulin administration. The rate of patients with insulin secretory insufficiency as defined by fasting immunoreactive insulin <5.0 μU/mL or fasting C-peptide reactivity <0.6 ng/dL was 41% (7/17). With regard to complications accompanying SC development, pseudocysts were found in 5 patients (26%) and pancreatic attacks caused by incarceration of pancreatic stones were seen in 2 patients (10%), with no patients exhibiting pancreatic cancer. Extracorporeal shock wave lithotripsy (ESWL) and surgical resection were respectively performed on 8 and 1 patients as interventional therapy for pancreatic stones.

Evaluation of steroid therapy effects

To assess the efficacy of steroid therapy to prevent AIP progression to CP, the incidence of SC was compared between

cases with and without steroids using Kaplan-Meier testing. The 2 patients already complicated with SC at the diagnosis of AIP were excluded. One was of a heavy-drinking patient without pancreatic head swelling, and the other had pancreatic head swelling. The remaining 143 patients were enrolled for the evaluation of steroid effectiveness. The baseline characteristics of patients with and without steroid therapy are compared in Table 1. The prevalences of abdominal/back pain, obstructive jaundice, pancreatic head swelling, and serum IgG elevation in patients receiving steroids were significantly higher than in those without steroids, which indicated that corticosteroid therapy was performed more frequently for cases of problematic symptoms or an active disease state. Three patients not given steroids at AIP diagnosis later received steroids upon SC detection. These patients were classified into the non-steroid treated group. In 1 case, pancreatic calcification was seen to improve with steroids, whereas pancreatic stones continued to increase slowly in number and size in the remaining 2 cases. The clinical and radiological course of the improved case is presented in Figure 2. In the Kaplan-Meier evaluation of all 143 AIP patients, the incidence of SC was significantly lower in cases with steroids than in those without (hazard ratio: 0.33, 95% confidence interval [CI] 0.12-0.94; p=0.025, log-rank test) (Figure 3a).

Evaluation of steroid therapy effects in cases with pancreatic head swelling

Pancreatic head enlargement is a reported risk factor for AIP progression to CP that is associated with pancreatic juice stasis[10, 11, 14, 15]. Therefore, the 143 AIP patients were classified based on the presence or absence of pancreatic head swelling (Figure 4). Of the 95 patients with pancreatic head swelling, 77 were treated with steroid therapy and 18 were not, with 10 and 7 cases displaying SC, respectively. On the other hand, no patients experienced SC among the 48 cases without pancreatic head swelling at AIP diagnosis. Therefore, AIP patients without pancreatic head swelling were not considered

to be at risk for SC development and excluded, leaving 95 patients with pancreatic head swelling for comparisons of the incidence of SC between cases with and without corticosteroids. Kaplan-Meier evaluation showed that the incidence of SC was significantly lower in cases with steroids (hazard ratio: 0.18, 95% CI 0.07-0.52; p<0.001, log-rank test) (Figure 3b).

Multivariate analysis was performed on the incidence of SC in cases with pancreatic head swelling, which were considered a risk group for SC (Table 2). Univariate analysis revealed MPD dilation at diagnosis to be significantly associated with a higher incidence of SC and steroid therapy to be significantly related to a lower incidence. Patients aged ≥65 years tended to have a higher incidence of SC. Multivariate analysis confirmed that steroid therapy was an independent factor contributing to a lower incidence of SC (hazard ratio: 0.11, 95% CI 0.03-0.34; p<0.001) and that MPD dilation at diagnosis was an independent factor associated with a higher SC incidence (hazard ratio: 4.02, 95% CI 1.43-11.7; p=0.009).

To identify the resistance factors to steroid therapy, the characteristics of 77 patients with pancreatic head swelling who received steroids were compared between cases with and without SC (Table 3). Relapse during follow-up was significantly associated with a higher incidence of SC (p=0.005).

Discussion

Characteristics of patients with AIP progressing to CP

The frequency of pancreatic calcification in AIP, which is the most common finding in CP, ranges from 5% to 40%[11, 13-16], with discrepancies in reported frequencies caused by differences in follow-up period, disease activity, and therapeutic strategy. Here, although only cases of SC meeting the clinical diagnostic criteria for CP were enrolled, 13% of patients experienced SC during a long-term observation period, which suggested that the progression to CP was not rare in AIP.

Most of the SC patients displayed exocrine and endocrine dysfunction similar to that in ordinary CP, and some exhibited problematic complications, such as pseudocysts and pancreatic attacks caused by pancreatic stone stasis. Thus, progressing to CP in AIP is a clinically serious problem. Marie et al.[9] evaluated the clinical course of 44 AIP patients for a 3-year period following diagnosis and observed pancreatic morphological abnormalities such as calcification, atrophy, and duct irregularities in 35% of cases, as well as exocrine and endocrine insufficiency in 34% and 39% of cases, respectively. Kanai et al.[8] examined exocrine and endocrine function in 92 AIP patients by comparing cases with and without severe pancreatic calcification. Exocrine dysfunction was found in 39% of the non-calcified group and 56% of the calcified group, while endocrine dysfunction was seen in 26% of the non-calcified group and 31% of the calcified group. Indeed, AIP patients can sometimes progress to CP characterized by SC over a long-term course. In such progressed situations, exocrine and endocrine insufficiency and problematic complications such as pseudocysts and pancreatic attacks can occur as in ordinary CP. Therefore, appropriate management and treatment strategies are required for preventing the progression to CP in AIP.

Evaluation of steroid therapy effects

Kaplan-Meier testing revealed that patients receiving corticosteroid therapy had a significantly lower incidence of SC, which indicated that steroids could prevent or delay the progression to CP in AIP. Since no patient without pancreatic head swelling displayed SC, we evaluated the incidence of SC only in patients with pancreatic head swelling as an at-risk population. Patients with steroid treatment had a remarkably lower incidence of SC and hazard ratio as compared with the former analysis, suggesting that steroid therapy targeting cases of pancreatic head swelling was more beneficial. Moreover, multivariate analysis confirmed steroid administration to reduce the risk of progression to CP in AIP patients with

pancreatic head swelling.

MPD dilation at AIP diagnosis was also revealed as an independent factor associated with SC in multivariate analysis. According to past reports[10, 11, 14, 15], pancreatic fluid stagnation from pancreatic head enlargement can induce AIP progression to CP. In agreement with this mechanism, no AIP patients without pancreatic head swelling experienced SC. MPD dilation is presumed to reflect the pancreatic juice stasis induced duct narrowing accompanied by pancreatic head swelling. AIP shows a favorable response to steroid therapy, with dramatic and rapid improvement of lymphoplasmacytic cell infiltration and fibrosis to ameliorate pancreatic duct narrowing and pancreatic swelling[5]. Pancreatic juice stagnation is released by steroid treatment due to the improvement of MPD narrowing, which culminates in the prevention of progression to CP.

We encountered a case of SC improvement after starting steroid therapy, which indicated that such treatment could not only prevent SC, but also ameliorate it. Tissue damage caused by AIP, including dense fibrosis, has been found to improve histologically by steroids[32]. Song et al.[33] described that type IV collagen was preserved in AIP tissues in comparison with CP tissues. Since collagen type IV is an important component of the basement membrane that plays a role in scaffolding to ensure the accurate regeneration of tissue form during renewal and repair, the original structure of AIP tissue may be regenerated after tissue injury. Based on these findings, chronic stage AIP might be considered to have a different pathophysiology from that of ordinary CP. Although ordinary CP is an irreversible condition, some CP cases originating from AIP may have the potential of tissue injury reversibility and regeneration; corticosteroid therapy may morphologically and histologically ameliorate the progressive condition of CP by relieving pancreatic juice stasis.

Among the patients receiving steroids, those suffering an AIP relapse had a significantly higher incidence of SC, which

implicated relapse as a resistance factor to treatment. Relapse is a reported susceptibility factor for pancreatic stone formation[13, 34]. A multinational survey showed that 46 (7%) of 659 patients had pancreatic calcification and that this condition was closely associated with relapse[13]. Similarly to repeated pancreatic attacks in CP facilitating the progression of disease state, multiple recurrences of AIP presumably contribute to remnant pancreatic duct stricture, pancreatic juice stasis, and transformation to CP.

Indication for steroid therapy

We previously examined the efficacy of endoscopic therapy and ESWL for pancreatic stones in 8 patients with chronic stage AIP and observed a lower rate of complete stone extraction from the MPD as compared with ordinary CP due to duct stenosis proximal to stones[35]. Since the therapeutic options for pancreatic stones are limited when AIP has progressed to CP, better strategies for preventing the progression to CP are required. According to the Japanese Consensus Guidelines, the standard indication for steroid therapy is obstructive jaundice and any symptom, such as abdominal pain, as well as other organ involvement associated with IgG4-related disease. However, these criteria focus on only the short-term prognosis of AIP patients. Although there is insufficient consensus on the efficacy of steroid therapy on the long-term prognosis of AIP, our findings indicate an effectiveness of steroids for preventing the progression to CP. AIP patients with both pancreatic head swelling and MPD dilation at diagnosis had a particularly higher incidence of SC. Therefore, steroid therapy may be suggested for such high-risk cases to prevent disease progression.

As relapse was a significant risk factor for SC development in the steroid-treated cases, strategies to prevent relapse require further consideration. In a multicenter randomized control trial from Japan, relapse rate was significantly lower in

patients with maintenance therapy who received prednisolone of 5-7.5 mg/day for 3 years than in those who discontinued the drug[36]. As we enrolled AIP patients who had been followed for more than 1 year and whose follow-up period was within 3 years, the effectiveness of maintenance therapy could not be fully examined. Maintenance therapy that can suppress relapse should be considered to prevent the progression to CP.

This investigation had several limitations. First, it was retrospective, contained a limited sample size, and was conducted at a single institution. The baseline characteristics of patients with and without steroid therapy varied with respect to a higher prevalence of abdominal/back pain, obstructive jaundice, pancreatic head swelling, and serum IgG elevation in the steroid-receiving group, which indicated that steroid treatment was more frequently performed in cases of problematic symptoms or an active disease state. Accordingly, multivariate analysis on the incidence of SC in cases with pancreatic head swelling was conducted to eliminate the influence of confounding as much as possible. Univariate analysis revealed that abdominal/back pain, obstructive jaundice, and serum IgG elevation were not remarkable factors contributing to AIP. Hence, symptoms and disease activity state, which were characteristics found more often in the steroid-receiving group, were not associated with progression to SC. We previously investigated the risk factors of pancreatic stone formation and progression to CP and revealed no significant associations between pancreatic stone formation and the degree of such published activity markers at AIP diagnosis as serum IgG, IgG, or complement or circulating immune complex[10, 15]. However, since it is impossible to completely exclude the influence of bias caused by comparisons of different groups with and without steroid therapy, larger prospective trials are required to validate our results in the clinical setting. Second, we did not compare pancreatic exocrine or endocrine function between patients with and without steroids; the long-term effects of corticosteroids on pancreatic function remain unclear. Since steroid therapy could effectively halt progression to CP, this

treatment was thought as effective for preventing pancreatic dysfunction in the long-term AIP course. According to earlier

reports, the short-term effects of steroid therapy on exocrine function have consistently been favorable, whereas those on

endocrine function are controversial, with studies showing recovery as well as worsening[16, 24-26, 37]. To fully elucidate the

effectiveness of steroids on long-term AIP course, further investigations that include pancreatic function are necessary.

Conclusions

In conclusion, the present study revealed that corticosteroid therapy appeared effective for preventing the progression to

CP in AIP patients, especially in those with pancreatic head swelling. Patients with CP originating from AIP exhibited

exocrine and endocrine insufficiency and such complications as pseudocysts and pancreatic attacks. AIP patients with both

pancreatic head swelling and MPD dilation at diagnosis have a higher incidence of progression to CP and may be indicated

for steroid therapy. As relapse is a possible resistance factor to treatment, maintenance therapy is advised for avoiding

potential relapse and conserving pancreatic function.

Conflict of interest: The authors declare that they have no conflicts of interest.

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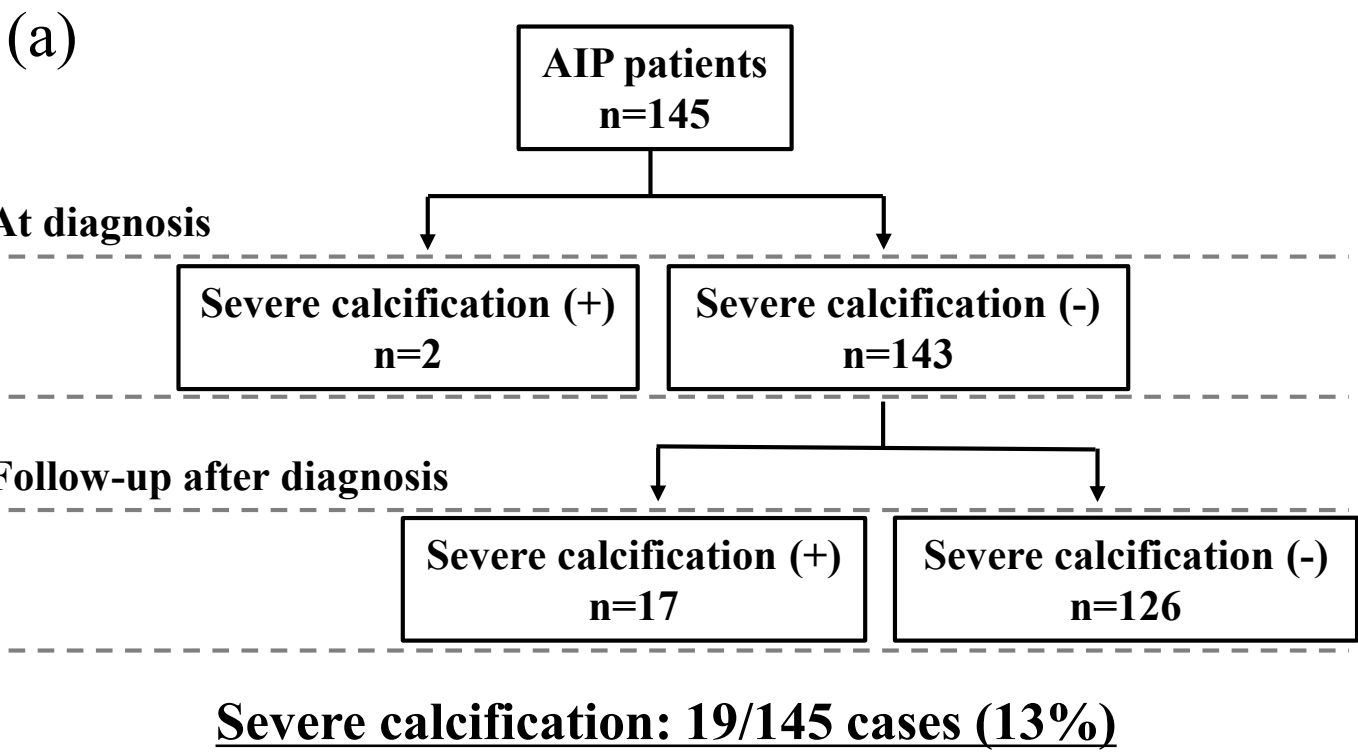
Figure legends

Figure 1. Prevalence of severe pancreatic calcification in autoimmune pancreatitis (AIP). (a) Flowchart of severe pancreatic calcification. Among the 145 recruited AIP patients, 19 (13%) exhibited severe pancreatic calcification and displayed characteristic image findings fulfilling the Japanese clinical diagnostic criteria for chronic pancreatitis. Severe calcification was detected at the initial diagnosis of AIP in 2 patients and during the follow-up period after diagnosis in 17 patients. (b) CT image findings of severe pancreatic calcification. Pancreatic duct stones were seen in 12 patients. Multiple calcifications distributed throughout the entire pancreas were found in 15 patients.

Figure 2. Clinical and radiological course of a patient who received steroid therapy after detection of severe calcification. (a) At the diagnosis of autoimmune pancreatitis, the patient exhibited diffuse pancreatic swelling, including pancreatic head swelling, following main pancreatic duct dilation. Steroid therapy was not indicated at this time. (b) Two years after diagnosis, multiple calcifications distributed throughout the pancreas were found and steroid therapy was initiated. (c) One year after starting steroid therapy, pancreatic calcifications had decreased in number. (d) Seven years after steroid therapy commencement, pancreatic calcification had remarkably improved and only a few stones remained.

Figure 3. Kaplan-Meier curves. A: The time to development of severe calcification between cases with and without steroid therapy in 143 enrolled autoimmune pancreatitis (AIP) patients. The incidence of severe calcification was significantly lower in cases with steroids than in those without (hazard ratio: 0.33, 95% CI 0.12-0.94; p=0.025, log-rank test). B: The time to development of severe calcification between cases with and without steroid therapy in 95 AIP patients
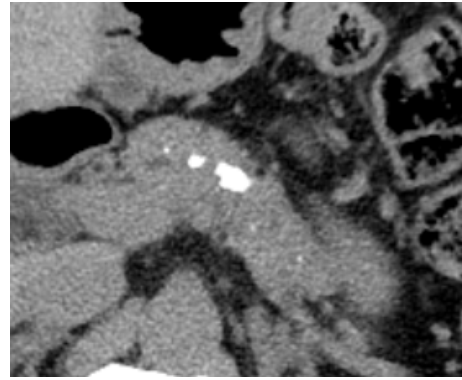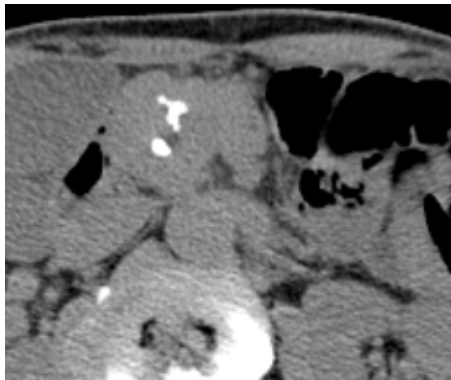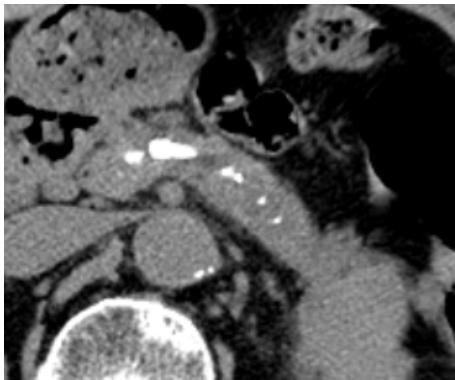
with pancreatic head swelling. The incidence of severe calcification was significantly lower in cases with steroids (hazard ratio: 0.18, 95% CI 0.07-0.52; $p<0.001$, log-rank test).

Figure 4. Flowchart classification of patients based on the presence or absence of pancreatic head swelling. Two patients who already had severe calcification at the diagnosis of autoimmune pancreatitis (AIP) were excluded, and the remaining 143 AIP patients were enrolled. There were 95 patients with pancreatic head swelling and 48 patients without. Among the 95 patients with pancreatic head swelling, 77 were treated with corticosteroids and 18 were untreated, with 10 and 7 patients exhibiting severe calcification, respectively. On the other hand, no patient without pancreatic head swelling displayed severe calcification among 48 cases.
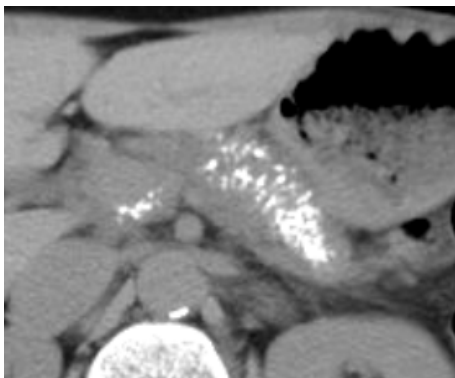
(a)

AIP patients
n=145

At diagnosis

Severe calcification (+)
n=2

Severe calcification (-)
n=143

Follow-up after diagnosis

Severe calcification (+)
n=17

Severe calcification (-)
n=126

Severe calcification: 19/145 cases (13%)

(b)

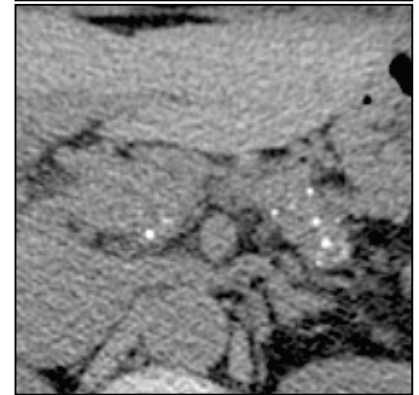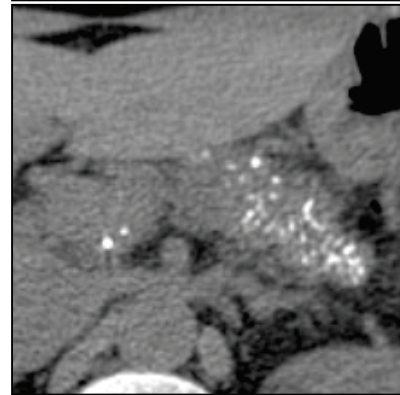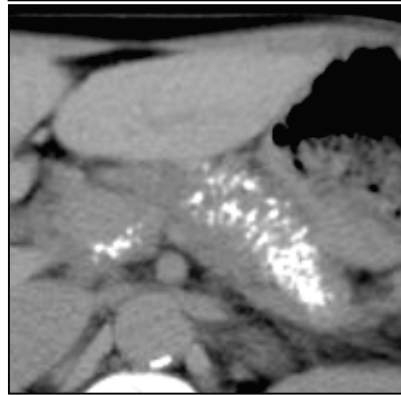**Pancreatic duct stones: 12 cases**
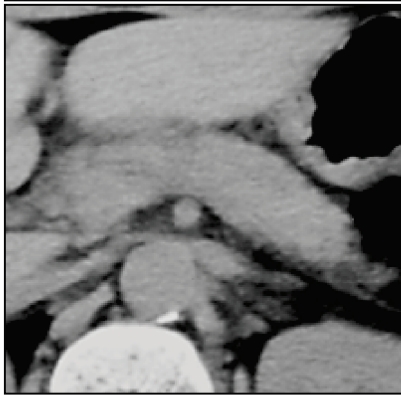
Multiple calcifications: 15 cases
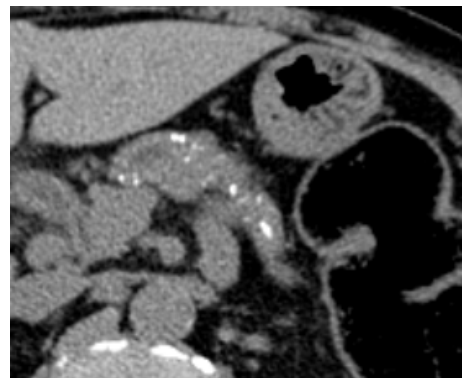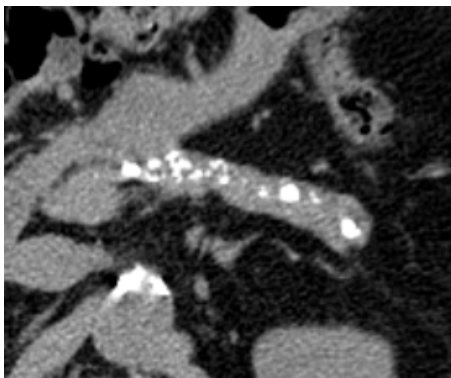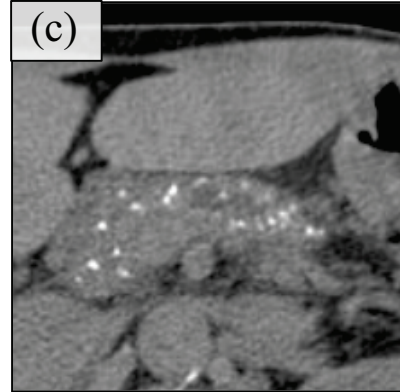
At diagnosis	**2 years** after diagnosis	**1 year** after starting steroid	**7 years** after starting steroid
(a)	(b)	(c)	(d)
Steroid (-)	**Start of steroid**	**Steroid (+)**	**Steroid (+)**
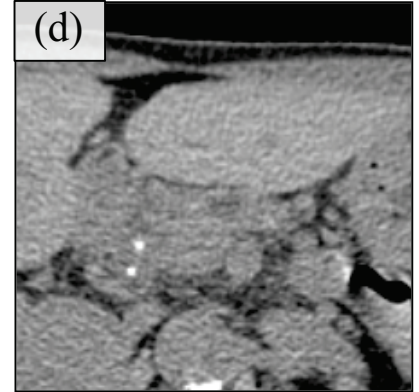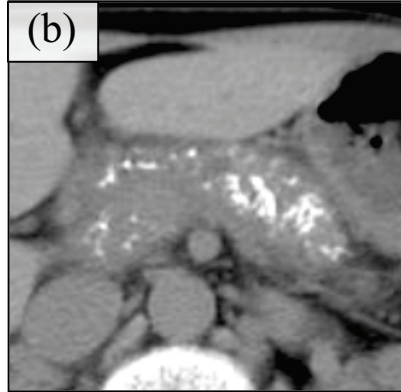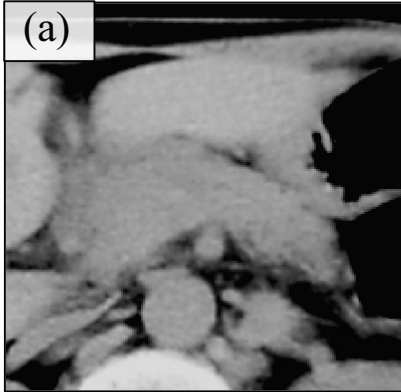
(a)
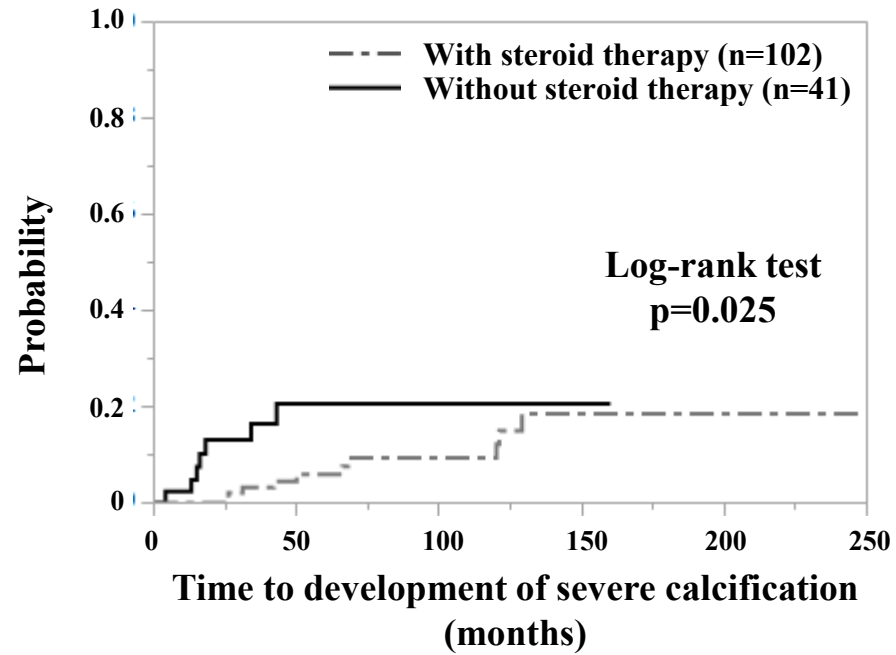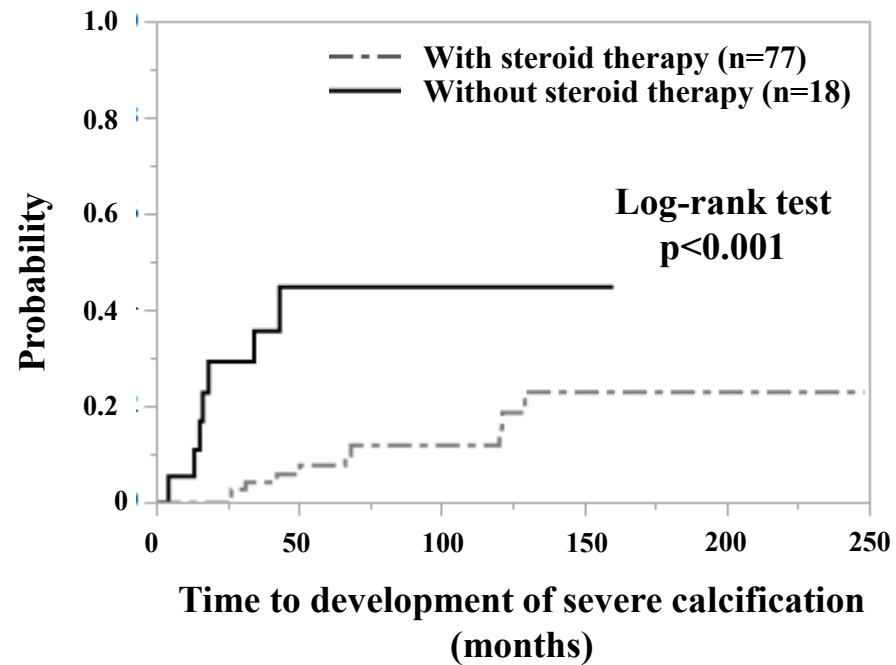
Probability

1.0
0.8
0.6
0.4
0.2
0

– – – With steroid therapy (n=102)
——— Without steroid therapy (n=41)

Log-rank test
p=0.025

0   50   100   150   200   250

Time to development of severe calcification (months)

(b)

Probability

1.0
0.8
0.6
0.4
0.2
0

– – – With steroid therapy (n=77)
——— Without steroid therapy (n=18)

Log-rank test
p<0.001

0   50   100   150   200   250

Time to development of severe calcification (months)

Table 1. Baseline characteristics of autoimmune pancreatitis patients with and without steroid therapy

Factor	Steroid therapy		p-value
	(+) n=102	(-) n=41	
Male, n (%)	77 (76%)	28 (68%)	0.378
Age ≥65 years, n (%)	59 (58%)	24 (59%)	0.939
Drinking habit, n (%)	46 (45%)	20 (49%)	0.690
Smoking habit, n (%)	65 (65%)	20 (50%)	0.101
Abdominal/back pain, n (%)	39 (38%)	8 (20%)	0.031
Obstructive jaundice, n (%)	37 (37%)	1 (3%)	<0.001
Pancreatic head swelling, n (%)	77 (75%)	18 (44%)	<0.001
Diffuse pancreatic swelling, n (%)	64 (63%)	20 (49%)	0.125
Other organ involvement, n (%)	73 (72%)	27 (66%)	0.500
Serum IgG elevation, n (%)	70 (69%)	18 (44%)	0.006
Serum IgG4 elevation, n (%)	89 (87%)	40 (97%)	0.061
Serum amylase elevation, n (%)	28 (27%)	10 (24%)	0.708
MPD dilation at diagnosis, n (%)	33 (32%)	11 (27%)	0.518

MPD: main pancreatic duct

Table 2. Univariate and multivariate analysis of factors associated with severe pancreatic calcification in autoimmune pancreatitis patients with pancreatic head swelling

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male	1.00 (0.32-4.34)	0.997		
Age ≥65 years	2.04 (0.76-6.08)	0.160	2.43 (0.86-7.64)	0.096
Drinking habit	1.13 (0.43-3.04)	0.790		
Smoking habit	1.16 (0.36-3.33)	0.787		
Abdominal/back pain	1.06 (0.39-2.83)	0.894		
Obstructive jaundice	0.55 (0.15-1.62)	0.290		
Diffuse pancreatic swelling	0.63 (0.23-1.98)	0.402		
Steroid therapy	0.18 (0.07-0.52)	0.002	0.11 (0.03-0.34)	<0.001
Serum IgG elevation	0.82 (0.31-2.37)	0.691		
Serum IgG4 elevation	0.71 (0.04-3.57)	0.734		
Serum amylase elevation	1.03 (0.35-2.75)	0.955		
Relapse	1.74 (0.65-4.58)	0.260		
MPD dilation at diagnosis	2.88 (1.08-7.84)	0.035	4.02 (1.43-11.7)	0.009

HR: hazard ratio, 95% CI: 95% confidence interval, MPD: main pancreatic duct

Table 3. Comparisons of clinical and demographic findings between autoimmune pancreatitis patients

accompanied with pancreatic head swelling and receiving steroid therapy with and without severe pancreatic

calcification

Factor	Severe pancreatic calcification		p-value
	(+) n=10	(-) n=67	
Male, n (%)	8 (80%)	52 (78%)	0.865
Age ≥65 years, n (%)	6 (60%)	36 (53%)	0.710
Drinking habit, n (%)	4 (40%)	31 (46%)	0.710
Smoking habit, n (%)	7 (78%)	44 (67%)	0.502
Abdominal/back pain, n (%)	6 (60%)	27 (40%)	0.240
Obstructive jaundice	4 (40%)	30 (45%)	0.747
Diffuse pancreatic swelling, n (%)	7 (70%)	53 (79%)	0.517
Other organ involvement, n (%)	6 (60%)	45 (67%)	0.655
Serum IgG elevation, n (%)	7 (70%)	43 (64%)	0.719
Serum IgG4 elevation, n (%)	9 (90%)	57 (85%)	0.678
Serum amylase elevation, n (%)	4 (40%)	17 (25%)	0.333
MPD dilation at diagnosis, n (%)	6 (60%)	22 (33%)	0.096
Relapse, n (%)	7 (70%)	17 (25%)	0.005

MPD: main pancreatic duct