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Challenges for clinicians treating autoimmune pancreatitis: Current perspectives

Seong-Hun Kim*, Yun Chae Lee*, and Hyung Ku Chon

Abstract

Autoimmune pancreatitis (AIP) is a rare disease clinically characterized by obstructive jaundice, unintentional weight loss, acute pancreatitis, focal pancreatic mass, and diabetes. AIP is classified into two subtypes—type 1 and type 2—according to pathological findings, clinical features, and serology test results, but some cases may be defined as type not otherwise in the absence of pathological findings and inflammatory bowel disease. To address the differences in diagnostic criteria by country, standard diagnostic criteria for AIP were proposed in 2011 by an international consensus of expert opinions. Differential diagnosis of AIP from pancreatic ductal adenocarcinoma is important but remains challenging for clinicians. Fortunately, all subtypes of AIP show dramatic response to steroid treatment. This review discusses the current perspectives on the diagnosis and management of AIP in clinical practice.

Key words: Autoimmune pancreatitis; Pancreatic cancer; International consensus diagnostic criteria; Steroid

Core tip:

Autoimmune pancreatitis (AIP) is a rare disease characterized by obstructive jaundice, acute pancreatitis, and focal pancreatic mass. Lymphoplasmacytic sclerosing pancreatitis (type 1) and idiopathic duct centric pancreatitis (type 2) are histopathologically distinct. Typical imaging features and pathologic findings are crucial in the diagnosis of AIP to distinguish it from pancreatic ductal adenocarcinoma. Responses to steroid treatment are dramatic, but relapses are common. A careful approach to maintenance treatment is thus required.

INTRODUCTION

Autoimmune pancreatitis (AIP) is a rare, unique, and clinically distinct form of pancreatitis, characterized by histological features of a lymphoplasmacytic infiltrate and fibrosis, frequent elevations of serum immunoglobulin G4 (IgG4), and a dramatic response to steroid treatment[1]. In 1961, Sarles et al. first reported a case of chronic inflammatory sclerosis of the pancreas with hypergammaglobulinemia[2], and in 1995, Yoshida et al. first used the term AIP to describe a pancreatic mass responding to steroid treatment[3]. In 2001, Hamano et al. reported that an increase in serum IgG4 in patients with AIP could be used as a diagnostic marker to differentiate AIP from similar diseases[4]. AIP should be distinguished from pancreatic ductal adenocarcinoma and extrahepatic cholangiocarcinoma to avoid unnecessary surgery or delayed management. However, clinicians may find it difficult to differentiate them because of overlapping clinical and imaging findings, such as stenosis of the bile duct, focal mass of the pancreas, diffuse pancreatic hypertrophy, and obstructive jaundice.

EPIDEMIOLOGY

The incidence and prevalence of AIP are not well established owing to a lack of epidemiological data. AIP accounts for 5-6% of chronic pancreatitis cases[5]. Type 1 AIP is reported more frequently in Asia, whereas type 2 AIP is more common in Europe and the Americas. According to a 2016 nationwide survey in Japan, the overall prevalence rate of AIP was 100.6 per 100,000 persons, and the annual incidence rate was 31.4 per 100,000 persons, which was twice as high as in the 2011 survey[6, 7]. The male-to-female ratio was 2.94:1, and the mean age was 68.1 years[6]. In a multicenter study in Korea, the mean age of patients with AIP was 56 years, the male-to-female ratio was 2.5:1, and less than 10% of the patients had type 2 AIP[8]. An Italian study reported that the male-to-female ratio for type 2 AIP was 1:1.1, and the average age at onset was 34.4 years[9]. In a study reported in Germany in 2017, the incidence of AIP was less than 1 per 100,000 persons[10].

CLASSIFICATION AND HISTOPATHOLOGICAL FEATURES

AIP is divided into two subtypes (type 1 or type 2), according to histopathological findings and clinical features. According to the International Consensus Diagnostic Criteria (ICDC)[11], AIP diagnosis requires a combination of the following five cardinal features: (1) imaging features (pancreatic parenchyma and pancreatic duct), (2) serology (IgG4, IgG, and antinuclear antibody), (3) extrapancreatic organ involvement, (4) histopathology of the

pancreas, and (5) response to steroid therapy. The imaging features and the steroid response are known to be the same in both type 1 and type 2 AIP, but the serologic findings, extrapancreatic organ involvement, and pancreatic histopathology are distinct between them. “Definitive type 1 AIP” can be diagnosed as a surrogate criterion for AIP without considering histopathology; however, "Definitive type 2 AIP" requires histopathological confirmation.

The histopathological features of lymphoplasmacytic sclerosing pancreatitis (LPSP) in type 1 AIP include (1) dense infiltration of plasma cells and lymphocytes, particularly periductal ones; (2) storiform fibrosis; (3) venulitis with lymphocytes and plasma cells often leading to obliteration of the affected veins; and (4) abundant (>10 cells per high-power field (HPF)) IgG4-positive plasma cells. The European guidelines recommend that the number of IgG4-positive plasma cells should exceed 50 cells/HPF in surgical specimens and 10 cells/HPF in biopsy specimens (average of three hotspots (400×)) for diagnosing type I AIP, and the IgG4/IgG ratio should be at least 40%[11]. However, an increased number of IgG4-positive plasma cells alone is insufficient for diagnosing type 1 AIP[12, 13].

The primary histopathological feature of type 2 AIP is idiopathic duct-centric pancreatitis (IDCP). IDCP and LPSP share characteristics of periductal lymphoplasmacytic infiltrate and storiform fibrosis, whereas the characteristics of granulocyte epithelial lesions (GELs) are observed in IDCP alone. GELs are intraluminal and intraepithelial neutrophils in medium- and small-sized ducts, as well as in acini, often leading to the destruction and obliteration of the duct lumen[14, 15]. Type 2 AIP typically has absent or very few (<10 cells/HPF) IgG4-positive plasma cells.

According to the ICDC, AIP type not otherwise specified (NOS) is defined as the absence of histological criteria and inflammatory bowel disease (IBD). Type NOS AIP is rarely diagnosed, and some studies have reported that this subtype has clinically similar characteristics to type 2 AIP and can therefore be converted to type 2 AIP[16, 17].

CLINICAL MANIFESTATIONS

Clinical manifestations of AIP mainly include obstructive jaundice, weight loss, acute pancreatitis, focal pancreatic mass, abdominal pain, diabetes mellitus (DM), and inflammatory bowel disease. The most common clinical symptom of type 1 AIP is obstructive jaundice, whereas that of type 2 AIP is acute pancreatitis[9, 18, 19]. Type 1 AIP is more commonly diagnosed in men, with the fifth to seventh decade of life being the predominant

onset age[7, 18]. In contrast, the incidence of type 2 AIP is similar in men and women, with the third to fourth decade of life being the predominant onset age[9, 19].

Type 1 AIP belongs to the spectrum of IgG4-related diseases involving the bile duct (sclerosing cholangitis), salivary gland (sialadenitis), lacrimal gland (dacryoadenitis), kidney (tubulointerstitial nephritis), retroperitoneum (retroperitoneal fibrosis), lungs, thyroid gland, lymph nodes, pituitary gland, and aorta (Figure 1). Development of extrapancreatic involvement may occur antecedent to, concurrently with, or metachronously with the diagnosis of type 1 AIP[20]. Conversely, type 2 AIP does not typically involve other organs but is accompanied by IBD in 15-45% of cases[18, 19]. A multicenter international study comparing 204 patients with type 1 AIP versus 64 patients with type 2 AIP found that patients with type 2 AIP were more likely to develop concurrent IBD, particularly ulcerative colitis (16% versus 1%, respectively)[18]. According to a systematic review, the pooled estimate for the prevalence of DM at the time of diagnosis of type 1 AIP was 44%, which was 11% higher than that of type 2 AIP[21]. In addition, the pooled estimated prevalence of exocrine insufficiency at the time of AIP diagnosis was 45%. Thus, the presence of DM and pancreatic exocrine insufficiency in AIP indicates that more than one-third of patients with AIP develop significant impairment of their pancreatic function. The clinicopathological characteristics of type 1 and type 2 AIP are summarized in Table 1.

DIAGNOSIS

1) *Imaging methods*

The imaging findings of AIP can be divided into parenchymal images using computed tomography (CT) or magnetic resonance imaging (MRI) and pancreatic duct imaging using endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP). The imaging findings of type 1 AIP and type 2 AIP are similar[22].

1-1 Computed tomography and magnetic resonance cholangiopancreatography **(Figure 2)**

I. Imaging of the pancreatic parenchyma

The typical radiologic findings of AIP include diffuse enlargement of the pancreas, a capsule-like rim, and homogeneous delayed enhancement[18, 23]. Diffuse or focal pancreatic edema by marked lymphocyte and plasma cell infiltration with fibrosis is observed as a

"sausage-like appearance," with a straightened edge of the pancreas[24]. The pancreatic parenchymal speckled/dotted enhancement on MRI is useful for differentiating AIP from PDAC[25]. A "capsule-like rim" reflecting dense fibrosis refers to a hypotonic band around the pancreas on CT and MRI scans and is another important finding to distinguish AIP from PDAC[26, 27]. However, this characteristic is less sensitive for small lesions, and caution should therefore be taken[28]. AIP usually exhibits specific and homogenous delay enhancement. Conversely, heterogeneous delay enhancement is observed in PDAC owing to tumor necrosis, hemorrhage, or degeneration[27, 28].

II. Imaging of the pancreatic duct

A duct penetrating sign of skipped narrowing of the main pancreatic duct (MPD) is a useful finding differentiating AIP from PDAC[24, 26, 27, 29-31]. Stenosis of the pancreatic duct caused by periductal fibrosis is commonly observed in AIP; it resembles the tapering of the tip of an icicle and is called an "icicle sign"[32, 33]. Linear enhancement along the MPD is often observed in AIP. This reflects inflammation around the MPD[24, 34]. Unlike AIP, PDAC exhibits upstream pancreatic duct dilatation and an abrupt ductal cut of the pancreatic duct[27].

1-2. Endoscopic retrograde cholangiopancreatography

ERCP is a useful modality for evaluating MPD. The characteristic ERCP findings of AIP are greater than one-third (5 cm) narrowing of the diffuse or segmental main pancreatic duct, multiple skipped narrowing with no upstream dilatation of the MPD above the narrowing (< 5 mm), and side branches arising from the narrowed segments[35, 36]. PDAC presents as a focal narrowing of the MPD and a short single MPD stricture with upstream dilatation[36-40]. ERCP is more useful than MRCP for differentiating focal AIP from PDAC[41, 42], but differentiation is difficult when the narrowing of the pancreatic duct is short (within approximately 3 mm)[35].

ERCP has the advantage of evaluating the pancreatic duct in addition to the performance of drainage of the pancreatic duct/bile duct and biopsy with cytology. However, ERCP is more invasive than MRCP, and procedure-related complications may occur as a result. ERCP may limit the evaluation of the upstream area of the MPD in case of MPD obstruction[36]. Thus, ERCP is being replaced by MRCP for the observation of the pancreatic duct owing to the improved quality and lesser invasiveness of MRCP.

1-3. Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) can be used to evaluate the pancreatic parenchyma and pancreatic ducts to aid in the differentiation of AIP from PDAC (Figure 3). In EUS, diffuse hypoechoic areas, diffuse enlargement, extrahepatic bile duct wall thickening, and peripancreatic hypoechoic margins are more characteristic in AIP than in PDAC but are also observed in other forms of pancreatitis[43, 44]. EUS alone is limited in the diagnosis of AIP. To overcome this limitation, trials have been performed to help diagnose AIP using contrast-enhanced EUS (CE-EUS) or elastography[45-48]. The most characteristic finding in the differentiation between focal type AIP and PDAC using CE-EUS was hyper- to iso-enhancement without irregular internal vessels (specificity, 94%)[49]. In addition, one report has indicated that measuring the strain ratio through elastography together with CE-EUS helps to differentiate it from PDAC[50]. However, CE-EUS and elastography are limited, and the most important role of EUS in diagnosing AIP is for tissue acquisition for histopathological confirmation.

2) Endoscopic ultrasound-guided fine needle aspiration and fine needle biopsy

EUS-guided tissue acquisition from patients with AIP is important not only for the differential diagnosis from PDAC but also for the differentiation between type 1 and type 2 AIP. No significant difference was observed between fine needle aspiration (FNA) and FN biopsy (FNB) in the diagnosis of PDAC, and both can be used to differentiate PDAC in patients with AIP [51-55]. However, histopathological diagnosis of AIP requires a larger amount of tissue than diagnosis of PDAC, so AIP diagnosis with FNA is uncertain[53, 56]. The needles used for FNB have been developed to allow the acquisition of intact histologic core specimens with preserved tissue architecture[57]. According to a recent meta-analysis of nine FNA studies and seven FNB studies, the diagnostic yields for AIP with level 1 or 2 histology criteria were 55.8% in FNA and 87.2% in FNB, indicating the superiority of FNB[58]. The size of the needle affects the amount of tissue that can be obtained, so a 19-gauge needle has a greater diagnostic yield than a 22-gauge needle (82-89% vs. 61-69%)[58, 59]. However, caution is required because large gauge needles are difficult to handle and carry a higher risk of complications[59, 60]. Diagnosis of AIP is not always simple, and in some cases distinguishing it from pancreatic cancer is difficult; while the occurrence of concomitant pancreatic tumors (benign and malignant) in patients with AIP has been documented in up to 7% of cases[61]. Therefore, surgery may be considered for patients in whom suspicion of

malignant/premalignant lesions cannot be excluded even after detailed diagnostic workup such as biopsy through EUS or ERCP[62].

3) Serology

Elevation of serum IgG or IgG4 is often observed in AIP, and the ICDC recommends serum IgG4 as a level 1 serological marker for type 1 AIP[1]. An increase in IgG4 is usually accompanied by type 1 AIP (seropositive), whereas type 2 AIP is seronegative. Serum IgG4 is reported to range from 135 to 140 mg/dL as the upper limit of the standard[63]. Elevated serum IgG4 level (>140 mg/dL) is used as a diagnostic criterion for AIP, with a sensitivity of 86% and a specificity of 90-96%[35, 64, 65]. Serum IgG4 elevations greater than twice the upper limit of the standard (>280 mg/dL) are highly specific for AIP (specificity increased to 96%); however, the positive predictive value is less than 50%[4, 65-69]. This is due to the presence of elevated IgG4 levels in approximately 10% of patients with PDAC or other diseases (e.g., parasitic diseases, chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis, or Sjogren's syndrome)[4, 35, 65, 70-73]. In addition, although LPSP with typical IgG4+ plasma cell abundance, a histological finding of type 1 AIP, was observed, the level of IgG4 in serum was sometimes lower than the cutoff value, so the level of IgG4 did not rise in all patients with type 1 AIP[74].

Patients with increased IgG4 concentrations have high disease activity, a high incidence of jaundice at onset, and a number of extrapancreatic manifestations[74, 75]. However, IgG4 levels are not sufficiently correlated with the onset of complications or recurrence[11, 74, 76, 77]; therefore, serological markers such as autotaxin are being studied for their relevance to relapse[78].

The c-antineutrophil cytoplasmic antibodies tends to be increased in some patients with type 2 AIP, which can help to distinguish type 1 from type 2[79]. However, despite research on various biomarkers (e.g., antibodies against the following: carboanhydrase II, plasminogen-binding protein, lactoferrin, Alpha 2A amylase, cationic (PRSS1) and anionic (PRSS2) trypsinogens, and pancreatic secretory trypsin inhibitor (PSTI/SPINK1) for the diagnosis of AIP and its differentiation from PDAC, verification of their specificity and sensitivity for commercialization is still insufficient[75, 80].

Elevation of carbohydrate antigen (CA) 19-9 levels are commonly observed in pancreatic cancer (sensitivity of 79-95%, specificity of 82-91%); however, up to 38% of patients with

AIP also have values > 100 U/mL[81-83]. Therefore, the measurement of CA19-9 or IgG4 alone is insufficient to differentiate between AIP and PDAC. However, one study reported that the combination of IgG4 > 100 mg/dL and CA19-9 < 74 U/mL was more likely to indicate AIP than PDAC (sensitivity of 94%, specificity of 100%)[83]. In addition, serum eosinophilia, raised total serum IgE levels, and serum microRNAs may be used to differentiate between AIP and PDAC[11, 75, 84, 85].

Diagnosis of AIP is still challenging even with a combination of imaging, histological, and serological tests. Therefore, follow up with a thorough clinical history and physical examination is required. In the case of type 1 AIP, additional imaging tests may be considered to determine other organ involvement; in contrast, in the case of type 2 AIP, the presence or absence of IBD can be confirmed through colonoscopy. The improvement of the lesion can be confirmed after an empirical short-term (2 weeks) steroid treatment if AIP is suspected but a definitive diagnosis is not possible despite the performance of several tests, and no malignancy is found in histopathological examinations[86]. If the lesion worsens on follow-up imaging after 2 weeks, biopsy may be performed again, and surgical treatment may be considered if necessary. However, a steroid trial with patients in whom differentiation from malignancy is an issue could result in delayed pancreatic cancer surgery and subsequent cancer progression, so sufficient information should be provided to the patient. In addition, novel biomarkers that have recently attracted attention may help distinguish PDAC from AIP in the future.

TREATMENT

The standard treatment for AIP is steroid therapy, which can successfully induce remission for both type 1 and type 2 AIP[87]. Therefore, the response to steroid treatment is sometimes used as a diagnostic criterion[1]. After induction of remission, the recurrence rate of type 1 AIP was higher than that of type 2 AIP (31% vs. 9%), and the need for treatment maintenance was suggested owing to the high recurrence of type 1 AIP[77, 87-89].

Indications

Treatment of AIP is required for symptomatic patients with pancreatic involvement (e.g., obstructive jaundice, abdominal pain, and back pain) or other organ involvement (e.g., jaundice due to bile duct stricture). In the case of asymptomatic patients, indications for treatment include persistent pancreatic mass on imaging tests or persistent abnormalities in

liver function tests in patients with IgG4-related sclerosing cholangitis[87]. Some patients with AIP (approximately 10-25%) improve spontaneously without intervention or steroid treatment, so "watchful waiting" may be considered in asymptomatic patients[76, 87, 88, 90, 91].

Initial treatment

Steroid therapy is recommended as the first-line treatment unless there is a contraindication for the use of steroids for induction of remission[87-89, 92, 93]. Assessment of the response to treatment using imaging and serological tests is recommended within 1-2 weeks after initiation of steroid therapy[86]. To induce remission, an initial dose of 0.6-1.0 mg/kg/day of prednisone, which is maintained for 2-4 weeks and then gradually reduced is recommended, [87]. In general, the dose is reduced to 5-10 mg/day every 1-2 weeks until a daily dose of 20 mg is reached, after which the dose is reduced by 5 mg every 2 weeks. Another acceptable regimen is to take 40 mg/day for 4 weeks and then taper by 5 mg/week until ceasing treatment[94]. The remission treatment period should be maintained for at least 12 weeks. Administration of high-dose corticosteroids (approximately 30-40 mg/day) leads to a faster induction of remission than conservative management does[76]. Since low-dose prednisolone (less than 20 mg/day) has a limited remission rate, a minimum of 20 mg/day is generally required to induce remission[95, 96]. Maintenance treatment to prevent AIP recurrence is not recommended for type 2 AIP or for type 1 AIP with low pre-treatment disease activity (i.e., involvement in the pancreas alone with segmental/focal lesions without any other organ involvement or complete radiological remission with normalized IgG/IgG4 in rapid response to steroid treatment). However, maintenance treatment with low-dose glucocorticoids or steroid-sparing agents may be helpful in some patients with type 1 AIP, such as those with remarkably high serum IgG4 levels before treatment (e.g., more than four times the normal upper limits), diffuse enlargement of the pancreas, delayed radiological remission, persistently high serum IgG4 after treatment (more than two times the normal upper limits), more than two other organs involved, or association with proximal IgG4-related sclerosing cholangitis before treatment[88, 94, 97-110]. Low-dose (2.5-7.5 mg/day) glucocorticoid maintenance therapy is recommended to lower the recurrence rate, and a maintenance period of 1-3 years is recommended, but this remains controversial[111, 112]. According to a recent meta-analysis, the glucocorticoid treatment group indicated calculated pooled relapse rates of 46.6% for less than 6 months, 44.3% for 6-12 months, 34.1% for 12-36 months, and 27.0% for more than 36 months[111].

Concerns have been raised about the side effects of long-term steroid treatment, and according to one study, most complications occurred after 3 years or after the accumulated amount of steroid exceeded 10,000 mg[112, 113]. Complications included poor glycemic control, osteoporosis, steroid myopathy, fungal infections, bacterial infections, cerebral infarctions, and atherosclerosis. Several studies have shown that people with AIP often have DM at diagnosis (33-78%)[114-117]. DM improves in some patients when standard corticosteroid therapy is administered[114, 116-118]. Therefore, steroid treatment may be considered even in patients with diabetes, and steroid treatment is particularly recommended in patients with AIP who have glucose intolerance[117]. Some patients do not relapse after cessation of steroids after achieving remission; however, some patients relapse during steroid reduction or require a relatively high-dose maintenance therapy. Therefore, the maintenance treatment period should be determined in consideration of each patient's age, comorbidities, recurrence risk, and individual preference for treatment[111].

There are rare cases of steroid non-response in patients with AIP[88, 92, 119]. Rituximab is recommended as an alternative treatment in the setting of steroid-refractory AIP[120-122]. Immunomodulatory agents, such as thiopurines (azathioprine and 6-mercaptopurine), mycophenolate mofetil, and methotrexate, are relatively inexpensive and can be administered to reduce the cumulative steroid dose, but immunomodulator monotherapy is ineffective[87, 121]. Therefore, the use of immunomodulators in combination with low-dose steroids is recommended[121].

In patients with AIP with obstructive jaundice, biliary stenting is usually performed along with biopsy through ERCP[77, 123]. Some studies have reported that obstructive jaundice should be treated with steroid treatment without biliary stents because AIP responds rapidly to steroid treatment[124, 125]. However, as AIP is sometimes difficult to differentiate from pancreatic cancer or concomitant cholangiocarcinoma, empirical steroid treatment can be challenging without insertion of a biliary stent and biopsy. In cases of biliary stent insertion, early biliary stent removal after diagnosis of AIP according to the guidelines should be considered owing to stent related complications such as migration or stent dysfunction.

Treatment of relapse

In patients with recurrent AIP, steroids and steroid-sparing agents may be used. Steroid re-administration or dose increase is recommended in patients who relapse after successful

induction of remission with initial steroid therapy[87]. In most patients with relapsed AIP, re-remission can be achieved with administration of prednisolone at the same dose as the initial treatment, although a more gradual reduction is required. Immune-modulators or rituximab are generally used as steroid-sparing agents[91, 121, 126-130]. Rituximab is used as a single agent for induction of remission, but immune-modulators are not as effective as single agents. Thiopurines and mycophenolate require 6-8 weeks of overlapping treatment with steroids[102, 121, 126]. Patients with jaundice may require 4-6 weeks of steroid treatment owing to the late onset of action of rituximab[121, 127].

PROGNOSIS

In patients with AIP, the prevalence of endocrine and exocrine insufficiency at the time of AIP diagnosis is high. In a recent meta-analysis, the pooled estimate rate for the overall prevalence of DM in patients at the time of AIP (combined type 1 and type 2 AIP) diagnosis was 37%[21]. At the time of AIP diagnosis, the prevalence of DM was higher in Asian countries than in Western countries, and the pooled estimate of the prevalence of DM was 44% in type 1 AIP and 11% in type 2 AIP. The pooled estimated prevalence of diabetes at follow up in patients with AIP with or without steroid treatment was 42% and 44%, respectively[21]. In studies conducted in Asian and Western countries, respectively, the pooled estimate rate of DM at follow up was 49% and 34%. In some studies, glycemic control was improved by steroid treatment when AIP was accompanied by DM[116-118]; however, in a previous meta-analysis, the prevalence of DM increased during long-term follow up[21, 131]. The pooled prevalence of exocrine pancreatic insufficiency in patients with AIP treated with steroids was 36%, which was improved from the time of diagnosis (45%). However, validation is warranted as other studies report an additional risk of exocrine pancreatic insufficiency during follow up in patients with AIP[131]. Histological analysis, changes in pancreatic volume and structure, obstruction of the main pancreatic duct, and decreased stimulation of the exocrine function suggest that islet cells in patients with AIP are fibrotic, and lymphoplasmatic cell infiltration is associated with endocrine and exocrine insufficiency of the pancreas[132-134]. Improvements in histological findings in patients with AIP following steroid treatment can sometimes lead to improvements in endocrine and exocrine function, but further studies and long-term follow up are still required to verify this. Furthermore, one study showed that chronic pancreatitis progressed in 22% of patients with AIP, and

approximately 40% of the patients developed pancreatic stones[135, 136]; as such, the occurrence of chronic pancreatitis-related complications is also expected to increase.

Patients with AIP may be associated with an increased risk of developing malignant disease than the general population[137-139]. A considerable number of patients with AIP are diagnosed with cancer at the time of AIP diagnosis or within 1 year, with cancer lesions occurring more often in other organs, such as the stomach, lung and prostate, than the pancreas[137, 140, 141]. These results suggest that AIP may be related to cancer more in other organs than in the pancreas itself. Based on this phenomenon, some studies have argued that because cancer and AIP occur simultaneously, AIP can sometimes occur in coexistence with cancer as a paraneoplastic syndrome[137, 142]. Studies on the incidence of PDAC in patients with AIP have reported conflicting results[140, 143, 144]. However, additional research is required, as one case report indicated that PDAC and cholangiocarcinoma developed during follow up after autoimmune pancreatitis treatment[145, 146]. Studies on patients with IgG4-related diseases have also shown that various malignant diseases (e.g., lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, lymphoma, and leukemia) may also occur with AIP [141, 147-149],which suggests that IgG4-related diseases are associated with an increased risk of malignant disease. Although whether AIP is a risk factor for malignancy remains controversial careful attention should be paid to the occurrence of malignancy at the time of AIP diagnosis and during follow up.

CONCLUSIONS

AIP is a rare disease that can be difficult to diagnose and treat unless the clinician has a high index of suspicion for AIP. Obstructive jaundice, narrowing of the bile ducts, and focal masses in the pancreas can occur in AIP and may result in a misdiagnosis of pancreaticobiliary cancer; therefore, performing a cytology test or biopsy along with imaging and serology testing is required. Although most patients respond well to steroid treatment, relapse is frequent. Therefore, standardization of the duration and the dose of maintenance treatment is necessary. Patients who are resistant to steroid therapy may be treated with rituximab or immunomodulatory medications, although more research to support this regimen is required. Finally, long-term follow up is required in patients with AIP because endocrine and exocrine insufficiency of the pancreas may persist or be induced and are

associated with the development of malignant tumors.

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