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Is a 2-week steroid trial after initial negative investigation for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? A prospective outcome study

S-H Moon, M-H Kim, D H Park, C Y Hwang, S J Park, S S Lee, D W Seo, S K Lee

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 controversy regarding 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 2-week steroid trial and subsequent assessment of its response” is a useful diagnostic tool for the differentiation of AIP from pancreatic cancer. A further aim was to discover the surgical and clinical outcome for a patient who followed the treatment algorithm based on the steroid responsiveness.

Patients and methods: From January 2004 to June 2007, in the setting of clinically suspected AIP, 22 consecutive patients with atypical imaging for AIP, while not meeting the classic imaging criteria for pancreatic cancer, were challenged to undergo 2 weeks of steroid therapy (0.5 mg/kg of oral prednisolone per day). After the 2-week steroid trial, steroid responsiveness was assessed based on a marked improvement of narrowing of the main pancreatic duct 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. The final diagnosis was made by surgical exploration or long-term clinical and radiological 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 for differentiation from pancreatic cancer due to atypical imaging for AIP, “a 2-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 only by specialists in pancreatology.

Autoimmune pancreatitis (AIP) can be defined as a chronic inflammation of the pancreas due to an autoimmune mechanism. AIP is a very attractive disease to doctors in terms of its impressive response to steroid therapy. 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. 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. This is because even in patients with AIP, histology and serology can reveal negative results, and imaging findings are not always typical for AIP. Including steroid responsiveness in 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.

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. 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 merely to distinguish AIP from pancreatic cancer. Japanese investigators worry about the possibility of cancer progression during a trial of steroid therapy in a resectable patient.

To date, details of the specificity of steroid responsiveness for AIP have 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 2-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 of AIP based on imaging findings

Based on the previously reported cardinal features of AIP, AIP was initially suspected when the imaging findings showed one of the following features (vs pancreatic cancer): (1) diffuse pancreatic enlargement with or without a capsule-like rim (vs parenchymal atrophy above the stricture); (2) delayed enhancement of the pancreatic mass...
They were treated with steroids, and follow-up imaging was performed in patients with negative results for malignancy. AIP was defined as diffuse pancreatic ductal narrowing due to marked upstream duct dilatation; double duct sign without a pancreatic mass in a patient with obstructive jaundice (vs a visible mass); association of hilar or intrahepatic duct strictures (vs common bile duct stricture alone); or other organ involvement unusual for pancreatic cancer such as salivary gland, kidney or retroperitoneal fibrosis (vs no other organ involvement).

Initial investigation to exclude malignancy before patient enrolment
Prior to the steroid trial, an investigation to exclude pancreatic malignancies was performed. Pancreas dynamic CT and endoscopic retrograde cholangiopancreatography (ERCP) were performed in all patients. Serum levels of immunoglobulin G (IgG) and IgG4, and tumour 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 visualised, 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 investigation, 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 investigation. Among them, 26 patients (20 men and 6 women) had typical imaging for AIP, which was defined as diffuse pancreatic ductal narrowing with delayed (rim) enhancement and diffuse or segmental irregular narrowing of the main pancreatic duct. They were treated with steroids, and follow-up imaging was performed 4–6 weeks after the initiation of steroid therapy.

The remaining 22 patients with clinically suspected AIP were enrolled in the study and prospectively managed by the treatment algorithm shown in fig 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 2 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 1.5 T 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 2 and 6 months after the initiation of steroid therapy. After achieving complete clinical remission, the laboratory tests were carried out every 2–3 months, and imaging studies such as CT scans or magnetic resonance imaging (MRI)/MRCP every 6 months until December 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 <3 weeks, regardless of dosage, is known to have an insignificant effect on the hypothalamic–pituitary–adrenal axis. A final diagnosis was made by surgical exploration or long-term clinical and radiological 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 narrowing of the main pancreatic duct or in the pancreatic mass after steroid therapy.

Terminology
A mass was defined as a lesion that had a different density compared with the surrounding pancreatic tissue by CT scan, whereas pancreatic enlargement was defined as an increase in the size of the gland without a discrete mass. We classified the extent of the main pancreatic ductal narrowing into three 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.

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 2-week steroid trial, 15 of 22 patients showed a positive response to steroids. The narrowing of the main pancreatic duct 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 (figs 2 and 3). In all patients with an initial response to steroids, complete clinical (symptomatic, radiological and serological) 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/day, 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 five patients by December 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 need for surgical exploration based on the revised Kim criteria.

Surgical outcome of the negative steroid responsiveness group
With the 2-week steroid trial, a follow-up ERCP/MRCP of 7 patients did not show any improvement in the narrowing of the main pancreatic duct (figs 4 and 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 two
underwent standard pancreaticoduodenectomy. Histopathology revealed pancreatic head cancer in all six patients: two cases were poorly differentiated adenocarcinoma and four were moderately differentiated adenocarcinoma. By TNM classification, T staging showed all of them to be in the T3 stage (tumour extended directly into the duodenum, bile duct or peripancreatic tissues), while N staging showed N1 (regional lymph node metastasis) in five cases and N0 (no regional lymph node metastasis) in one case. Complete resection was possible in all six patients, and there was no operation-related morbidity or mortality in these patients. In our six patients with pancreatic resection, pancreatic cancer recurred in three patients after surgery. As regards survival, one patient died 12 months after surgery (2 months after recurrence). The remaining five patients are still alive (median follow-up 12 months). The one patient who refused an operation revisited our hospital 7 months after the initial steroid trial, and he was finally diagnosed as having pancreatic cancer with liver metastasis (fig 6).

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) Pretreatment: dynamic CT showed a pancreatic mass at the body (asterisk), and endoscopic retrograde cholangiopancreatography showed long segmental narrowing (arrows) of the main pancreatic duct with relatively mild upstream dilatation. (C, D) Post-treatment: after the 2-week steroid trial, the main pancreatic duct improved to almost normal and the mass was markedly reduced.
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 analysed retrospectively (table 1).

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, serological and histopathological features

On dynamic CT, five cases had diffuse pancreatic enlargement; four had focal pancreatic enlargement; and six had a suspected pancreatic mass. EUS was performed in the six cases with a suspected pancreatic mass on CT, but a mass was visualised in only one case. On ERCP examination, three patients showed diffuse irregular narrowing of the main pancreatic duct; two showed segmental main pancreatic ductal narrowing with upstream dilatation; and 10 showed focal narrowing with pseudocysts around the pancreatic head.

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–C) Pretreatment: dynamic CT showed focal enlargement of the pancreas head, and endoscopic retrograde cholangiopancreatography showed focal narrowing (arrows) of the main pancreatic duct with upstream dilatation. (D) Post-treatment: after the 2-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–C) Pretreatment: dynamic CT showed diffuse pancreatic enlargement without a discrete mass, and magnetic resonance cholangiopancreatography showed focal narrowing (arrows) of the main pancreatic duct with mild upstream dilatation. (D) Post-treatment: after the 2-week steroid trial, there was no improvement in the narrowing (arrows) of the main pancreatic duct, and upstream dilatation became more prominent. Pseudocysts around the pancreatic head had recently developed.
upstream dilatation. The double duct sign was noted in 67% (10 of 15) of patients.

The serum IgG level was elevated (≥1800 mg/dl) in 40% (6 of 15) of the patients, and the 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 serological evidence of AIP. Serum levels of CEA were normal in all patients, and levels of CA 19-9 were elevated to 37 and 100 U/ml in 27% (4 of 15) and 13% (2 of 15) of patients, respectively.

Histopathological examination of the pancreas was performed in 10 patients; EUS-guided fine needle aspiration (FNA) was done in one case, transpapillary brush cytology for a narrowed pancreatic duct was performed in one case and transabdominal US-guided pancreatic core biopsy was performed in eight. The pathological results were as follows: two cases of lymphoplasmacytic infiltration and fibrosis, one of lymphoplasmacytic infiltration only, four of fibrosis only and three of non-specific inflammatory cells. Endobiliary brush cytology and endobiliary biopsy were done in all patients 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 having AIP were analysed: six cases showed a suspected pancreatic mass; four had focal pancreatic enlargement; 10 showed focal main pancreatic ductal narrowing; and three 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 seven patients with negative responses to steroids who were finally diagnosed as having pancreatic cancer was analysed 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, serological and histopathological features
On dynamic CT, four cases had diffuse pancreatic enlargement and three had focal pancreatic enlargement. On ERCP examination, all seven cases showed focal main pancreatic ductal narrowing with upstream duct dilatation and double duct sign. There was no case showing evidence of disease progression including enlargement of the primary mass or appearance of new lymph node metastasis in follow-up images, except one case of development of pseudocysts probably related to obstructive pancreatitis. In all cases, serum levels of IgG and IgG4 were within the normal range and autoantibodies were not detected. Serum levels of CEA were normal in all of the seven patients, and levels of CA 19-9 were elevated to >37 and 100 U/ml in 57% (4 of 7) and 14% (1 of 7) of the patients, respectively.

Histopathological examination of the pancreas by EUS-FNA was performed in four cases, which showed non-specific 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 analysed: four cases showed diffuse pancreatic enlargement; six cases showed relatively mild upstream duct dilatation despite localised stenosis, one case had no discrete mass on pancreas dynamic CT despite a long segmental main pancreatic ductal narrowing and marked upstream dilatation; and four cases showed double duct sign, while no mass was found by CT.
## Table 1 Clinical and imaging features of patients with positive steroid responsiveness who were finally confirmed as having AIP

<table>
<thead>
<tr>
<th>Case no</th>
<th>Age/sex</th>
<th>Chief complaint</th>
<th>Imaging findings</th>
<th>Laboratory results</th>
<th>Histopathological findings</th>
<th>F/U period (months)</th>
<th>Final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44/M</td>
<td>Wt loss</td>
<td>Mass</td>
<td>Diffuse irregular narrowing</td>
<td>Pancreatogram (ERCP/MRCP)</td>
<td>IgG (mg/dl) 48</td>
<td>RF 1.8</td>
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<td>2</td>
<td>52/F</td>
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<td>Pancreatogram (ERCP/MRCP)</td>
<td>IgG (mg/dl) 48</td>
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<td>Mass</td>
<td>Diffuse irregular narrowing</td>
<td>Pancreatogram (ERCP/MRCP)</td>
<td>IgG (mg/dl) 1060</td>
<td>RF 1.0</td>
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<tr>
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<td>Jaundice</td>
<td>Focal enlargement</td>
<td>Focal narrowing with upstream dilatation, double duct sign</td>
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<td>ANA 5.0</td>
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<td>Focal narrowing with upstream dilatation, double duct sign</td>
<td>Pancreatogram (ERCP/MRCP)</td>
<td>IgG (mg/dl) 2190</td>
<td>RF 1.0</td>
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<td>73/M</td>
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<td>Focal narrowing with upstream dilatation, double duct sign</td>
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<td>IgG (mg/dl) 2570</td>
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<td>Focal narrowing with upstream dilatation</td>
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<td>70/M</td>
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<td>Diffuse enlargement</td>
<td>Focal narrowing with upstream dilatation, double duct sign</td>
<td>Pancreatogram (ERCP/MRCP)</td>
<td>IgG (mg/dl) 1530</td>
<td>ANA, RF 1.0</td>
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<td>Segmental narrowing with upstream dilatation</td>
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<td>IgG (mg/dl) 1620</td>
<td>Negative 0.5</td>
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<td>Mass</td>
<td>Segmental narrowing with upstream dilatation, double duct sign</td>
<td>Pancreatogram (ERCP/MRCP)</td>
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<td>ANCA 2.9</td>
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<td>Mass</td>
<td>Focal narrowing with upstream dilatation, double duct sign</td>
<td>Pancreatogram (ERCP/MRCP)</td>
<td>IgG (mg/dl) 1140</td>
<td>Negative 0.5</td>
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</table>

**Note:** *Negative for malignancy.*

Abd, abdominal; AIP, autoimmune pancreatitis; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; F/U, follow-up; IgG, immunoglobulin G; MRCP, magnetic resonance cholangiopancreatography; N-C, not checked; RF, rheumatoid factor; US, transabdominal ultrasound; Wt loss, weight loss.
Table 2  Clinical and imaging features of patients with negative steroid responsiveness who were finally confirmed as having pancreatic cancer

<table>
<thead>
<tr>
<th>Case no</th>
<th>Age/sex</th>
<th>Chief complaint</th>
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<th>Histopathological findings</th>
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<td>53/M</td>
<td>Abd pain</td>
<td>Diffuse</td>
<td>Focal narrowing with upstream dilatation, double duct sign</td>
<td>IgG (mg/dl) 1090</td>
<td>IgG4 (mg/dl) 65</td>
<td>Autoantibodies Negative</td>
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<tr>
<td>2</td>
<td>68/F</td>
<td>Abd pain</td>
<td>Diffuse</td>
<td>Focal narrowing with upstream dilatation Double duct sign</td>
<td>IgG (mg/dl) 1600</td>
<td>IgG4 (mg/dl) 41</td>
<td>Autoantibodies Negative</td>
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<tr>
<td>3</td>
<td>62/M</td>
<td>Jaundice</td>
<td>Focal</td>
<td>Focal narrowing with upstream dilatation Double duct sign</td>
<td>IgG (mg/dl) 1230</td>
<td>IgG4 (mg/dl) 64</td>
<td>Autoantibodies Negative</td>
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<tr>
<td>4</td>
<td>51/M</td>
<td>Abd pain</td>
<td>Mass, diffuse</td>
<td>Focal narrowing with upstream dilatation Double duct sign</td>
<td>IgG (mg/dl) 785</td>
<td>IgG4 (mg/dl) 3</td>
<td>Autoantibodies Negative</td>
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<td>IgG4 (mg/dl) 63</td>
<td>Autoantibodies Negative</td>
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<td>IgG4 (mg/dl) 68</td>
<td>Autoantibodies Negative</td>
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<tr>
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<td>51/M</td>
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<td>IgG (mg/dl) 1040</td>
<td>IgG4 (mg/dl) 36</td>
<td>Autoantibodies Negative</td>
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</table>

*Negative for malignancy.

Abd, abdominal; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FNA, fine needle aspiration; IgG, immunoglobulin G; MRCP, magnetic resonance cholangiopancreatography; N-C, not checked.
DISCUSSION

The most important factor in diagnosing AIP is to distinguish it from pancreatic cancer. Frequent stenosis of the common bile duct, an elevated level of serum CA 19-9, focal pancreatic enlargement or focal narrowing of the main pancreatic duct, an inflammatory pseudotumour of the pancreas and angiographic abnormalities can cause confusion in the differential diagnosis between AIP and pancreatic cancer. Because of this diagnostic uncertainty, many patients undergo unnecessary major operations for benign lesions. Indeed, in one Japanese study, around 20% of patients with AIP were misdiagnosed as having pancreatobiliary malignancies and were surgically treated. 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.

In our study, steroids were given only to clinically suspected AIP patients with initial negative investigations for malignancies. This is because it may be unethical to attempt steroid trials 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 1091 patients and major pancreatic surgery for pancreatic cancer was carried out on 348 patients at our institution during the study period.

The known typical imaging features of AIP are diffuse enlargement of the pancreas with delayed (rim) enhancement and diffuse or segmental irregular narrowing of the main pancreatic duct. With the increasing number of AIP cases reported, however, various atypical imaging findings in AIP are being encountered. According to the Mayo Clinic report, only 27% of patients with AIP showed typical imaging, and one Japanese study found that only 19% showed typical radiographic findings. 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, and double duct sign. In our study, it was extremely difficult to differentiate AIP with a mass or focal stricture from pancreatic cancer solely based on the imaging features.

Hamano et al reported that the specificity of serum IgG4 levels for distinguishing AIP from pancreatic cancer was 97%. In a recent study, however, elevations in serum IgG4 were seen in about 10% (18 of 155) of pancreatic cancer patients. 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 2900 U/ml) with subsequent normalisation after steroid therapy, suggesting that this elevation was induced by cholestasis, cholangitis or pancreatitis. In our study, serum levels of CA 19-9 were elevated in 29% of patients with AIP and 27% of patients with pancreatic cancer, while levels of CEA were normal in all patients of both groups. Although CEA and CA 19-9 are the most frequently studied serum tumour markers in the diagnosis of pancreatic cancer, 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, one study showed that LPSP histology of the pancreas was observed in only 26% of core biopsy specimens from AIP patients. 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 histological 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.

In a broad sense, response to steroids may include improvement in clinical symptoms, normalisation of elevated levels of serum IgG/IgG4 and reversion of abnormal pancreatic imaging. Due to the anti-inflammatory effect of steroids, pancreatic enlargement developed from obstructive pancreatitis associated with ductal adenocarcinoma may be relieved with steroid therapy. In our study, therefore, steroid responsiveness was defined not simply as improvement of pancreatic swelling but more stringently as relief of the main pancreatic ductal...
narrowing and resolution of a pancreatic mass. As a result, our study showed excellent outcomes for a 2-week steroid trial in differentiating AIP from pancreatic cancer in a clinical setting of suspected AIP (fig 6).

The reasons for assessing steroid responsiveness after a short duration (2 weeks) of therapy were as follows: (1) radiological improvement of AIP can occur as early as 1–2 weeks after steroid therapy,2 20 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 six patients (100%) who underwent surgery after the 2-week trial. Given the resection rate of <20% for pancreatic ductal adenocarcinoma,34–36 a 2-week delay in operation may not adversely affect the surgical outcome of potentially resectable pancreatic cancer. With a 2-week steroid trial, we were able to diagnose 15 AIP patients without the need for surgical exploration, and we detected seven pancreatic cancer patients without a 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 aetiology and should be given only to suspected AIP patients with a negative investigation for pancreaticobiliary malignancies.37 If possible, every effort should be made to obtain tissue specimens from pancreatic and bile duct lesions. Histopathological 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 the sensitivity of EUS-FNA for solid pancreatic mass, 34–36 and the sensitivity of EUS-FNA for solid malignancy preoperatively, at least for now. Although EUS is performed by specialists in the field of pancreatology. Clinicians at community-based hospitals, since the expertise, local facilities and clinical experience vary widely from centre to centre.

Our institution is a tertiary referral centre, and this study was performed by specialists in the field of pancreatology. Clinicians must be aware that AIP is a rare disease and, as present, corticosteroid therapy is probably not advisable unless a high suspicion for AIP is present based on the cardinal features of this disease.27

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 2-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 reach a diagnosis should be introduced after thorough investigations to exclude pancreaticobiliary malignancies in patients in whom there is a high level of suspicion of AIP based on the cardinal features of this disease.

Competing interests: None.

Ethics approval: The study was approved by the institutional review board.

Patient consent: Obtained.

REFERENCES


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