Risk Factors for Pancreatic Stone Formation in Autoimmune Pancreatitis over a Long-term Course

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Short title: Risk factors for pancreatic stone in AIP

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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 the present study is 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.

Key words

autoimmune pancreatitis, pancreatic stone, Wirsung duct, Santorini duct

Abbreviations

AIP autoimmune pancreatitis, CT computed tomography,

ERCP endoscopic retrograde cholangiopancreatography

Main Article

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 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]. Based on these findings, we have 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 is 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 period, 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 autoimmune pancreatitis [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 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 3 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 2 or 3 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 3 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 2 or 3 areas were 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 < 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 (Figure 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 months 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).

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, Figure 2).

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, Figure 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.

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 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 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 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 months 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.

Acknowledgements

This work was supported partially by the Research Program of Intractable Disease provided by the Ministry of Health, Labor, and Welfare of Japan, and in part by Grants-in-aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan (23591012).

We thank Trevor Ralph for his English editorial assistance.

Conflict of interest

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

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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

Table 2 Clinical features and laboratory tests at diagnosis

	Stone-forming Group (n = 28)	Non-stone-forming Group (n = 32)	*P* value
Clinical Features			
	median (range)		
Observation period §	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	median (range)		
Amylase	94 (17 - 431)	86 (22 - 478)	0.678
IgG	2187 (892 - 7236)	2183 (1194 - 5545)	0.686
IgG4	640 (154 - 2855)	424 (4 - 2970)	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 - 2260)	940 (257 - 4695)	0.130
CIC	5.1 (1.9 - 40)	5.5 (1.9 - 27.5)	0.392

§ Period from diagnosis of AIP to the most recent observation (months)

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

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

* $P < 0.05$

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

Table 5 Pancreatic function during the course of the study

	Non-stone-forming Patients	Stone-forming Patients	*P* value [1)]	Intraductal Stone-forming Patients (n = 9)	*P* value [2)]
Amylase	median (range)			median (range)	
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	median (range)			median (range)	
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

1) Non-stone-forming patients vs. Stone-forming patients

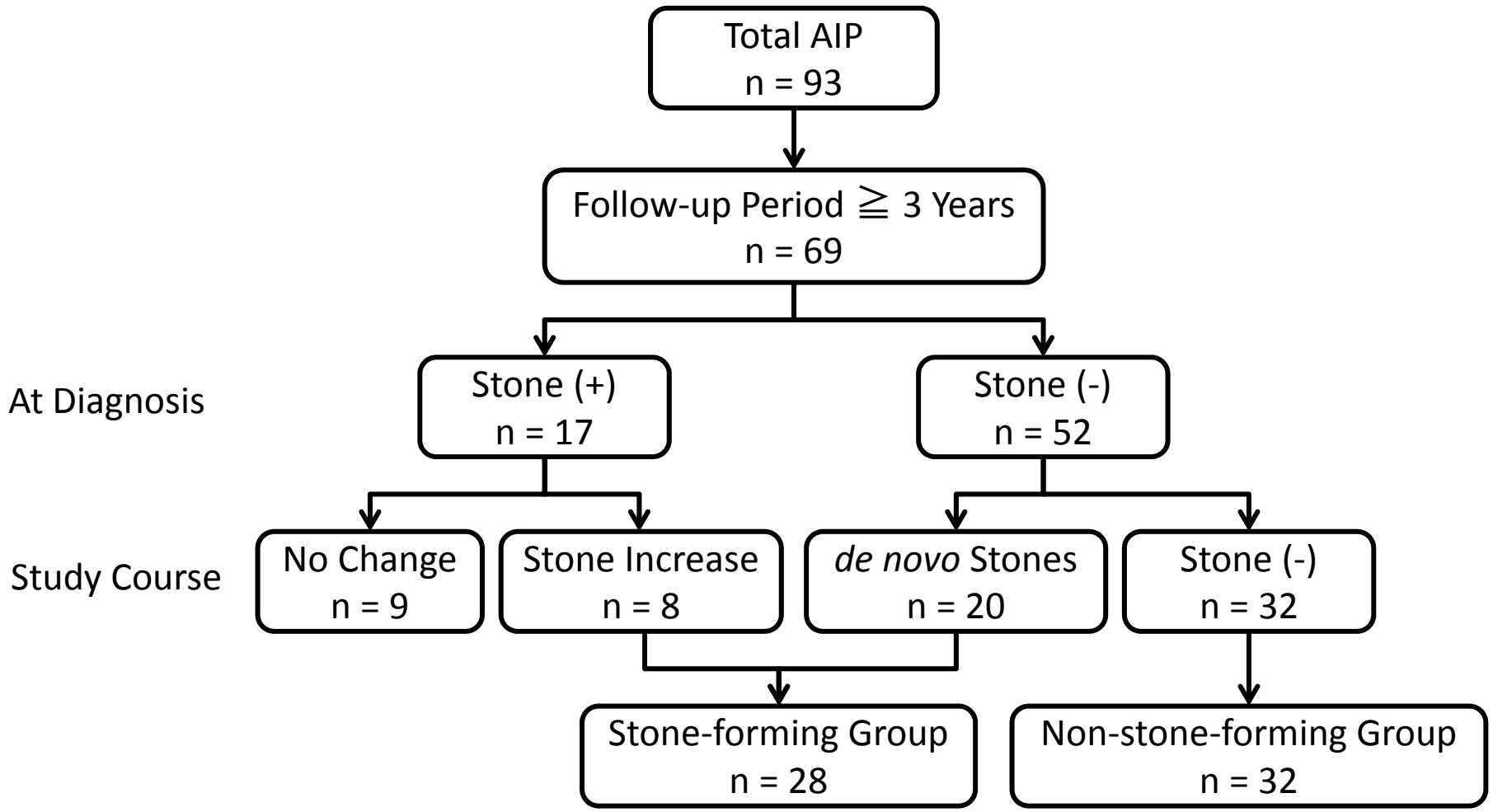
2) Non-stone-forming patients vs. Intraductal stone-forming patients

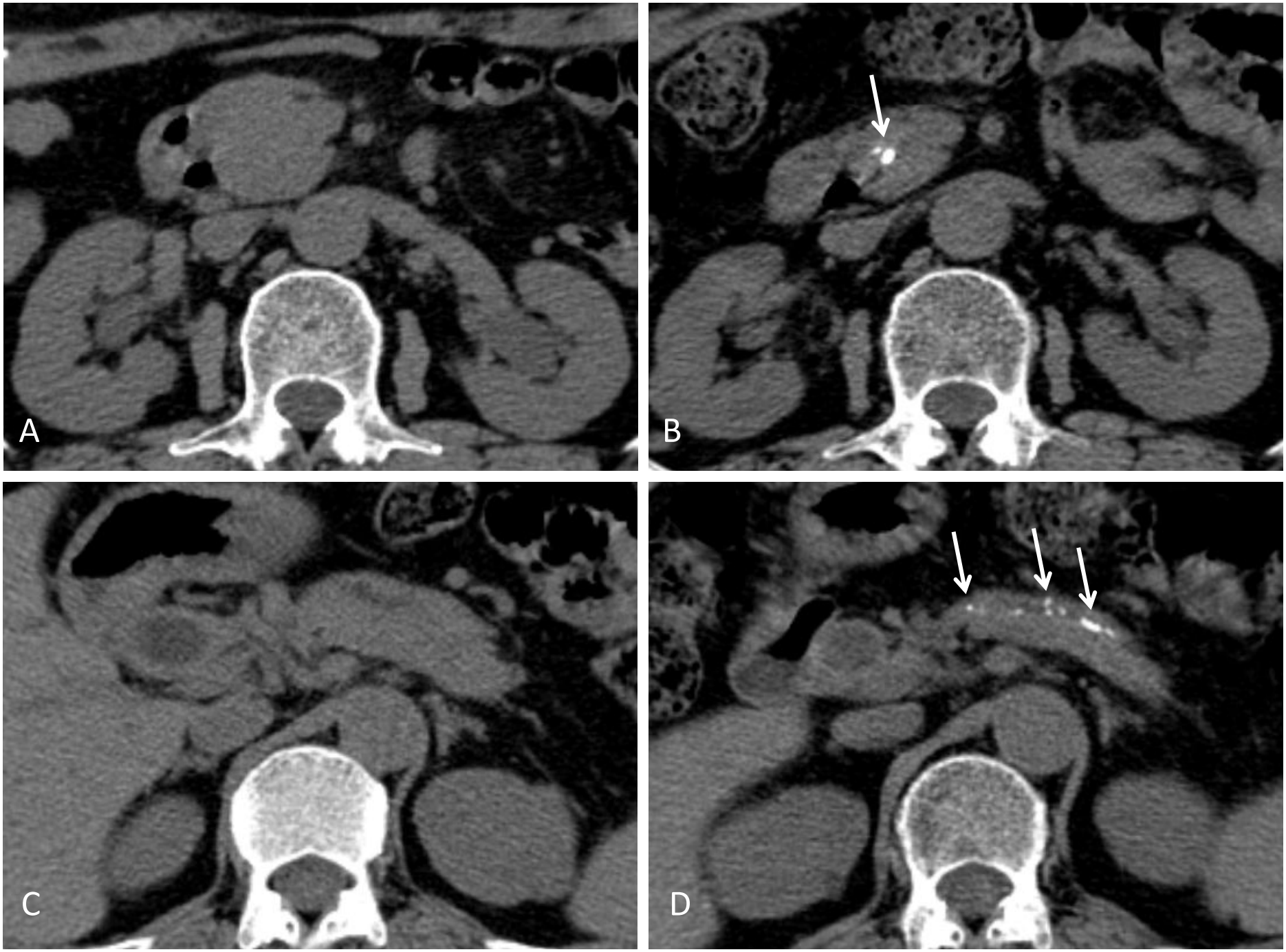
Figure legends

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).

Fig. 2 CT findings in a 67-yr-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-yr-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.


Total AIP
n = 93
Follow-up Period ≧ 3 Years
n = 69
At Diagnosis
Stone (+)
n = 17
Stone (-)
n = 52
Study Course
No Change
n = 9
Stone Increase
n = 8
de novo Stones
n = 20
Stone (-)
n = 32
Stone-forming Group
n = 28
Non-stone-forming Group
n = 32


A
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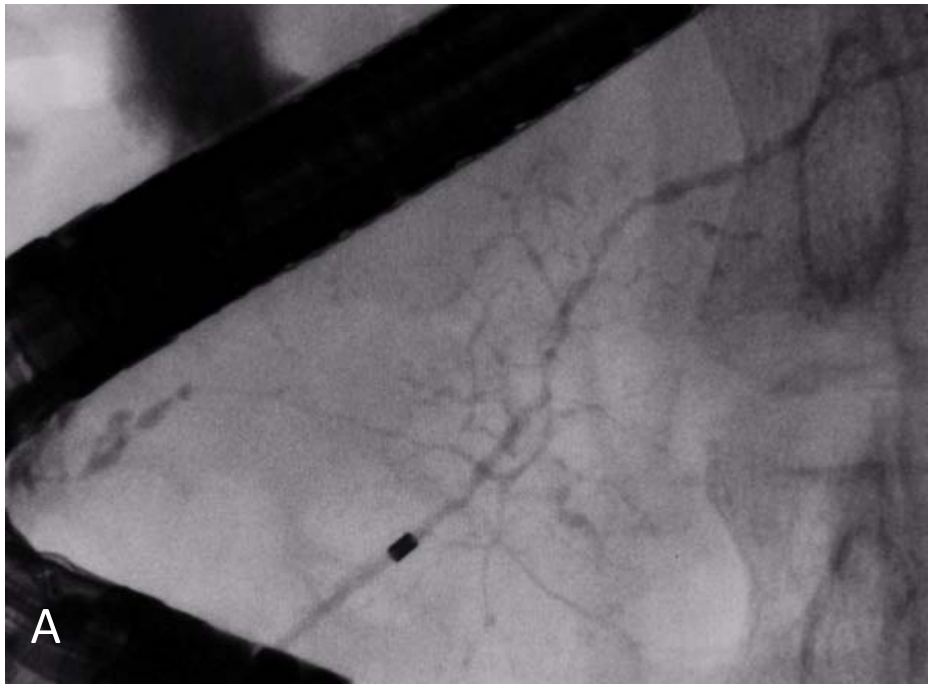
C
D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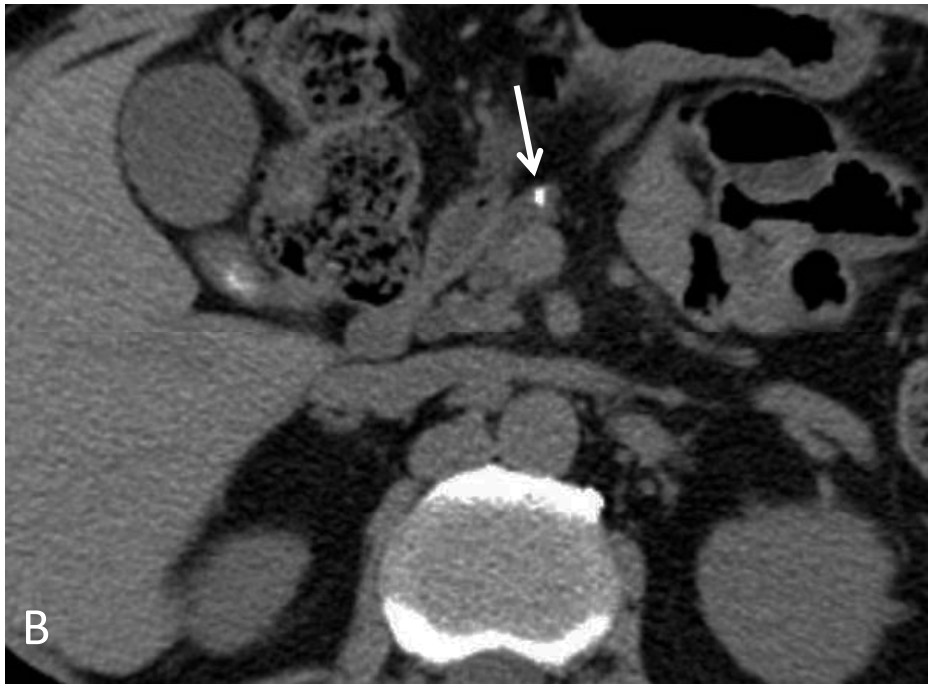
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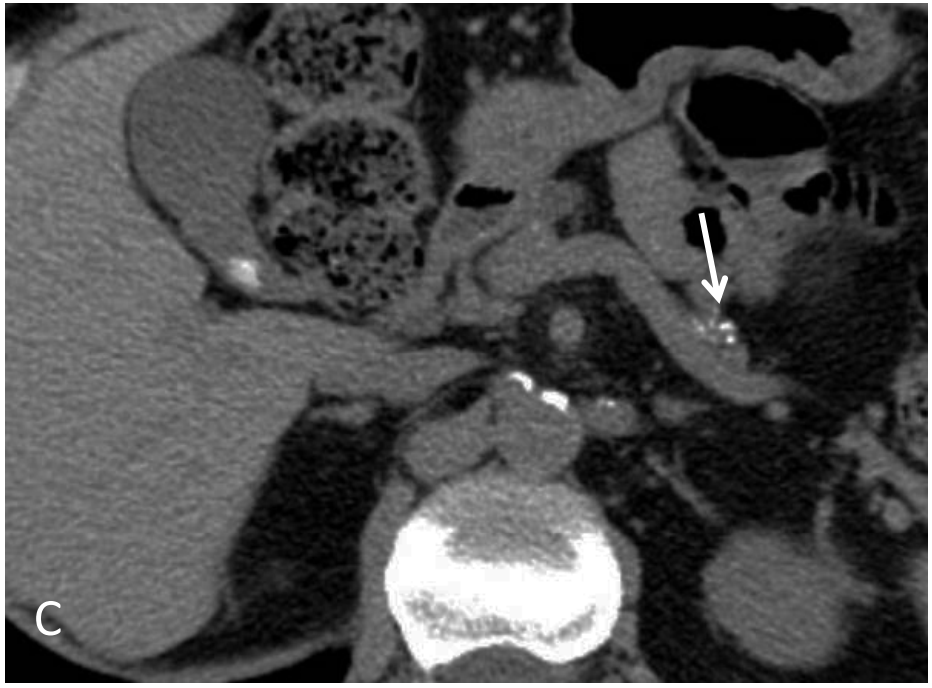
C