PANCREATIC DISEASE

Long-term prognosis of autoimmune pancreatitis with and without corticosteroid treatment

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Objectives: Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis, and has a favourable response to corticosteroid treatment (CST). Little is known, however, about the long-term outcome of AIP. This study aimed to document the prognosis without and with CST, and to examine the indication for CST.

Patients and methods: The prognosis and clinical features of 23 patients without CST and 19 patients treated with CST from onset were investigated. In addition, factors concerning the late occurrence of unfavourable events related to AIP were examined.

Results: The patients without CST were 19 men and four women, with an average age of 66 years. After an average observation period of 25 months, 16 patients (70%) developed unfavourable events including obstructive jaundice as a result of distal bile duct stenosis in four, growing pseudocyst in one, sclerogenic changes of extrapancreatic bile duct in nine, hydronephrosis as a result of retroperitoneal fibrosis in one, and interstitial nephritis in one. Patients with obstructive jaundice at onset showed a higher cumulative event occurrence rate ($p=0.025$). The patients treated with CST were 16 men and three women, with an average age of 64 years. After an average observation period of 23 months, six patients (32%) developed unfavourable events consisting of interstitial pneumonia in three, and a recurrence of obstructive jaundice in three. In multivariate analysis, CST (HR 0.33, 95% CI 0.12–0.89, $p=0.029$) and obstructive jaundice at onset (HR 3.09, 95% CI 1.14–8.32, $p=0.026$) were significant predictive factors for unfavourable events.

Conclusion: CST could reduce AIP-related unfavourable events. The early introduction of CST is recommended especially for patients with obstructive jaundice.

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis characterised by irregular narrowing of the pancreatic duct, swelling of the pancreas, lymphoplasmacytic infiltration and fibrosis, and favourable response to corticosteroid treatment (CST).^{1–12} Serologically, elevation of IgG4 is the most remarkable characteristic of this disease.^{13–14} Pathologically, IgG4-positive plasma cells and obliterative phlebitis are characteristic features.^{15–16} There are also many reports about associated extrapancreatic lesions such as sclerosing cholangitis,^{2–5 7 15 17} retroperitoneal fibrosis,^{5 18} sialoadenitis,^{19–21} interstitial nephritis,^{21 22} and interstitial pneumonia.^{23 24} They often appear simultaneously at the diagnosis of AIP, but sometimes appear before or after the diagnosis of pancreatic lesions. As the concept of AIP becomes widespread, atypical cases without remarkable pancreatic swelling or ductal change have also been reported.⁶

Previous studies have shown that CST is effective for patients with AIP at least in the short term.^{1–3 5–12 17–19 22–24} Some studies have, however, reported that clinical symptoms of patients were resolved without CST.^{3 10 25} As the long-term prognosis of AIP especially without CST is not well known, it still remains to be determined whether CST is necessary for all patients with AIP.

We conducted the present study to elucidate these issues. Initially, we had basically treated the patients without CST by relieving symptoms such as by biliary drainage. We then began to employ CST in many patients after we noticed the late occurrence of sclerosing cholangitis without CST.⁵ Such AIP-related sclerosing cholangitis, which represents multiple bile duct strictures affecting the intra and extrahepatic biliary trees, has been recognised as one form of extrapancreatic lesion.^{2 5 7 11 12 15 17} We thus investigated the precise incidence of unfavourable events in these patients. In addition, some non-CST cases are still being followed, especially atypical or

asymptomatic cases. We reviewed the outcome and clinical features of all cases with AIP, especially focusing on patients followed without CST, and evaluated the indication for CST in AIP.

PATIENTS AND METHODS

Between 1997 and 2005, 42 patients were diagnosed as having AIP at the University of Tokyo Hospital and affiliated hospitals. Diagnosis was based on the following clinicopathological findings: enlargement of the pancreas or narrowing of the main pancreatic duct; increased serum γ -globulin including IgG and IgG4; the presence of autoantibodies; and characteristic histological findings of fibrotic change with lymphoplasmacytic infiltration. The diagnosis of AIP was made prospectively in all patients except one (patient 13 in table 1), who was diagnosed with unidentified obstructive jaundice in 1993 before the publication of the paper by Yoshida *et al.*,¹ and who was diagnosed as having AIP six years later. As a result, patients diagnosed with AIP by us turned out to fulfill the diagnostic criteria of AIP recently proposed by the Mayo Clinic¹¹ or the revised criteria of the Japan Pancreas Society.¹² We diagnosed patients with sclerogenic changes (diffuse irregular strictures) of the extrapancreatic bile duct as sclerosing cholangitis, based on the findings of endoscopic retrograde cholangiography or percutaneous transhepatic cholangiography. When bile duct stricture was limited to the distal (intrapancratic) area, we did not regard it as sclerosing cholangitis because it could be influenced by pancreatic oedema. Sialoadenitis was diagnosed on the basis of the findings of palpation, imaging studies such as gallium scintigraphy, and the absence of sicca syndrome A

Abbreviations: AIP, autoimmune pancreatitis; CST, corticosteroid treatment

and sicca syndrome B antibodies. Retroperitoneal fibrosis was diagnosed on the basis of the findings of computed tomography; that is, a soft tissue density mass around the abdominal aorta was diagnosed as retroperitoneal fibrosis. Obstructive jaundice was defined as a condition in which increased levels of biliary enzymes and total bilirubin (>1.5 mg/dl), together with dilatation of the bile duct, were observed. Abdominal pain included abdominal discomfort in this study.

Among 42 patients, 23 patients were followed up without CST because they were asymptomatic or became asymptomatic after biliary drainage. Most of them (20/23) had been diagnosed before 2003, from when we became concerned about the late occurrence of sclerosing cholangitis in AIP without CST.⁵ The other 19 patients received CST from onset. CST was indicated for obstructive jaundice caused by distal bile duct stenosis, sclerosing cholangitis, and pancreatic pseudocyst.²⁶ Prednisolone at an initial dose of 25–50 mg/day (30–40 mg in most cases) was administered for 2–4 weeks. It was then tapered by 5 mg every 2–4 weeks until reaching 5 mg/day, and 2.5–5 mg/day was continued as maintenance therapy.

After diagnosis, all patients were carefully followed, with particular attention being paid to the probability of the occurrence of AIP-related unfavourable events such as obstructive jaundice from distal bile duct stenosis, increased levels of biliary enzymes caused by sclerosing cholangitis confirmed on imaging findings, growing pancreatic pseudocyst, and others associated with extrapancreatic lesions,^{5 18 19–24} for which simple observation seemed very inadequate. Imaging studies (ultrasonography, computed tomography or magnetic resonance imaging) were performed every six months, and biochemical parameters were assessed every 3–6 months.

Differences were evaluated by Student's *t*-test, Welch *t*-test or Fisher's exact test. Cumulative event occurrence rate curves were analysed using the Kaplan–Meier technique with log-rank test. Possible predictors for unfavourable events included seven

variables: age, gender, obstructive jaundice, abdominal pain, diffuse pancreatic ductal change, serum IgG4 levels, and CST. Age and serum IgG4 levels were transformed into categorical data consisting of two ordinal numbers by median values. Parameters that proved to have a low *p* value (<0.2) in the univariate analysis were tested by the stepwise multivariate Cox proportional hazards model. A *p* value of less than 0.05 was considered statistically significant. In the subgroup analysis (group with CST and group without CST), predictive factors for unfavourable events were examined by log-rank test because of the small number.

RESULTS

Patient profile

The detailed clinical profiles of 23 patients without CST (19 men and four women, average age 66 years) are shown in table 1. The mean follow-up was 61 months (range 11–162 months). The characteristics of 19 patients treated with CST from onset (16 men and three women, average age 64 years) are shown in table 2. The mean follow-up was 41 months (range 10–114 months), shorter than that of patients without CST ($p = 0.031$). There were 11 patients whose serum IgG4 was not measured at onset, but the serum IgG4 measured during follow-up was high (≥ 135 mg/dl) in all of them. The clinical characteristics at onset of the 23 non-CST patients and the 19 CST patients are compared in table 3. Body weight loss (>5 kg in the past three months) was more frequently observed in CST than in non-CST patients ($p < 0.001$). Patients with extrapancreatic lesions at onset were more frequent in the CST than in the non-CST group ($p = 0.010$).

Prognosis of patients without CST

During follow-up, unfavourable events were observed in 16 out of 23 patients (70%) after 25 months on average (range 1–92 months) from onset. Among these 16 patients, sclerosing

Table 1 Clinical profiles of 23 patients without corticosteroid treatment

Patient no.	Age at onset	Sex	Obstructive jaundice	Abdominal pain	Pancreatic ductal change	Total bilirubin (mg/dl)	Alkaline phosphatase (IU/l)	IgG4 (mg/dl)	BT-PABA (%)	Initial treatment	Event during follow-up	Period to event occurrence or observation period (months)
1	70	M	+	+	Diffuse	4.1	800			EBD	OJ	5
2	66	M	+	–	Diffuse	3.6	605			EBD	SC	40
3	69	M	+	–	Diffuse	7.4	848	305	72	EBD	SC	4
4	49	M	+	–	Diffuse	6.9	640	222	52	EBD	SC	12
5	80	M	+	–	Diffuse	1.6	1975			EBD	SC	4
6	56	M	–	–	Local	0.7	174			None	OJ	19
7	79	M	+	+	Diffuse	3.3	1949	420	61	EBD	SC	1
8	70	M	+	–	Diffuse	5.8	1126	2170		EBD	OJ	5
9	41	M	–	+	Local	0.5	197			DP	OJ	18
10	76	M	+	–	Diffuse	14.1	778	65.2		EBD	SC	1
11	65	F	–	–	Diffuse	0.6	219	374	70	None	Appearance of pseudocyst	30
12	68	M	+	+	Local	2.0	1546		27	None	SC	24
13	70	M	+	–	Diffuse	4.1	581			PTBD	SC	89
14	65	M	+	–	Diffuse	2.1	1632			None	SC	92
15	64	M	–	+	Local	0.5	877	670	70	None	Interstitial nephritis	13
16	66	M	–	–	Local	0.4	202	135		DP	Retroperitoneal fibrosis	43
17	76	M	–	–	Local	0.8	339	812		None	None	79
18	75	M	–	–	Diffuse	0.7	164	770		None	None	45
19	79	M	–	–	Local	0.6	168	554	69	None	None	43
20	68	F	–	–	Local	0.6	192	553	72	None	None	59
21	58	F	–	–	Local	0.6	139	592	69	None	None	36
22	61	F	–	–	Diffuse	0.4	183	354	80	None	None	22
23	52	M	–	–	Local	0.7	112	164		PD	None	10

BT-PABA, N-benzoyl-L-tyrosyl-p-aminobenzoic acid test $>70\%$ normal; DP, distal pancreatectomy; EBD, endoscopic biliary drainage; OJ, obstructive jaundice caused by intrapancreatic bile duct stenosis; PD, pancreatoduodenectomy; PTBD, percutaneous transhepatic biliary drainage; SC, sclerosing cholangitis. Normal range: Total bilirubin, 0.3–1.3 mg/dl; alkaline phosphatase, 60–201 IU/l; IgG4, <135 mg/dl.

Table 2 Clinical profiles of 19 patients with corticosteroid treatment

Patient no.	Age at onset	Sex	Obstructive jaundice	Abdominal pain	Pancreatic ductal change	Total bilirubin (mg/dl)	Alkaline phosphatase (IU/l)	IgG4 (mg/dl)	BT-PABA (%)	Initial dose of PSL (mg)	Cessation of CST (months after initiation)	Event during follow-up	Period to event occurrence or observation period (months)
1	70	F	+	-	Diffuse	5.8	1643	133		40	-	IP	26
2	57	M	+	-	Diffuse	10.6	418			25	29	IP	45
3	75	M	+	-	Diffuse	6.7	1427	354		30	-	IP	15
4	63	M	+	+	Local	3.0	850	691	45	30	-	OJ	4
5	58	M	+	+	Local	9.2	2744			50	5	OJ	22
6	61	M	-	-	Local	0.4	740	410		40	-	OJ	27
7	69	F	-	+	Diffuse	0.4	996	249	54	40	-	None	72
8	66	M	+	+	Local	5.3	2299	525	75	40	-	None	56
9	55	M	+	+	Diffuse	1.7	222	320		40	-	None	53
10	66	M	-	+	Diffuse	0.5	113	310		30	-	None	54
11	73	M	+	+	Local	5.4	1041	360	50	30	-	None	49
12	72	F	+	-	Diffuse	1.6	1968	1400	44	30	-	None	36
13	61	M	+	+	Local	1.6	1290	578	63	30	-	None	27
14	58	M	+	-	Diffuse	6.9	1004	481		30	-	None	21
15	71	M	-	-	Local	0.6	420	470		30	-	None	15
16	55	M	+	-	Diffuse	2.9	728			30	-	None	13
17	61	M	-	+	Local	0.5	217	974	64	30	-	None	15
18	65	M	+	+	Local	5.4	481	1260		30	-	None	12
19	64	M	-	-	Diffuse	0.4	171	361	36	30	-	None	11

BT-PABA, N-benzoyl-L-tyrosyl-p-aminobenzoic acid test >70% normal; IP, interstitial pneumonia; OJ, obstructive jaundice caused by intrapancreatic bile duct stenosis; PSL, prednisolone. Normal range: Total bilirubin, 0.3–1.3 mg/dl; alkaline phosphatase, 60–201 IU/l; IgG4, <135 mg/dl.

cholangitis was observed in nine, obstructive jaundice caused by distal bile duct stenosis in four, growing pseudocyst in one, hydronephrosis caused by retroperitoneal fibrosis in one, and interstitial nephritis in one. The nine sclerosing cholangitis cases were diagnosed at 30 months on average (median 12 months) after onset. Diagnosis was made during the periodic exchange of biliary plastic stents in five, and after their removal in four. We had one troublesome case for drainage therapy, in which multiple bile duct strictures appeared in a short period of just one month after the occurrence of distal bile duct obstruction, necessitating the use of multiple stents to control biliary infection (fig 1). The rate of event occurrence was 30.7% at one year and 49.6% at two years according to cumulative event occurrence rate curves.

Unfavourable events occurred in two of the three patients treated by pancreatectomy. One had re-occurrence of obstructive jaundice caused by swelling of the residual pancreas head (patient 9 in table 1), and the other had left hydronephrosis caused by retroperitoneal fibrosis (patient 16 in table 1).

Comparing the event-occurrence group with the event-free group, the ratio of patients with obstructive jaundice was significantly higher in the former group (table 4).

When patients were divided into two groups by age ($\geq$ median or $<$ median), sex, obstructive jaundice, abdominal

pain, diffuseness of pancreatic ductal change, and IgG4 levels at onset ($\geq$ median or $<$ median, for the 15 patients with IgG4 measured at onset), patients with obstructive jaundice ($p=0.025$) and abdominal pain ($p=0.013$) had higher cumulative event occurrence rates (log-rank test). The cumulative event occurrence rate curves of patients with and without obstructive jaundice at onset are shown in figure 2.

Three patients died during follow-up. One died from cerebral infarction, one from lung cancer, and the other from pancreatic cancer. Judging from clinical symptoms, imaging findings and laboratory data, no patient developed liver cirrhosis or portal hypertension. Steatorrhea or emaciation suggestive of pancreatic insufficiency was not observed. Patients suffering from diabetes mellitus increased from five to seven.

Prognosis of patients treated with CST from onset

Imaging findings and laboratory data were improved in all cases four weeks after CST, as reported previously.^{5–9,10} During follow-up, unfavourable events occurred in six out of 19 patients (32%) at an average of 23 months (range 4–45 months) after CST (table 2). Two of the six patients had discontinued maintenance therapy. Three developed interstitial pneumonia and three obstructive jaundice caused by distal bile duct stenosis. Sclerosing cholangitis was not observed. The rate of

Table 3 Comparison of clinical characteristics at the onset between patients without and with corticosteroid treatment

	Patients without CST (n = 23)	Patients with CST (n = 19)
Age	66 (41–80)	64 (55–75)
Male/female	19/4	16/3
Obstructive jaundice	11	13
Abdominal pain	5	10
Body weight loss (>5 kg in the past 3 months)	0	9
Pancreatic ductal change	13/10	10/9
IgG4 (mg/dl)	544 (65–2170)	555 (133–1400)
Extrapancreatic lesions	5 lesions in 4 patients	15 lesions in 11 patients
Sclerosing cholangitis	0	6
Retroperitoneal fibrosis	3	5
Sialoadenitis	2	4

CST, Corticosteroid treatment.

Figure 1 (Patient 10 in table 1). (A) Magnetic resonance cholangiopancreatography at onset showed narrowing of the main pancreatic duct in the head and severe stenosis of the intrapacreatic common bile duct causing obstructive jaundice. Strictures of hilar bile ducts were not seen. The patient received endoscopic biliary drainage, and was followed without corticosteroid treatment (CST). (B) One month later, the patient showed high fever because of biliary infection. Endoscopic retrograde cholangiopancreatography showed severe stenotic change at the hilus. One plastic stent was not enough for the control of biliary infection. Finally, three plastic stents were placed. (C) Four weeks after CST (prednisolone 30 mg), improvement in bile duct changes was observed.

Table 4 Comparison between event occurrence group and event free group in the patients without corticosteroid therapy

Parameters	Event-occurrence group (n = 16)	Event-free group (n = 7)	p Value
Age (years)	65.9 ± 10.2	67.0 ± 10.3	0.810
Sex (male/female)	15/1	4/3	0.067
Obstructive jaundice	11	0	0.0046
Abdominal pain	5	0	0.147
Pancreatic ductal change diffuse/focal	11/5	2/5	0.169
IgG4 (mg/dl)	545 ± 683 (n = 8)	543 ± 226 (n = 7)	0.993

event occurrence was 5.1% at one year and 19.6% at two years according to cumulative event occurrence rate curves.

No significant difference was noted between the event-occurrence and event-free groups in terms of age, sex, existence of obstructive jaundice and abdominal pain, pancreatic ductal change, IgG4, initial dose of prednisolone, and cessation of CST (table 5). Analysis by log-rank test revealed no significant risk factors for unfavourable events.

Among the 19 patients treated with CST, one patient had lumbar vertebra fracture and one had avascular necrosis of the femoral head during follow-up. These were possibly related to CST.

Figure 2 Patients followed up without corticosteroid treatment were analysed. Kaplan-Meier curves comparing event occurrence rates between groups without and with obstructive jaundice at onset.

One patient died from acute myelocytic leukemia during follow-up. No patient developed liver cirrhosis or portal hypertension. Steatorrhea or emaciation suggestive of pancreatic insufficiency was not observed. Two patients discontinued maintenance therapy because of exacerbated diabetes mellitus, but an improvement in diabetes mellitus was not attained. Among eight patients diagnosed as having no diabetes mellitus at the initial evaluation, there was no new onset of diabetes mellitus except for these two patients.

Predictive factors for unfavourable events in AIP patients

Seven parameters were analysed to clarify the predictors of unfavourable events. Univariate analysis using the Cox proportional hazards model revealed no significant parameters, but obstructive jaundice at onset and CST had a comparatively low p value (<0.2). Stepwise multivariate analysis by the Cox proportional hazards model was performed using these two parameters. Results indicated that obstructive jaundice ($p = 0.026$) and CST ($p = 0.029$) retained significance as independent predictive factors (table 6).

DISCUSSION

CST has become accepted as a standard treatment for AIP. Because this disease was only recognised quite recently, however, its long-term prognosis is still obscure. In addition, some reports have suggested that patients can be treated without the use of CST.^{3 10 24} In this regard, CST carries the risk of a variety of adverse effects including susceptibility to infection, impaired glucose tolerance and osteoporosis. Therefore, it remains unclear whether CST is indispensable for all patients with AIP. With these issues in mind, we closely

Table 5 Comparison between event-occurrence group and event-free group in patients with corticosteroid treatment

Parameters	Event-occurrence group (n = 6)	Event-free group (n = 13)	p Value
Age (years)	64.0 ± 7.1	64.3 ± 6.1	0.923
Sex (male/female)	5/1	11/2	1.00
Obstructive jaundice	5	8	0.605
Abdominal pain	2	8	0.350
Pancreatic ductal change diffuse/focal	3/3	7/6	1.00
IgG4 (mg/dl)	397 ± 230 (n = 4)	607 ± 386 (n = 12)	0.222
Initial dose of PSL (mg)	36 ± 9.1	32 ± 4.3	0.405
Cessation of CST	2	0	0.088

CST, Corticosteroid treatment; PSL, prednisolone.

reviewed the outcome of AIP patients treated with and without CST in the present study.

The cumulative event occurrence rate was higher, especially in patients with obstructive jaundice or abdominal pain at onset when they did not receive CST. Obstructive jaundice remained as an only predictive factor after the analysis shown in table 6. The number of patients with abdominal pain in the non-CST group might be too small for a precise analysis.

All nine patients whose unfavourable event was sclerosing cholangitis had shown obstructive jaundice at onset, perhaps indicating that obstructive jaundice at onset is particularly related to the late occurrence of sclerosing cholangitis. Here, it is noteworthy that the late occurrence of sclerosing cholangitis was not observed in any of the CST-treated patients. As CST seems very effective, especially in preventing bile duct lesions, this treatment appears reasonable for patients with obstructive jaundice. As shown in fig 1, a particularly difficult condition is that of sclerosing cholangitis accompanied by biliary infection.

In patients treated with CST from the onset, unfavourable events were recognised in six (interstitial pneumonia and distal bile duct stenosis in three each). Because of the small number of unfavourable events, it was difficult to indicate significant risk factors. The cessation of CST may, however, have had a negative influence on prognosis, as both patients who discontinued CST suffered from late unfavourable events (interstitial pneumonia and distal bile duct stenosis in one each; table 2). An issue requiring further investigation will be the optimal duration of maintenance therapy, as continued CST may reduce AIP-related unfavourable events but may also increase the risk of CST-induced adverse events.

The late occurrence of interstitial pneumonia was remarkable in patients treated with CST. Although this condition was improved by increased prednisolone, a higher dose was necessary to maintain remission than for biliary involvement.²⁴ CST may be less preventive of interstitial pneumonia.

Whether asymptomatic patients, most of whom present with localised pancreatic changes and are free of obstructive jaundice, should be treated with CST or not is a question that might be answered only after a long observation period. The late occurrence of obstructive jaundice as a result of aggravated residual pancreas swelling was observed in one patient even after distal pancreatectomy. This might imply the gradual progression of pancreatic lesions leading to severe symptoms in presently asymptomatic patients. In addition, there is a possibility of extrapancreatic lesions appearing during long-term follow-up without CST.¹⁰ Furthermore, the potentially beneficial effect of CST on pancreatic endocrine and exocrine function should also be taken into account.^{19 27 28} Taken together then, observation may be acceptable for asymptomatic patients in consideration of their lower incidence of unfavourable events for now (fig 2), but this issue must be revisited in the near future.

It is unknown whether high serum IgG4 is related to prognosis, although its elevation is the most characteristic feature in AIP.^{13 14} As we previously reported cases in which IgG4 increased at the time of the later occurrence of interstitial pneumonia,²⁴ we expected that serum IgG4 levels were related to the prognosis of AIP. In our series, however, serum IgG4 levels at onset showed no correlation with prognosis. Although changes in IgG4 levels may give clinically useful information, singly tested IgG4 levels are not likely to be sufficiently informative for the prediction of severity or prognosis.

The major weak point of this study was that it was not a randomised controlled trial. There were background differences between patients with and without CST. Considering that AIP is still a rare disease without a long history, however, planning a randomised controlled trial several years ago would have been difficult.

In conclusion, CST could reduce AIP-related unfavourable events. The early introduction of CST is recommended

Table 6 Predictive factors for unfavourable events in autoimmune pancreatitis patients

Variables	Univariate analysis		Stepwise multivariate analysis	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Age (>65 years)	0.95 (0.40 to 2.30)	0.916		
Sex (male)	2.57 (0.59 to 11.1)	0.208		
Obstructive jaundice	2.20 (0.85 to 5.75)	0.106	3.09 (1.14–8.32)	0.026
Abdominal pain	1.00 (0.40 to 2.51)	0.998		
Diffuse pancreatic ductal change	1.17 (0.49 to 2.84)	0.723		
IgG4 (>420 mg/dl)	0.46 (0.14 to 1.52)	0.201		
CST	0.47 (0.18 to 1.22)	0.120	0.33 (0.12–0.89)	0.029

CI, Confidence interval; CST, corticosteroid treatment.

especially for patients accompanied by obstructive jaundice in order to prevent the late occurrence of complicated sclerosing cholangitis.

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