CLINICAL STUDY

Dilemmas in autoimmune pancreatitis. Surgical resection or not?

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ABSTRACT
Surgical treatment is not commonly recommended in the management of autoimmune pancreatitis. The article describes a dilemma in diagnostics and treatment of a 68-year old man with the mass in the head of the pancreas that mimicked pancreatic cancer and that was diagnosed as a type 1 autoimmune pancreatitis (IgG4-related pancreatitis) after a surgical resection. Diagnosis of the autoimmune pancreatitis is a real clinical challenge, as in the current diagnostic criteria exists some degree of overlap in the findings between autoimmune pancreatitis and pancreatic cancer (indicated by the similarity in radiologic findings, elevation of IgG4, sampling errors in pancreatic biopsy, and the possibility of synchronous autoimmune pancreatitis and pancreatic cancer). Despite the generally accepted corticosteroids as the primary treatment modality in autoimmune pancreatitis, we believe that surgical resection remains necessary in a specific subgroup of patients with autoimmune pancreatitis (Fig. 4, Ref. 37). Text in PDF www.elis.sk.

KEY WORDS: autoimmune pancreatitis, IgG4-related pancreatitis, obstructive jaundice, resection of pancreas.


Introduction

The term “autoimmune pancreatitis“ (AIP) was first proposed by Yoshida and colleagues in 1995(1). AIP is a rare disorder, with a reported overall prevalence known only in Japan, of approximately 2.2/100 000 (2). The peak age of onset is in the seventh decade, with 95 % of patients older than 45 years (2, 3). AIP is at least twice common in men as in women (in 4) and represents 2–10 % of the patients with chronic pancreatitis (2). AIP is a unique form of chronic pancreatitis, which could be classified into two distinct subtypes, type 1 and type 2 (4–6).

Type 1 autoimmune pancreatitis (type 1 AIP) is also known as IgG4-related pancreatitis or lymphoplasmocytic sclerosing pancreatitis (7, 8). It is considered to be a part of a systemic disease named IgG4-related disease (IgG4-RD) and associated with elevated levels of immunoglobulin G subtype 4 (IgG4) producing plasma cells and serum IgG4 elevation (> 140 mg/dl) (7, 9). IgG4-RD has been recognized as a novel clinical entity with multiorgan involvement and an abnormal immunological process of unknown origin; involved organs showing diffuse or focal enlargement and mass-forming or nodular/thickened lesions due to the prominent infiltration of lymphocytes and IgG4-positive plasma cells associated with fibrosis (7). IgG4-RD has been found to affect the pancreas, bile duct tree, liver, gastrointestinal tract, lacrimal glands, salivary glands, central nervous system, thyroid, lungs, kidneys, prostate, retroperitoneum, mediastinum, arteries, lymph nodes, skin, and breast (4, 10). The diagnosis of type 1 AIP is based on histopathologic features characterized by a diffuse lymphoplasmacytic infiltrate with abundant infiltration of IgG4+ plasmocytes > 10 cells per high power field and fibrosis. The fibrosis is invariably organized in a storiform pattern. The inflammatory cells tend to aggregate around ducts, but the periductal infiltrate is seldom as prominent as seen in type 2 AIP and ductal epithelium is preserved. The inflammatory infiltrate also extends into peripancreatic adipose tissue. Obliterative fibrin is readily identified (11).

Type 2 autoimmune pancreatitis (type 2 AIP) is a specific pancreatic disorder, which is not a part of the IgG4-RD spectrum (8) and has different histologic pattern (a dense periductal collar of lymphoplasmacytic inflammation, accompanied by neutrophilic microabscesses within the lumen of the duct, the so called granulocytic epithelial lesion, which often causes destruction and obliteration of the pancreatic duct). The type 2 AIP lacks both elevated levels of serum IgG4 and IgG4-positive plasma cells (6).

The most common presenting symptom of the AIP is obstructive jaundice (up to 75 % of cases) secondary to entrapment of the intrapancreatic bile duct by the inflammatory process and aggravated by the IgG4-associated cholangitis. This occurs in approximately 75 % of patients with the type 1 AIP and 50 % of patients with the type 2 AIP. However, patients with the type 2
AIP present more commonly with acute pancreatitis (34%) and abdominal pain (68%) than patients with the type 1 AIP (12).

A variety of diagnostic scoring systems for the AIP have been advocated around the world. In the United States, Chari and colleagues (13) introduced the mnemonic HISORt criteria based on diagnostic histology, characteristic imaging [on cross-sectional imaging with contrast-enhanced computed tomography or magnetic resonance imaging], pancreas diffusely enlarged, with featureless borders and/or loss of lobular architecture, or “sausage-shaped” (14, 15), elevated serum IgG4 levels on serologic testing, other organ involvement (in type 1 AIP), and response to glucocorticoid therapy. It was one of the most commonly used diagnostic criteria in the United States.

In 2011, an international panel of experts developed International Consensus Diagnostic Criteria (ICDC) for the AIP, which focused on the distinction between type 1 and type 2 AIP (6). These criteria are based on the clinical profile of AIP, including characteristic histology, and imaging, serum IgG4 levels, extrapancreatic manifestations, and response to steroid treatment. For each criterion, there are two levels of evidence: typical or highly suggestive evidence (level 1), and indeterminate/suggestive evidence (level 2). With this stratification, the type 1 AIP can be confirmed with a variety of combinations of level 1 and level 2 evidence. However, definitive diagnosis of the type 2 AIP requires histology (6, 11).

Histology is the “gold standard” for the diagnosis of the AIP. Tissue acquisition for histological diagnosis may be obtained by endoscopic ultrasound (EUS) with core biopsy (4, 16). Fine needle aspiration biopsy, which typically obtain only aspirate for cytology is not recommended for the diagnosis. Core biopsy needle preserves tissue architecture, allowing immunostaining and examination to diagnose AIP (17). The study from Denmark has recently demonstrated that laparoscopic or percutaneous ultrasound-guided core needle biopsy had the highest sensitivity for diagnosis of AIP in comparison to endoscopic ultrasound-guided core needle biopsy (18).

The AIP is referred to be very responsive to steroid therapy, therefore making therapy a component of the diagnostic criteria (4, 16, 19–21). One commonly used regimen includes treatment with 40mg of prednisone for four weeks, followed by a taper by 5mg each week for a total of an 11-week course (11). Patients, who relapse, are treated with a second course of corticosteroids (19). Given the relatively high relapse rates, some centres routinely continue maintenance corticosteroid therapy for up to three years (21). Further, the steroid-sparing immunomodulator, azathioprine, can be used to maintain remission after the first or second relapse (19). In patients refractory to steroids, azathioprine, mycophenolate mofetil, cyclophosphamide, and rituximab have all been tried in addition to, or instead of, steroid therapy (16, 20).

Material and methods

68-year-old man presented with a history of weight loss about seven kilograms in seven weeks and obstructive jaundice. A physical examination was normal with the exception of jaundice; there was no evidence of ascites, lymphadenopathy or hepatosplenomegaly. Routine laboratory analysis revealed typical sign of obstructive icterus (total bilirubin 97.1 umol/l, alkaline phosphatase 2.70 ukat/l, γ-glutamyl transpeptidase 5.14 ukat/l, aspartate aminotransferase 2.35 ukat/l, alanine aminotransferase 3.90 ukat/l), and borderline levels of serum amylase (1.95 ukat/l), serum lipase (1.90 ukat/l). Level of C-reactive protein (0.5 mg/l) and tumor marker CA 19-9 (10.0 kU/l) was normal. Complete blood count was normal. Abdominal ultrasound examination reported hypoechoic 50 mm large lesion in head of pancreas; gallblader was normal without lithiasis. Abdominal computed tomography (Fig 1a,b) showed enlargement of the head of the pancreas (52 x 38 x 31 mm) in comparison to the atrophic pancreatic body and tail, slightly dilated pancreatic duct (3 mm) with concomitant common bile duct dilatation (11 mm), and slight intrahepatic bile duct dilata-

![Fig. 1a, b. Coronal reconstruction contrast-enhanced CT images showed (a) enlargement of the pancreatic head (thick arrow) in comparison (b) to the atrophic pancreatic body with dilatated pancreatic duct (thin arrow).](image-url)
tion. Endoscopic retrograde cholangiopancreatography (ERCP) revealed edema in D2 part of duodenum and extreme rigidity of papilla of Vater. Because of the rigidity, biliary plastic stent was unable to place even by very experienced endoscopist.

Patient refused a pancreatic biopsy. In case of increasing obstructive jaundice without a possibility to insert biliary stent via ERCP, we considered steroid treatment for 2–4 week as a therapeutic modality that could increase risk of acute cholangitis. Alternative percutaneous biliary drainage in combination with steroid trial would share the same risk.

The patient was referred for surgical management. In keeping with preoperative examination, the surgical exploration demonstrated firm mass in the pancreatic head extending into the body and tail of pancreas. The patient underwent a standard pylorus preserving total pancreatectomy with splenectomy and standard lymphadenectomy. In reconstruction phase retrocolic reconstruction with single limb for all anastomoses (hepaticojejunostomy and duodenojejunostomy) was performed.

Gross pathological finding showed a not well circumscribed firm grey to tan mass (45 x 35 x 65 mm) in the pancreatic head (Fig. 2). Microscopic evaluation revealed dense periductal lymphoplasmocytic infiltration, storiform intralobular fibrosis with secondaryatrophy of exocrine acinar component (Fig. 3) and oblitative phlebitis. The IgG4 immunohistochemistry showed dense infiltration of IgG4-positive plasma cells (70 cells per HPF) (Fig. 4). Fibrosis and scarring involved also distal part of common bile duct leading to its obstruction.

Subsequently we obtained the result of IgG4 in serum. IgG4 level of 3.52 g/l (352 mg/dl) well corresponded with diagnosis of type 1 autoimmune pancreatitis.

**Discussion**

The clinical presentation of autoimmune pancreatitis can mimic difficult-to-treat disorders such as pancreatic cancer (16). Autoimmune pancreatitis most often presents with obstructive jaundice, weight loss, abdominal pain and new onset of diabetes mellitus (16, 22). This presentation is similar to that of pancreatic cancer. In 20–40 % of cases of the AIP, a focal pancreatic mass is found, which makes the distinction from pancreatic cancer rather difficult (16, 23).

Above mentioned diagnostic criteria for AIP should be applied with caution as there is some degree of overlap in the findings between the AIP and pancreatic cancer indicated by the similarity in radiologic findings, elevation of IgG4, sampling errors in pancreatic biopsy, and the possibility of synchronous AIP and pancreatic cancer (24).

Serum IgG4 levels alone are unsuitable for distinguishing AIP from pancreatic cancer; serum IgG4 level > 140 mg/dl has a sensitivity of 76 % and specificity of 93 % in diagnosing of AIP (9). Notably, 5 % of healthy persons and approximately 10 % of the patients with pancreatic cancer have slightly (about 2-fold) elevated IgG4 (9, 25, 26). Increasing the cutoff to 280 mg/dl decreases sensitivity, but improves specificity to 99 % in diagnosis of AIP (16).

Diagnostic accuracy of serum biomarker CA 19-9 level is limited as well, as 9 % of the patients with AIP have elevated CA 19-9. However, patients with pancreatic cancer are more likely to have elevated CA 19-9 of > 100 U/ml than AIP patients (71 % vs 9 %) (9).

Biopitic sample errors could be possible because of the patchy distribution of the characteristic histological findings in AIP (17).

Diagnostic criteria for AIP include response to steroid therapy. However, steroid trials should be performed only after a negative workup for pancreaticobiliary cancer (24). It had been shown that radiological improvement of the pancreas on cross-sectional CT/ MRI imaging should be evident within 4 weeks after the start of steroid therapy (24). Some studies suggested that two weeks of steroid therapy might be sufficient to determine the response (i.e. resolution of abnormal imaging, and improvement in clinical and biochemical parameters), which may be of particular importance to avoid any delay in differentiating the AIP from pancreatic cancer (27, 28).

However, subjective improvement in symptoms or decline in serum IgG4 levels can occur even in pancreatic cancer and should not be used as separate response criteria (24).

Recently, US Mayo Clinic and Japan Pancreas Society outlined strategies to distinguish between AIP a pancreatic cancer (15, 28).
According to the Mayo Clinic Strategy, CT findings should be used to stratify the patients into 3 groups: 1) highly suggestive of the AIP, 2) indeterminate (supportive of the AIP) and 3) highly suggestive of the pancreatic cancer. All the patients in groups 2 and 3 should undergo a workup for pancreatic cancer and the AIP; because pancreatic cancer is on balance of probabilities more likely than AIP, a workup for pancreatic cancer is the first step (biopsy of the lesion, CA 19-9 level in serum, and metastasis evaluation). In most (70 %) patients, AIP is successfully diagnosed by pancreatic CT imaging, serum IgG4 levels, and determination of other organ involvement. But in patients without supportive serologic evidence or other organ involvement, the definitive diagnosis of AIP requires a pancreatic core biopsy, steroid trial, or operative intervention. Steroid trial (Prednison 40 mg/day for two weeks) is strongly discouraged in the absence of collateral evidence for the AIP and in the positive workup for the cancer (15).

Japanese strategy differentiates AIP from pancreatic cancer in patients presenting with mass-like lesion in the pancreatic head. This strategy relies on radiologic cross-sectional imaging, serologic IgG4 level, and histologic data obtained by resection or biopsy. An endoscopic or percutaneous biliary drainage with cytologic examination of the biliary or pancreatic ducts is recommended routinely (28).

Japanese strategy concerns only mass-forming AIP, but Mayo Clinic strategy evaluates all imaging type of AIP. Both groups reported that the use of their strategies did not result in the inappropriate treatment of cancer with steroids (24). Strategies for distinguishing between AIP a pancreatic cancer have strengths and weaknesses, and they reflect differences in clinical practice in the USA and Japan.

Conclusion

It is generally accepted that an accurate diagnosis of the AIP can avoid major pancreatic surgery.

The role of the surgery in AIP remains still to be exactly determined. But there are some arguments that support the importance of pancreatic surgery in AIP:

- The relapse rate in patients with type 1 AIP ranges from 30–50 % (4, 12, 29).
- Relapses are associated with chronic pancreatic injury (including development of pancreatic duct stones in 33–55 %) (16).
- More than 50 % of patients with AIP may have findings, which are highly suggestive of pancreatic cancer (including elevated CEA, CA 19-9, and bile duct stenosis) (30).
- Case reports of pancreatic cancer associated with the AIP are described (31–34).
- Recent studies have highlighted an increased risk of malignancy (about 3–5 times greater than the general population) in patients with IgG4-related disease (35) and in patients with the AIP (36).
- Almost 15 % of patients with AIP developed cancer, with the highest risk of occurring within the first year after the diagnosis of AIP (37).
- The patchy involvement of AIP limits histologic diagnosis (16).
- The consensus guidelines (International Consensus Diagnostic Criteria) for the AIP discourage the use of the diagnostic steroid trials alone to diagnose AIP. As IgG4 elevation associated with pancreatic cancer may decline and give a false diagnosis of autoimmune pancreatitis (6).

We believe, that surgical intervention is necessary as a first step in patient with pancreatic masses (despite suspicion on AIP) in the subgroup of patient with unclear diagnosis, with endoscopically untreated obstructive jaundice (because of risk of acute cholangitis), with probable coincidence of AIP and pancreatic cancer or in patients that refused pancreatic biopsy.

References


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