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Is a two-week steroid trial after initial negative workup for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? : A prospective outcome study

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Keywords: Autoimmune pancreatitis, Pancreatic cancer, Steroid

Abbreviations: AIP (Autoimmune pancreatitis)
ERCP (Endoscopic retrograde cholangiopancreatography)
MRCP (Magnetic resonance cholangiopancreatography)
EUS (Endoscopic ultrasonography)
EUS-FNA (Endoscopic ultrasonography-guided fine needle aspiration)
US (Ultrasonography)
CEA (Carcinoembryonic antigen)
CA 19-9 (Carbohydrate antigen 19-9)

ABSTRACT

Background: Autoimmune pancreatitis (AIP) is a peculiar type of chronic pancreatitis that responds dramatically to steroid therapy. To date, there are no worldwide consensus criteria for AIP. Different criteria with institutional preference (HISORt, revised Kim, and the revised Japanese criteria) are being used to diagnose AIP, and there is a controversy on the inclusion of steroid responsiveness in the diagnostic criteria. In contrast to the HISORt and revised Kim criteria, the revised Japanese criteria do not include steroid responsiveness as a diagnostic component.

Aims: This study was performed to evaluate whether "a two-week steroid trial and subsequent assessment of its response" is a useful diagnostic tool for the differentiation of AIP from pancreatic cancer. We also wanted to discover the surgical and clinical outcome for a patient who followed our treatment algorithm based on the steroid responsiveness.

Design: Prospective study.

Patients and methods: From January 2004 to June 2007, in the setting of clinically suspected AIP, twenty-two consecutive patients with atypical imaging for AIP while not meeting the classic imaging criteria for pancreatic cancer were challenged to undergo two weeks of steroid therapy (0.5mg/kg of oral prednisolone per day). After the two-week steroid trial, steroid responsiveness was assessed based on a marked improvement of the main pancreatic ductal narrowing and a reduction of the pancreatic mass. The steroid trial was continued in the case of positive steroid responsiveness, whereas surgical exploration was conducted in the case of negative steroid responsiveness. Final diagnosis was made by surgical exploration or long-term

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clinical and radiologic follow-up.
Results: All patients (n=15) who responded to steroids were diagnosed as having AIP, whereas all patients (n=7) who did not show a response to steroids were confirmed as having pancreatic cancer. Complete resection was possible in all (6/6; 100%), except one individual who refused surgery.
Conclusion: In the clinical setting of suspected AIP with the continued need of differentiation from pancreatic cancer due to atypical imaging for AIP, "a two-week steroid trial and subsequent assessment of its response" may be helpful in confirming the diagnosis of AIP without negative consequences for resectable pancreatic cancer. However, a steroid trial should be performed carefully by only specialist in pancreatology.

Autoimmune pancreatitis (AIP) can be defined as a chronic inflammation of the pancreas due to an autoimmune mechanism.[1-3] AIP is a very attractive disease to clinicians in terms of its impressive response to steroid therapy.[4-7] If AIP is properly diagnosed, it can be treated without laparotomy or pancreatic resection. According to the revised Japanese criteria, diagnosis of AIP is made based on the combination of radiographic and laboratory and/or histopathological findings.[8] As clinical experience has increased, however, a certain fraction of AIP patients have failed to satisfy the Japanese criteria, and yet still respond to steroid therapy.[9] That is because even in patients with AIP, histology and serology can reveal negative results and imaging findings are not always typical for AIP.[7, 10, 11] Including steroid responsiveness to the criteria may be helpful in the preoperative diagnosis of such difficult cases, because the response in patients with AIP to even a short duration of steroid therapy is dramatic.[4]

At present, there are no worldwide consensus criteria for AIP. A number of groups have proposed their own diagnostic criteria (HISORt, revised Kim, and the revised Japanese criteria) to aid in the recognition of AIP.[4, 12, 13] In contrast to the HISORt and revised Kim criteria, the revised Japanese criteria do not include steroid responsiveness as a diagnostic component because its inclusion may encourage the use of this facile technique to merely distinguish AIP from pancreatic cancer.[14] Japanese investigators worry about the possibility of cancer progression during a trial of steroid therapy in a resectable patient.

To date, the specificity of steroid responsiveness for AIP has not been published and its utility will rest on its ability to distinguish AIP from pancreatic cancer. This study was therefore performed to evaluate whether "a two-week steroid trial and subsequent assessment of its response" is a useful diagnostic tool for the differentiation of AIP from pancreatic cancer. We also wanted to discover the surgical and clinical outcome for a patient who followed our treatment algorithm based on the steroid responsiveness.

METHODS

Initial suspicion for AIP based on imaging findings

Based on the previously reported cardinal features of AIP,[3, 10, 11, 15, 16] AIP was initially suspected when the imaging findings showed one of the following features (versus pancreatic cancer): (1) diffuse pancreatic enlargement with or without capsule-like rim (versus parenchymal atrophy above the stricture); (2) delayed enhancement of pancreatic mass (versus poor enhancement); (3) diffusely attenuated main pancreatic duct with irregular wall (versus single localized stricture); (4) none-to-mild upstream duct dilatation despite of long stricture (versus marked upstream duct dilatation); (5) double duct sign without a pancreatic mass in a patient with obstructive jaundice (versus visible mass); (6) association of hilar or intrahepatic duct strictures (versus common bile duct stricture alone); or (7) other organ involvement unusual for pancreatic cancer such as salivary gland, kidney or retroperitoneal fibrosis (versus no other organ involvement).

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Initial work-up to exclude malignancy before patient enrollment

Prior to the steroid trial, a work-up to exclude pancreatobiliary malignancies was performed. Pancreas dynamic CT and endoscopic retrograde cholangiopancreatography (ERCP) were performed in all patients. Serum levels of IgG and IgG4 and tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were also checked for all patients. Endoscopic ultrasonography (EUS) was performed in patients with a suspected pancreatic mass on cross-sectional imaging and if a mass was visualized, a pancreatic biopsy or cytology was done under the guidance of EUS or transabdominal ultrasonography (US). Endobiliary biopsy and brush cytology were performed at the time of ERCP in the case of obstructive jaundice associated with distal common bile duct narrowing. After this initial work-up, only patients with negative results for malignancy were registered in the study.

Study population and our treatment algorithm

From January 2004 to June 2007, 48 consecutive patients were clinically suspected as having AIP after the initial work-up. Among them, 26 patients (20 men and 6 women) had typical imaging for AIP which was defined as diffuse pancreatic enlargement with delayed (rim) enhancement and diffuse or segmental irregular narrowing of the main pancreatic duct.[8, 17] They were treated with steroids, and follow-up imaging was performed 4 to 6 weeks after the initiation of steroid therapy.

The remaining twenty-two patients with clinically suspected AIP were enrolled in the study and prospectively managed by the treatment algorithm shown in figure 1. They all had atypical imaging for AIP while not meeting the classic imaging criteria for pancreatic cancer. In these patients, trials of steroid therapy were attempted by means of oral prednisolone 0.5 mg/kg per day. Informed consent was obtained from every patient before the steroid trial. Steroid responsiveness was assessed two weeks after the initiation of the steroid therapy by means of pancreas dynamic CT and ERCP/MRCP (magnetic resonance cholangiopancreatography). MRCP was used as a follow-up imaging tool only if the image quality of a baseline MR pancreatography was comparable with that of ERCP. MRCP was performed with a 1.5T magnetic resonance system (Magnetom Vision or Magnetom Avanto; Siemens Medical Solution, Erlangen, Germany).

In the case of positive steroid responsiveness, the steroid trial was continued and laboratory tests, CT scans, and ERCP/MRCP were conducted two months and six months after the initiation of steroid therapy. After achieving complete clinical remission, the laboratory tests were carried out every two to three months, and imaging studies such as CT scans or magnetic resonance imaging (MRI)/MRCP every six months until Dec 2007. In the case of negative steroid responsiveness, steroid administration was withdrawn and subsequently surgical exploration was performed. Steroids were completely discontinued without tapering because use of steroids for less than a three-week duration, regardless of dosage, is known to have an insignificant effect on the hypothalamic-pituitary-adrenal axis.[18] A final diagnosis was made by surgical exploration or long-term clinical and radiologic follow-up. Our study was approved by the institutional review board of our hospital.

Steroid responsiveness

Positive steroid responsiveness was defined as complete resolution or marked improvement of the main pancreatic ductal narrowing after steroid therapy and if present, resolution or measurable reduction of the pancreatic mass as well. Negative steroid responsiveness was defined as no improvement of the main pancreatic ductal narrowing or pancreatic mass after steroid therapy.

Terminology

A mass was defined as a lesion that had a different density compared with the surrounding

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pancreatic tissue by CT scan, whereas pancreatic enlargement was defined as an increase in the size of the gland without a discrete mass.[4] We classified the extent of the main pancreatic ductal narrowing into 3 types: diffuse (narrowed segment being greater than two thirds of the entire duct), segmental (between diffuse and focal), and focal (less than a third of the entire duct), respectively. A double duct sign was defined as the dilatation of the common bile duct and pancreatic duct with biductal strictures in the head of the gland.[19]

RESULTS

During the study period, 22 clinically suspected AIP patients with atypical imaging (18 men and 4 women; median age 64 years, range 36-78 years) were eventually enrolled in the study group.

Clinical outcome of the positive steroid-responsiveness group

With the two-week steroid trial, 15 of 22 patients showed a positive response to steroids. The main pancreatic ductal narrowing markedly improved to almost normal in follow-up ERCP/MRCP, and a measurable reduction of the pancreatic mass was noted in follow-up dynamic CT scans (figure 2 & figure 3). In all patients with an initial response to steroids, complete clinical (symptomatic, radiologic, and serologic) remission was achieved on a regimen of prednisolone 0.5 mg/kg per day for 1-2 months followed by a gradual taper of 5-10 mg per month to the maintenance dose of 2.5-7.5 mg/d, which was continued for an average of 6 months and then stopped. During a median follow-up of 27 months (range 6-47 months), 3 of 15 (20%) patients experienced a relapse of AIP, either during maintenance steroid therapy (1 of 3) or after a complete discontinuation of steroids (2 of 3). Relapses were treated with another course of steroids and all patients achieved remission again. Complete withdrawal of steroids was possible in 5 patients by Dec 2007. Not a single patient developed a malignancy during the follow-up period. As a result, final diagnosis of AIP could be made in all 15 patients without the necessity of surgical exploration based on the revised Kim criteria.[12]

Surgical outcome of the negative steroid-responsiveness group

With the two-week steroid trial, a follow-up ERCP/MRCP of 7 patients did not show any improvement in the narrowed main pancreatic duct (figure 4 & figure 5). After confirming no response to steroids, pancreatic surgery was performed the next day on all but one patient who had refused surgery. Four patients underwent pylorus-preserving pancreaticoduodenectomy, whereas 2 underwent standard pancreaticoduodenectomy. Histopathology revealed pancreatic head cancer in all 6 patients; 2 cases were poorly differentiated adenocarcinoma, and 4 were moderately differentiated adenocarcinoma. By TNM classification, T staging showed all of them to be in the T3 stage (tumor extended directly into duodenum, bile duct, or peripancreatic tissues), while N staging showed N1 (regional lymph node metastasis) in 5 cases and N0 (no regional lymph node metastasis) in one case. Complete resection was possible in all 6 patients, and there was no operation-related morbidity or mortality in these patients. In our 6 patients with pancreatic resection, pancreatic cancer recurred in 3 patients after surgery. As for survival, one patient died 12 months after surgery (2 months after recurrence). Remaining 5 patients are still alive (median follow-up, 12 months). The one patient who refused operation revisited our hospital 7 months after the initial steroid trial, and he was finally diagnosed as having pancreatic cancer with liver metastasis (figure 6).

Analysis of the patients with positive steroid responsiveness who were finally confirmed as having AIP

A prospectively collected database of 15 patients with positive steroid responsiveness who were finally confirmed as having AIP were analyzed retrospectively (table 1).

Table 1 Clinical and imaging features of patients with positive steroid responsiveness who were finally confirmed as AIP

Case No.	Age /Sex	Chief complaint	Imaging Findings		Laboratory Results					Histopathologic Findings		F/U period (mo.)	Final Diagnosis
			CT (pancreas)	Pancreatogram (ERCP/MRCP)	IgG (mg/dL)	IgG4 (mg/dL)	Auto-anti bodies	CEA (ng/mL)	CA19-9 (U/mL)	Pancreas	Bile duct		
1	44/M	Wt.loss	Mass	Diffuse irregular narrowing	1,370	48	RF	1.8	3	US†-guided core biopsy: fibrosis	Endobiliary biopsy & cytology: N-C,	38	AIP
2	52/F	Jaundice	Focal enlargement	Focal narrowing with upstream dilatation, Double duct sign	1,340	48	Negative	1.2	28	US-guided core biopsy: fibrosis	Endobiliary biopsy & cytology: negative§	29	AIP
3	36/M	Jaundice	Mass	Diffuse irregular narrowing	1,060	50	RF	1.0	35	US-guided core biopsy: fibrosis	Endobiliary biopsy & cytology: negative	39	AIP
4	70/M	Jaundice	Focal enlargement	Diffuse irregular narrowing	2,370	910	ANA	0.9	21	US-guided core biopsy: fibrosis	Endobiliary biopsy & cytology: negative	27	AIP
5	71/M	Jaundice	Focal enlargement	Focal narrowing with upstream dilatation, Double duct sign	1,540	529	Negative	0.6	120	US-guided core biopsy: lymphoplasma cell infiltration	Endobiliary biopsy & cytology: negative	23	AIP
6	67/M	Abd. pain	Focal enlargement	Focal narrowing with upstream dilatation, Double duct sign	2,190	540	RF	1.0	14	EUS-FNA: inflammatory cells	Endobiliary biopsy & cytology: negative	13	AIP
7	73/M	Abd. pain	Mass	Focal narrowing with upstream dilatation, Double duct sign	2,570	720	Negative	2.3	15	EUS: no visualized mass	Endobiliary biopsy & cytology: negative	17	AIP

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8	65/M	Abd. pain	Diffuse enlargement	Focal narrowing with upstream dilatation,	5,920	1,630	Negative	0.8	3	N-C	Endobiliary biopsy & cytology: N-C	11	AIP
9	78/M	Jaundice	Diffuse enlargement	Focal narrowing with upstream dilatation, Double duct sign	1,530	72	ANA, RF	1.0	14	EUS: no visualized mass	Endobiliary biopsy & cytology: negative	6	AIP
10	68/M	Jaundice	Diffuse enlargement	Focal narrowing with upstream dilatation, Double duct sign	1,830	105	Anti-histone	5.0	21	US-guided core biopsy: lymphoplasma cell infiltration and fibrosis	Endobiliary biopsy & cytology: negative	47	AIP
11	68/M	Jaundice	Diffuse enlargement	Focal narrowing with upstream dilatation, Double duct sign	3,550	1,360	ANA	3.1	51	N-C	Endobiliary biopsy & cytology: negative	43	AIP
12	63/M	Jaundice	Diffuse enlargement	Focal narrowing with upstream dilatation, Double duct sign	1,780	658	RF	3.3	108	US-guided core biopsy: lymphoplasma cell infiltration and fibrosis	Endobiliary biopsy & cytology: negative	41	AIP
13	66/F	Abd. pain	Mass	Segmental narrowing with upstream dilatation	1,620	41	Negative	0.5	3	EUS: no visualized mass	Endobiliary biopsy & cytology: N-C	6	AIP
14	65/F	Abd. pain	Mass	Segmental narrowing with upstream dilatation Double duct sign	1,560	78	ANCA	2.9	80	US-guided core biopsy: infiltration of neutrophils and eosinophils	Endobiliary biopsy & cytology: negative	40	AIP
15	41/M	Abd. pain	Mass	Focal narrowing with upstream dilatation, Double duct sign	1,140	19	Negative	0.5	3	EUS: no visualized mass Brush cytology via ERCP: negative for malignancy	Endobiliary biopsy & cytology: negative	9	AIP

†Transabdominal ultrasonography, §negative for malignancy

AIP, autoimmune pancreatitis; Abd., abdominal; Wt. loss, weight loss; N-C, not checked; RF, rheumatoid factor; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; EUS-FNA, endoscopic ultrasonography-guided fine needle aspiration; F/U, follow-up; mo., months

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Demographics and clinical features

Fifteen patients (12 men, 3 women) ranged in age from 36 to 78 years (median, 66 years). Most of the patients (80%) were older than 50 years of age and a male predominance (80%) was noted. The frequency of symptoms was as follows: jaundice (53%), abdominal pain (40%), and weight loss (33%). No patient had severe abdominal or back pain associated with attacks of acute pancreatitis. Diabetes was found in 73% of the patients.

Radiographic, serologic and histopathologic features

On dynamic CT, 5 cases had diffuse pancreatic enlargement; 4 had focal pancreatic enlargement; 6 had a suspected pancreatic mass. EUS was performed in the 6 cases with a suspected pancreatic mass on CT but a mass was visualized in only one case. On ERCP examination, 3 patients showed diffuse irregular narrowing of the main pancreatic duct; 2 showed segmental main pancreatic ductal narrowing with upstream dilatation; and 10 showed focal narrowing with upstream dilatation. Double duct sign was noted in 67% (10 of 15) of patients.

Serum IgG level was elevated (≥1,800 mg/dL) in 40% (6 of 15) of the patients and serum IgG4 level was elevated (≥135 mg/dL) in 47% (7 of 15). Autoantibodies were detected in 9 of 15 cases. Autoantibodies against lactoferrin and carbonic anhydrase II were not checked in our study. Overall, 80% (12 of 15) of the patients had serologic evidence of AIP. Serum levels of CEA were normal in all patients and levels of CA 19-9 were elevated to greater than 37 U/mL and 100 U/ml in 27% (4 of 15) and 13% (2 of 15) of patients, respectively.

Histopathologic examination of the pancreas was performed in 10 patients; EUS-FNA (endoscopic ultrasonography-guided fine needle aspiration) was done in one, transpapillary brush cytology for narrowed pancreatic duct was performed in one case, and transabdominal US-guided pancreatic core biopsy was performed in 8. The pathologic results were as follows: 2 cases of lymphoplasmacytic infiltration and fibrosis, 1 of lymphoplasmacytic infiltration only, 4 of fibrosis only, and 3 of non-specific inflammatory cells. Endobiliary brush cytology and endobiliary biopsy were done in all who had distal common bile duct strictures (12 of 15), which showed no malignant cells.

Atypical imaging features for AIP

Atypical radiographic features which were the reasons for short-interval imaging in patients finally diagnosed as AIP were analyzed: 6 cases showed suspected pancreatic mass, 4 had focal pancreatic enlargement; 10 showed focal main pancreatic ductal narrowing; and 3 had main portal vein invasion due to inflammatory cell infiltration.

Analysis of the patients with negative steroid responsiveness who were finally confirmed as having pancreatic cancer

A Prospectively collected database of 7 patients with negative responses to steroids who were finally diagnosed as having pancreatic cancer were analyzed retrospectively (table 2).

Demographics and clinical features

Seven patients (6 men, 1 woman) ranged in age from 44 to 68 years (median, 53 years). Most of the patients (86%) were older than 50 years of age and a male predominance (86%) was also noted. The frequency of symptoms was as follows: jaundice (57%), weight loss (57%), and abdominal pain (43%). Diabetes was found in 43% of the patients.

Radiographic, serologic and histopathologic features

On dynamic CT, 4 cases had diffuse pancreatic enlargement and 3 had focal pancreatic enlargement. On ERCP examination, all 7 cases showed focal main pancreatic ductal narrowing with upstream duct dilatation and double duct sign. There was no case showing evidence of

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disease progression including enlargement of primary mass or appearance of new lymph node metastasis in follow-up images except one case of pseudocysts development probably related to obstructive pancreatitis. In all cases, serum levels of IgG and IgG4 were within normal range and autoantibodies were not detected. Serum levels of CEA were normal in all of the 7 patients and levels of CA 19-9 were elevated to greater than 37 U/mL and 100 U/ml in 57% (4 of 7) and 14% (1 of 7) of the patients, respectively.

Histopathologic examination of pancreas by EUS-FNA was performed in 4 cases, which showed nonspecific inflammatory cells in all. Endobiliary brush cytology and biopsy were performed on all patients. No malignant cells were found.

Radiographic features unfit for classic imaging of pancreatic cancer

Imaging features which lead to the suspicion of AIP in patients finally diagnosed as having pancreatic cancer were also analyzed: 4 cases showed diffuse pancreatic enlargement; 6 cases showed relatively mild upstream duct dilatation despite of localized stenosis, 1 case had no discrete mass on pancreas dynamic CT despite of a long segmental main pancreatic ductal narrowing and marked upstream dilatation; 4 cases showed double duct sign while no mass was found by CT.

Table 2 Clinical and imaging features of patients with negative steroid responsiveness who were finally confirmed as pancreatic cancer

Case No.	Age /Sex	Chief complaint	Imaging Findings		Laboratory Results					Histopathologic Findings		Final Diagnosis
			CT (pancreas)	Pancreatogram (ERCP/MRCP)	IgG (mg/dL)	IgG4 (mg/dL)	Auto-anti bodies	CEA (ng/mL)	CA19-9 (U/mL)	Pancreas	Bile duct	
1	53/M	Abd. pain	Diffuse enlargement	Focal narrowing with upstream dilatation, Double duct sign	1,090	65	negative	0.4	83	EUS-FNA: benign pancreatic cells	Endobiliary biopsy & cytology: negative§	Pancreatic cancer Completely resected
2	68/F	Abd. pain	Diffuse enlargement	Focal narrowing with upstream dilatation, Double duct sign	1,600	41	negative	1.8	31	EUS: no visualized mass	Endobiliary biopsy & cytology: negative	Pancreatic cancer Completely resected
3	62/M	Jaundice	Focal enlargement	Focal narrowing with upstream dilatation, Double duct sign	1,290	64	negative	0.5	579	EUS-FNA: non-specific inflammatory cells	Endobiliary biopsy & cytology: negative	Pancreatic cancer Completely resected
4	51/M	Abd. pain	Mass, diffuse enlargement	Focal narrowing with upstream dilatation, Double duct sign	785	3	negative	0.9	75	EUS: no visualized mass	Endobiliary biopsy & cytology: negative	Pancreatic cancer Completely resected
5	44/M	Jaundice	Focal enlargement	Focal narrowing with upstream dilatation, Double duct sign	996	63	negative	1.1	46	N-C	Endobiliary biopsy & cytology: negative	Pancreatic cancer Completely resected
6	53/M	Jaundice	Mass	Focal narrowing with upstream dilatation, Double duct sign	1,340	68	negative	3.5	15	EUS-FNA: neutrophils with ductal cells	Endobiliary biopsy & cytology: negative	Pancreatic cancer Completely resected
7	51/M	Jaundice	Mass, diffuse enlargement	Focal narrowing with upstream dilatation, Double duct sign	1,040	36	negative	0.6	20	EUS-FNA: benign pancreatic cells	Endobiliary biopsy & cytology: negative	Pancreatic cancer

§negative for malignancy; Abd., abdominal; Wt. loss, weight loss; N-C, not checked; EUS-FNA, endoscopic ultrasonography-guided fine needle aspiration

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DISCUSSION

The most important point in diagnosing AIP is to distinguish it from pancreatic cancer. Frequent stenosis of common bile duct, elevated level of serum CA 19-9, focal pancreatic enlargement or focal narrowing of the main pancreatic duct, inflammatory pseudotumor of the pancreas, and angiographic abnormalities can cause confusion in the differential diagnosis between AIP and pancreatic cancer.[6, 11, 20] Because of this diagnostic uncertainty, many patients undergo unnecessary major operations for benign lesions. Indeed, around 20% of patients with AIP were misdiagnosed as having pancreatobiliary malignancies and were surgically treated in one Japanese study.[6] Conversely, according to a study by the Mayo Clinic, up to 15% of pancreatic cancer patients were misdiagnosed as having AIP on CT imaging alone.[21]

In our study, steroids were given only to clinically suspected AIP patients with initial negative work-up for malignancies. That is because it may be unethical to attempt steroid trial in patients with a definite diagnosis of pancreatic cancer. Hence, only a small population of pancreatic cancer was included in our study. Actually, pancreatic cancers were diagnosed in 1,091 patients and major pancreatic surgeries for pancreatic cancer were done on 348 patients at our institution during the study period.

The known typical imaging features of AIP are diffuse enlargement of pancreas with delayed (rim) enhancement and diffuse or segmental irregular narrowing of the main pancreatic duct.[8, 17] With the increasing number of AIP cases reported, however, various atypical imaging findings of AIP are being encountered.[6, 10, 11, 22] By the Mayo Clinic report, only 27% of patients with AIP showed typical imaging,[4] and one Japanese study found that only 19% showed typical radiographic findings.[6] Atypical imaging features of AIP include a discrete pancreatic mass, focal pancreatic enlargement, focal narrowing of the main pancreatic duct with or without upstream duct dilatation, double duct sign, and so on.[4] In our study, it was extremely difficult to differentiate AIP with mass or focal stricture from pancreatic cancer solely based on the imaging features.

Hamano *et al*. reported that specificity of serum IgG4 levels for distinguishing AIP from pancreatic cancer was 97%.[23] In a recent study, however, elevations in serum IgG4 were seen in about 10% (13 of 135) of pancreatic cancer patients.[24] It appears that serum IgG4 elevations are characteristic, but not exclusively diagnostic, of AIP, and false positive elevations do occur. In our study, IgG4 levels were elevated in only 47% of AIP patients and were not elevated in any pancreatic cancer patient. There are several reports of serum levels of CA 19-9 being elevated in AIP patients (up to 2,900 U/mL) with subsequent normalization after steroid therapy, suggesting that this elevation was induced by cholestasis, cholangitis, or pancreatitis.[10, 20] In our study, serum levels of CA 19-9 were elevated (>37 U/ml) in 57% of patients with pancreatic cancer and 27% of patients with AIP, while levels of CEA were normal in all patients of both groups. Although CEA and CA 19-9 are the most frequently studied serum tumor markers in diagnosis of pancreatic cancer,[25] they may not be specifically used to diagnose pancreatic cancer because of lack of sensitivity and specificity.

While lymphoplasmacytic sclerosing pancreatitis (LPSP), that is, periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis, is known as the pathognomonic finding for AIP,[4, 26] one study showed that LPSP histology of pancreas was observed in only 26% of core biopsy specimens from AIP patients.[27] This may occur because pancreatic biopsies do not show the complete spectrum of changes in LPSP due to small sample size and possible sampling error. In our AIP patients who underwent pancreatic biopsy, none had histological evidence of AIP in the form of LPSP. The role of preoperative histologic examination in patients with suspected AIP may therefore be used to exclude other diseases such as cancer rather than to provide definitive evidence for a diagnosis of AIP.[2, 28]

In a broad sense, response to steroids may include improvement in clinical symptoms, normalization of elevated levels of serum IgG/IgG4, and reversion of abnormal pancreatic

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imaging.[28, 29] Due to anti-inflammatory effect of steroids, pancreatic enlargement developed by obstructive pancreatitis associated with ductal adenocarcinoma may be relieved with steroid therapy.[6] In our study, therefore, steroid responsiveness was defined not simply as improvement of pancreatic swelling but more stringently to relief of the main pancreatic ductal narrowing and resolution of a pancreatic mass. As a result, our study showed excellent outcomes for a two-week steroid trial in differentiating AIP from pancreatic cancer in a clinical setting of suspected AIP (figure 6).

The reasons for assessing steroid responsiveness after a short duration (2 weeks) of therapy were as follows: (1) radiologic improvement of AIP can occur as early as one to two weeks after steroid therapy;[2, 10, 30] and (2) possible cancer progression in resectable patients during a trial of steroid therapy is a concern. In our study, however, complete resection was possible in all 6 patients (100%) who underwent surgery after the two-week trial. Given the resection rate of less than 20% for pancreatic ductal adenocarcinoma,[31, 32] a two-week delay in operation may not adversely affect the surgical outcome of potentially resectable pancreatic cancer. With a two-week steroid trial, we were able to diagnose 15 AIP patients without the necessity of surgical exploration and detect 7 pancreatic cancer patients without negative influence on surgical outcome.

Based on our results, a trial with steroids can be a useful diagnostic tool when used in a "proper fashion." A steroid trial should not be used as a substitute for a thorough search for etiology and should be given only to suspected AIP patients with a negative work-up for pancreatobiliary malignancies.[4, 33] If possible, every effort should be made to obtain tissue specimens from pancreatic and bile duct lesions. Histopathologic diagnosis using biopsy or cytology specimens may not be perfect, but it is still the best way to rule out malignancy preoperatively, at least for now. Although EUS is superior to other radiographic modalities in the detection of a pancreatic mass,[34-36] and sensitivity of EUS-FNA for solid pancreatic lesions is reported to be nearly 90%,[36] we should keep in mind that EUS±FNA may show false negative results for malignancy as in our cases (table 2). Even after pancreatic biopsy or cytology shows negative results, if there are any clinical or radiological doubts on the presence of malignancy, short-interval imaging after the initiation of steroid therapy should be used to assess steroid responsiveness. If the response to steroids is negative, surgical exploration should be performed.

It is not certain whether our excellent results will be reproducible in a study conducted by general gastroenterologists at community based hospitals, since the expertise, local facilities, and clinical experience vary widely from center to center. Our institution is a tertiary referral center, and this study was performed by specialists in the field of pancreatology. Clinicians must be cognizant that AIP is a rare disease and till now, corticosteroid therapy is likely not advisable unless a high suspicion for AIP is present based on the cardinal features of this disease.[37]

In conclusion, in the clinical setting of suspected AIP, with a continued need for differentiation from pancreatic cancer due to atypical imaging for AIP, "a two-week steroid trial and subsequent assessment of its response" may be helpful in confirming the diagnosis of AIP without negative consequences for resectable pancreatic cancer. However, the use of steroids to make a diagnosis should be done after thorough work-up for excluding pancreatobiliary malignancies in patients highly suspected of AIP based on the cardinal features of this disease.

Competing interest**: None to declare**
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FIGURE LEGENDS

Figure 1 Therapeutic algorithm for study patients with clinically suspected autoimmune pancreatitis (AIP)

Figure 2 Serial images from a 66-year-old woman with positive steroid responsiveness who was finally diagnosed as having autoimmune pancreatitis (patient 13 in table 1)
(A, B) Pre-treatment: Dynamic CT showed a pancreatic mass at body (asterisk) and ERCP showed long segmental narrowing (arrows) of the main pancreatic duct with relatively mild upstream dilatation. (C, D) Post-treatment: After the two-week steroid trial, the main pancreatic duct improved to almost normal and the mass was markedly reduced.

Figure 3 Serial images from a 71-year-old man with positive steroid responsiveness who was finally diagnosed as having autoimmune pancreatitis (patient 5 in table 1)
(A, B, C) Pre-treatment: Dynamic CT showed focal enlargement of pancreas head, and ERP showed focal narrowing (arrows) of the main pancreatic duct with upstream dilatation. (D) Post-treatment: After the two-week steroid trial, focal narrowing (arrows) reverted to almost its normal size with a resolution of upstream duct dilatation.

Figure 4 Serial images from a 53-year-old man with negative steroid responsiveness who was finally diagnosed as having pancreatic cancer (patient 1 in table 2).
(A, B, C) Pre-treatment: Dynamic CT showed diffuse pancreatic enlargement without a discrete mass and MRCP showed focal narrowing (arrows) of the main pancreatic duct with mild upstream dilatation. (D) Post-treatment: After the two-week steroid trial, there was no improvement in the narrowing (arrows) of the main pancreatic duct and upstream dilatation became more prominent. Pseudocysts around pancreatic head had recently developed.

Figure 5 Serial images from a 68-year-old woman with negative steroid responsiveness who was finally diagnosed as having pancreatic cancer (patient 2 in table 2).
(A, B,C) Pre-treatment: Dynamic CT showed no pancreatic mass despite of long segmental main pancreatic ductal narrowing (arrows) with marked upstream dilatation. (D) Post-treatment: After the two-week steroid trial, there was no improvement in the main pancreatic ductal narrowing (arrows).

Figure 6 Clinical and surgical outcome

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Figure 1

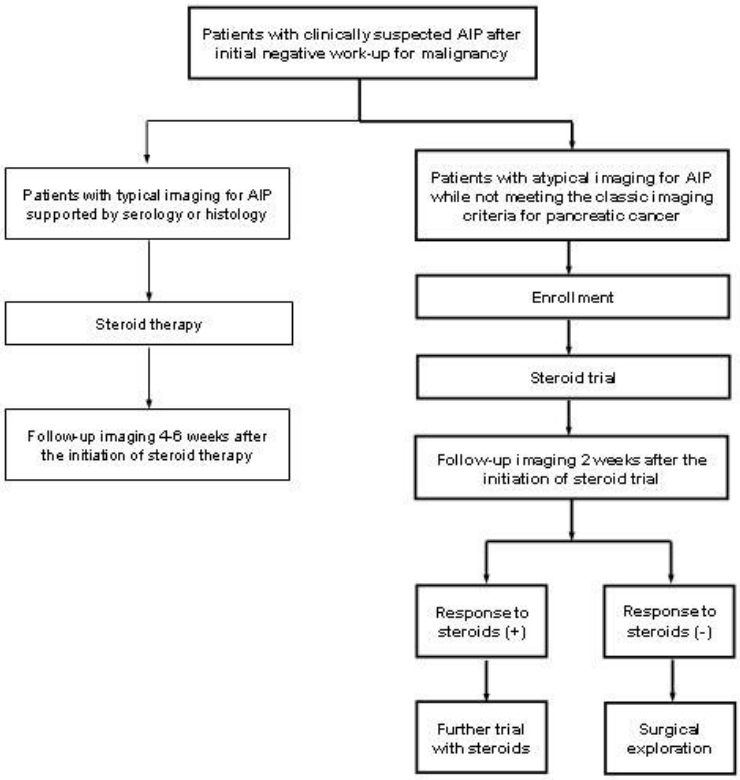

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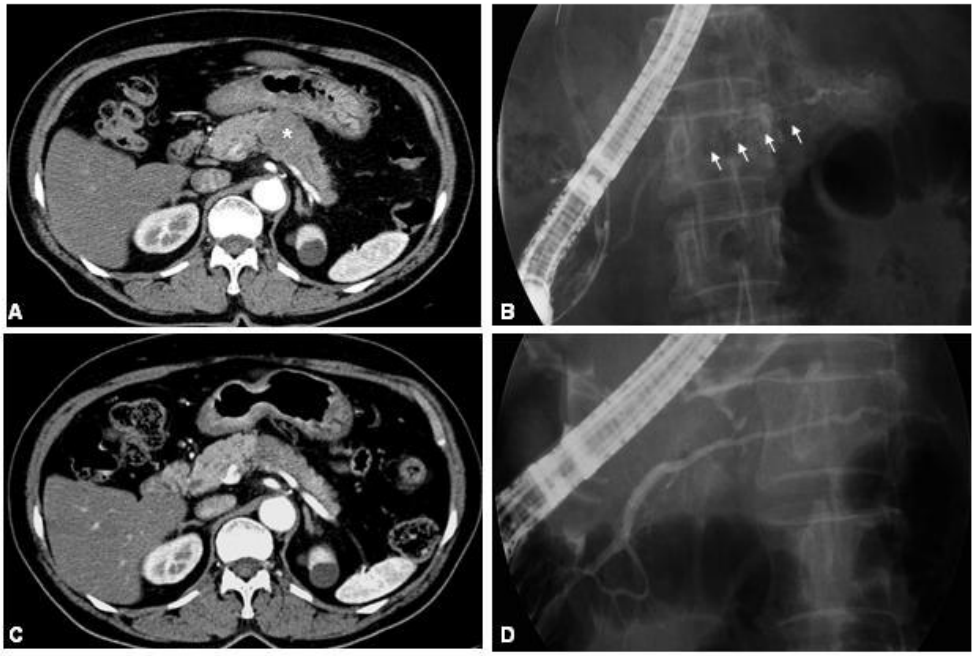
Figure 2



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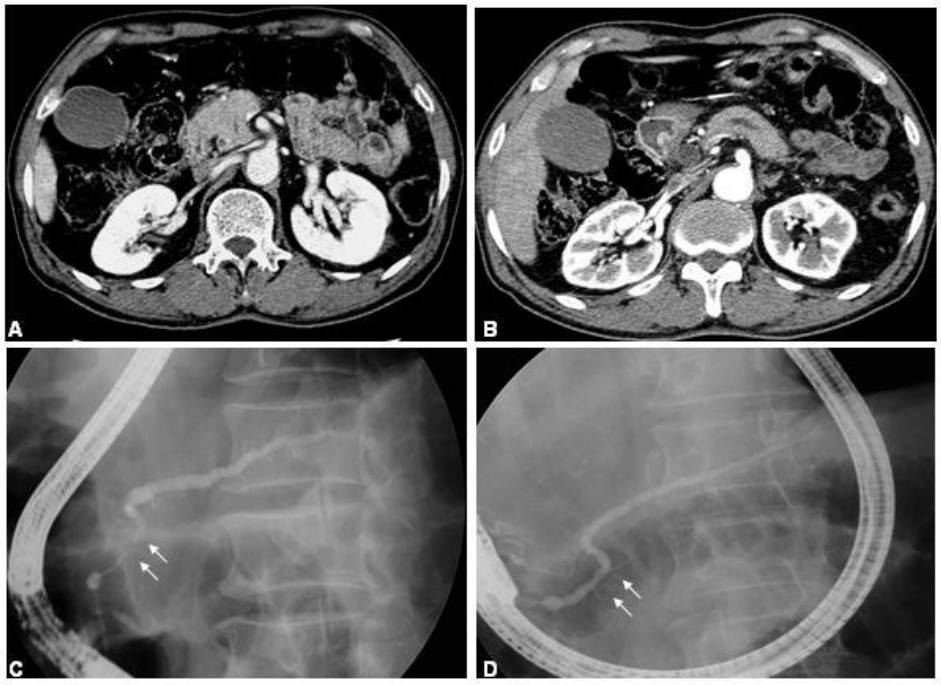

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Figure 4

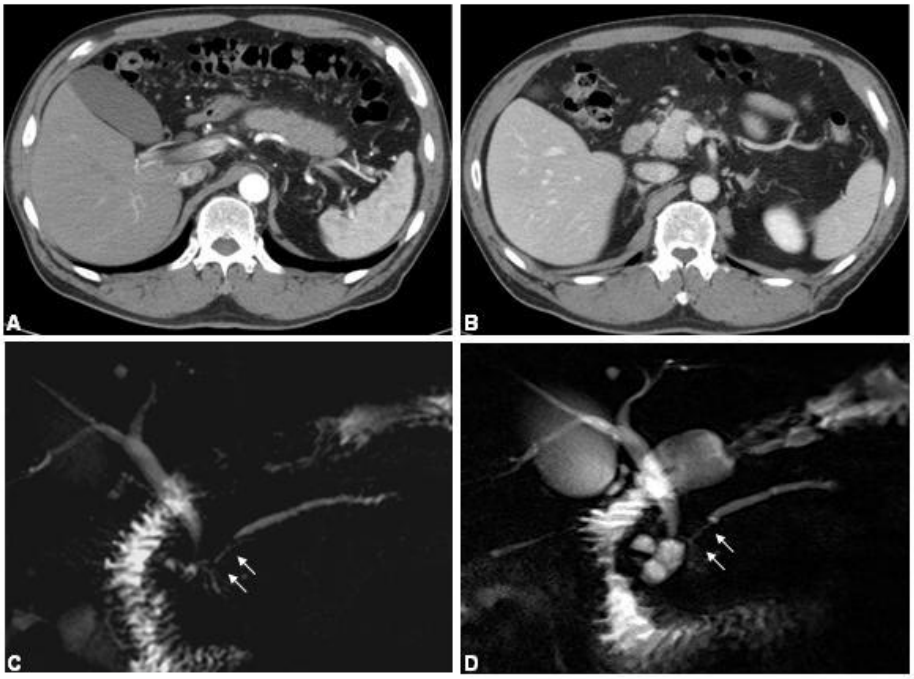

Figure 5

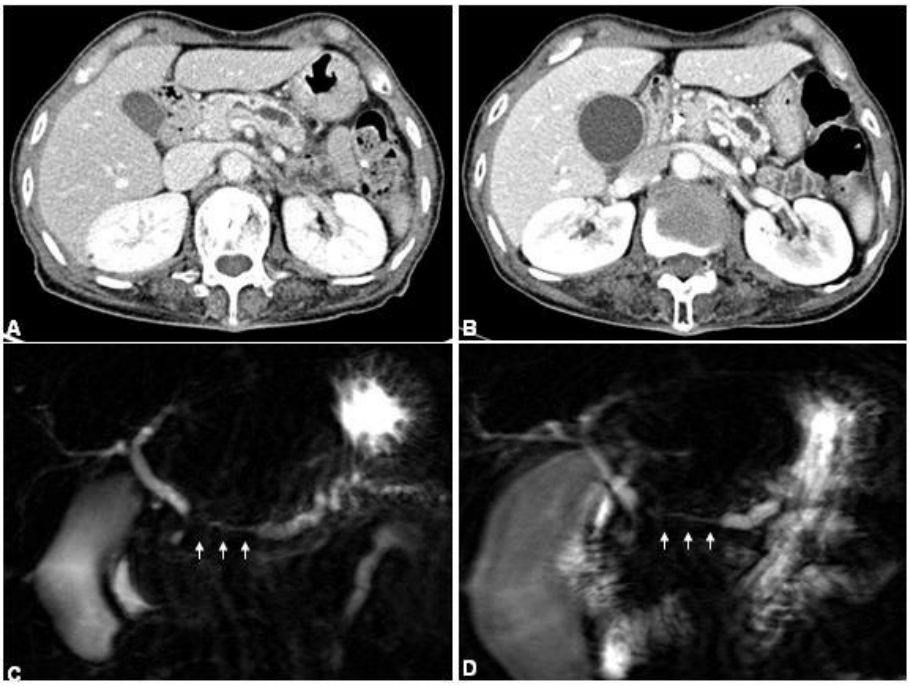

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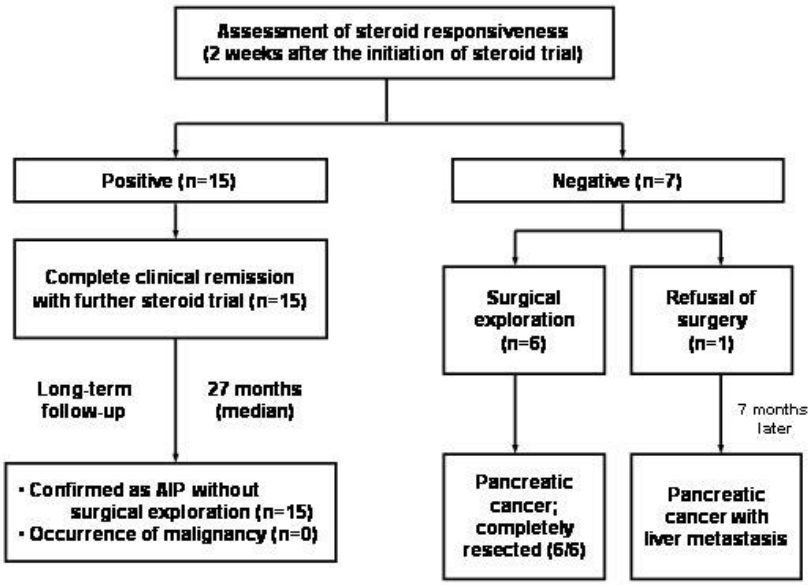
Figure 6



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