Autoimmune pancreatitis: current concepts

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Autoimmune pancreatitis (AIP) is a distinct type of chronic pancreatitis with unique clinical, pathological, serological, and imaging features. AIP usually presents with obstructive jaundice. Imaging studies often reveal enlargement of the pancreas with a pancreatic mass and strictures of the main pancreatic duct. Two subtypes of AIP have recently been identified. Type I AIP is more prevalent in elderly Asian males and is characterized by lymphoplasmacytic sclerosing pancreatitis, obliterative phlebitis, and infiltration of large numbers of IgG4-positive plasma cells. Type II AIP is more prevalent in Caucasians and is characterized by granulocyte epithelial lesions. Most patients with type I AIP have a significantly elevated serum IgG4 concentration, which is an important feature for diagnosis and for differentiating between AIP and other conditions such as pancreatic cancer. Extrapancreatic complications are common, such as sclerosing cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis in type I AIP, and ulcerative colitis in type II AIP. A rapid response to glucocorticoids treatment is suggestive of AIP, but the relapse rate is high, warranting the use of immunosuppressant treatment. B-cell depletion with rituximab may be a promising therapy. The prognosis of AIP is generally benign if treated promptly, and spontaneous remission occurs in a proportion of patients.

autoimmune pancreatitis, IgG4, pancreatic cancer, glucocorticoids

Autoimmune pancreatitis (AIP) is an uncommon form of chronic pancreatitis with a presumed autoimmune etiology and unique clinical, pathological, serological, and imaging features. Increasing numbers of cases have been reported over the past several decades. Chronic pancreatitis with sclerosis was first described as an autoimmune condition by Sarles et al. in 1961 [1], but it was not until 1995 that Yoshida et al. [2] proposed the term "autoimmune pancreatitis". In 2001, elevated serum immunoglobulin (Ig) G4 concentrations were detected in a large proportion of patients with AIP [3]. Two years later, Kamisawa et al. [4] reported extensive IgG4-positive plasma cell infiltration and fibrosis in the pancreas and other organs of patients with AIP. From then on, AIP has been considered to be part of a systemic sclerosing disorder. Similar cases with pathological features of multifocal fibrosclerosis were identified as early as the 1960s [5], and are now retrospectively described as IgG4-related sclerosing disease.

The nomenclature for AIP has evolved over the past decade, and now includes the terms lymphoplasmacytic sclerosing pancreatitis (LPSP), granulocyte epithelial lesion (GEL)-associated pancreatitis, and idiopathic duct-centric chronic pancreatitis. This changing nomenclature reflects our increasing understanding of this previously underestimated disease.

1 Subtypes of AIP

The cases of AIP reported in Asian patients (mainly Japanese patients) differ from those reported in Caucasian patients in terms of clinical manifestations and pathological

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characteristics [6,7]. In 2011, AIP was classified into two subtypes by an international consensus meeting for AIP coordinated by the Autoimmune Pancreatitis International Study Group [8]. Type I AIP usually affects elderly Asian males and has histopathological characteristics of LPSP; this is currently considered to be a pancreatic manifestation of IgG4-related disease. Type II AIP, previously called GEL-associated AIP, more commonly affects young Caucasian patients, with no sex predominance. Type II AIP features neutrophil infiltration in and around the pancreatic duct, and is associated with inflammatory bowel disease [9]. The characteristics of these two subtypes are summarized in Table 1.

2   Epidemiology

The worldwide prevalence of AIP remains unknown. Most studies are of type I AIP in the Japanese population. According to a nationwide study, the estimated prevalence of AIP in Japan is 0.82/100000 [10], but this prevalence may be underestimated because of a lack of awareness of the disease and lack of availability of IgG4 testing. AIP accounts for 2%–6% of chronic pancreatitis [10,11]. In patients who underwent pancreatic resection for suspected malignancy, 2.5%–8% were ultimately diagnosed with AIP without malignancy [10,12]. Data from the Mayo Clinic revealed that 11% of 245 patients who underwent pancreatic resection for the treatment of chronic pancreatitis were ultimately diagnosed with AIP [13]. In Italy, type II AIP was diagnosed in 40% of highly selected surgical specimens from patients with idiopathic chronic pancreatitis without pseudocysts, calculi, irregular duct dilatation, pancreas divisum, and duodenal wall cysts [14].

Type I AIP is more prevalent in patients aged 60–70

years, whereas type II AIP tends to affect the younger population. As shown in Table 1, type I AIP has a male: female ratio of approximately 2.85:1 [10], whereas there is no sex predominance in type II AIP.

3   Pathology

The characteristic pathological findings are more important for the diagnosis of AIP than an elevated serum IgG4 concentration or IgG4-positive plasma cell infiltration. The major histopathological findings in type I AIP include dense periductal lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis, which are described as LPSP. Immunohistochemical examination showing infiltration of large numbers of IgG4-positive cells (>10 per high-power field) is also helpful for diagnosing type I AIP. At least three of these four pathological features are required for a diagnosis of type I AIP. Mild to moderate eosinophil infiltration may also be present. The inflammatory lesion frequently forms a tumefactive mass that may lead to the destruction of the pancreas [9]. The pancreatic duct is compressed by surrounding fibrosis and lymphoplasmacytic infiltration. Unlike in type II AIP, neutrophil infiltration and granuloma formation are rare in type I AIP, and the ductal epithelium is usually intact. The retroperitoneal peripancreatic soft tissue frequently has extensive inflammatory cell infiltration. Type II AIP is characterized by neutrophil infiltration in and around the pancreatic duct leading to duct destruction, which is described as GEL. Although lymphoplasmacytic infiltration and storiform fibrosis may be observed in type II AIP, they are less common than in type I AIP [14]. Intrapancreatic pseudocysts, intraductal protein plugs, and pancreatic stones are seldom observed in either subtype of AIP, which differentiates AIP from other forms

Table 1   Subtypes of autoimmune pancreatitis

	Type I	Type II
Demographics		
Race	Asian	Caucasian
Male/female ratio	2.85:1	~1:1
Clinical manifestation		
Pancreatic	Painless obstructive jaundice is common	Obstructive jaundice with acute pancreatitis-like abdominal pain
Extra-pancreatic	Sclerosing cholangitis, cholecystitis, sialadenitis, dacryoadenitis, etc.	Ulcerative colitis
Serology	Hypergammaglobulinemia, Elevated serum IgG4, auto-antibodies	Unremarkable
Imaging	Swollen pancreas, mass formation, multiple pancreatic duct strictures	Swollen pancreas, mass formation, multiple pancreatic duct strictures
Pathology	IgG4-positive plasma cells and T-lymphocytes infiltration, storiform fibrosis, obliterative phlebitis, eosinophil infiltration	Neutrophilic infiltration in/around the pancreatic duct, duct destruction, obliterative phlebitis rare
Treatment		
Steroids response	Prompt response	Prompt response
Relapse rate	High	Low

of chronic pancreatitis.

In type I AIP, similar pathological features to those seen in the pancreas are also seen in other affected organs such as the biliary ducts, salivary glands, lacrimal glands, and thyroid, suggesting that type I AIP is the pancreatic manifestation of a systemic IgG4-related sclerosing disease. Pathological differences may occur between organs. For example, obliterative phlebitis is common in the pancreas and submandibular glands of patients with type I AIP, but is much less common in the pancreas of patients with type II AIP and in the lacrimal glands.

Although the presence of IgG4-positive plasma cells is important for the diagnosis of AIP, these cells are also found in a wide variety of other inflammatory diseases. Detection of IgG4-positive plasma cell infiltration is therefore not pathognomonic for AIP. However, a ratio of IgG4-positive to total IgG-positive plasma cells of >50% is very suggestive of AIP [15].

4 Clinical manifestations

Most patients with AIP do not have constitutional inflammatory manifestations. Fever and an elevated serum C-reactive protein level are uncommon. Most patients have an insidious onset, and AIP is usually identified incidentally on radiological examination or unexpectedly in pathological specimens. The clinical manifestations of AIP may be both pancreatic and extrapancreatic.

The most typical pancreatic finding in both subtypes of AIP is obstructive jaundice with sclerosing cholangitis. Occasionally, AIP presents with mild abdominal pain and elevated serum amylase or lipase levels, mimicking acute pancreatitis. AIP may also present with steatorrhea and pancreatic calcification that is suggestive of chronic pancreatitis. In the chronic phase of AIP, patients may present with pancreatic atrophy leading to steatorrhea. In some cases, biliary system involvement with obstructive jaundice is easily misdiagnosed as cholangiocarcinoma. In 60%–70% of patients, AIP is complicated by impaired glucose tolerance or diabetes mellitus. One third of patients have diabetes mellitus prior to the onset of AIP, and half of patients develop diabetes simultaneously with AIP [16,17]. Glucocorticoid treatment is helpful for glycemic control in a proportion of these patients, suggesting that the diabetes is associated with inflammation of the pancreas.

Awareness of extrapancreatic involvement is important, because it may be helpful in the diagnosis of AIP when the pancreatic manifestations are equivocal, and can provide alternative or additional biopsy sites. Extrapancreatic involvement can also be used to monitor the response to treatment. Some patients with AIP have isolated pancreatic manifestations for many years before diagnosis, whereas others may present with subtle or obvious extrapancreatic manifestations together with pancreatic symptoms. Extra-

pancreatic involvement includes Mikulicz's syndrome, retroperitoneal fibrosis, Kuttner's tumor, inflammatory pseudotumor, Riedel's thyroiditis, and tubulointerstitial nephritis [18,19]. These conditions have similar pathological features to those seen in type I AIP. Spontaneous recovery is reported in some patients.

5 Laboratory findings

5.1 IgG4 detection

Although most patients with type I AIP have elevated serum IgG4 concentrations, approximately 30% have normal serum IgG4 concentrations, despite typical histopathological and immunohistochemical findings [20]. Recent studies reported that serum IgG4 concentration has a sensitivity of 77% and specificity of 90% for diagnosing AIP, which is much lower than previously estimated [3,21,22]. In another study of type I AIP, elevated serum IgG4 concentrations were found in 80% of patients [23]. The diagnostic value of an elevated serum IgG4 concentration increases with a higher cut-off point; the cut-off point for diagnosis is currently set at twice of the upper limit of normal. However, an elevated serum IgG4 concentration is not a specific diagnostic marker for AIP [24], especially in patients with mild to moderate elevation. It is extremely important to avoid over-diagnosis of AIP because of over-reliance on mild to moderate elevation of serum IgG4 concentration and IgG4-positive plasma cell infiltration as diagnostic markers.

It is important not to use serum IgG4 concentration as an isolated indicator of disease activity. The use of serial measurements of IgG4 concentration to monitor disease activity is controversial. Only 30% of patients with persistently elevated IgG4 concentrations experience relapses, and up to 10% of patients with normal IgG4 concentrations at follow-up experience relapse [25]. Although the serum IgG4 concentration decreases after glucocorticoid treatment in the majority of patients, it seldom returns to the normal range [20,26]. Serum IgG4 concentration rebounds after discontinuation of glucocorticoids treatment in most patients, but fortunately only a small proportion of these patients experience relapse. A multicenter study in Japan showed that serum IgG4 concentration failed to normalize in 115 of 182 patients (63%) undergoing glucocorticoid treatment [25]. The study also found that the disease remained in remission in most patients, despite the persistent elevation in serum IgG4 concentration.

5.2 Autoantibodies

It has been reported that most patients with AIP have antibodies against the plasminogen-binding protein (PBP) of *Helicobacter pylori* [27]. The antibodies directed against the bacterial components are presumed to act as auto-antibodies

by means of molecular mimicry in genetically predisposed individuals. The study suggested that detection of anti-PBP antibodies together with an elevated serum IgG4 concentration might improve the diagnostic accuracy of AIP. Of the 35 patients in the study, two tested negative for anti-PBP antibodies but had elevated IgG4 concentrations, and 16 had normal IgG4 concentrations (maybe type II AIP patients) but tested positive for anti-PBP antibodies. The reported sensitivity and specificity of anti-PBP antibodies for differentiating between AIP and pancreatic cancer were 94% and 95%, respectively. It is unclear whether anti-PBP antibodies are associated with the subtype of AIP.

Other AIP-related antibodies have also been reported, such as anti-lactoferrin, anti-carbonic anhydrase-II/IV [28,29], anti-pancreatic secretory trypsin inhibitor [30], anti-amylase-alpha [31], and anti-heat-shock protein-10 antibodies [32]. However, data about these auto-antibodies are not available in Caucasian patients, most of whom have type II AIP. The clinical significance of these autoantibodies in AIP therefore remains unclear.

6   Imaging studies

Imaging is often necessary for the diagnosis of AIP, even though the imaging findings are generally nonspecific and cannot reliably differentiate between AIP and malignancy.

6.1   Computerized tomography (CT) and magnetic resonance imaging (MRI)

In patients with AIP, CT commonly shows a swollen, "sausage-like" pancreas with poorly visualized borders and a capsule-like low-density rim [33]. The enlarged pancreas is well enhanced in the delayed phase (Figure 1). A peripancreatic halo indicates a fibroinflammatory process extending into the peripancreatic adipose tissues, and diffuse narrowing of the pancreatic duct indicates non-occlusive peri-ductal inflammation [34].
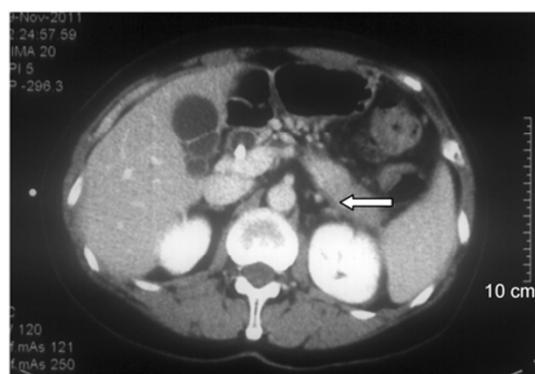
Figure 1   A 56-year-old woman with type I autoimmune pancreatitis. Enhanced abdominal CT showed a diffusely enlarged pancreas ("sausage-like") with enhancement, and a capsule-like low-density rim (arrow).

On MRI, T1-weighted images (T1WI) and T2WI often have less intense signal than the liver. Magnetic resonance cholangiopancreatography (MRCP) is a less invasive modality for imaging the pancreatic and bile ducts. The presence of diffuse narrowing and side branches without upstream dilation of the main pancreatic duct supports a diagnosis of AIP [35].

6.2   Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS)

ERCP is helpful for diagnosing AIP. Images may show a long, narrow ductal stricture (>1/3 of the main pancreatic duct) with side branches extending from the stricture, or multiple non-continuous strictures [36].

EUS is also useful for diagnosing AIP. The pancreas may show diffuse hypoechoic swelling with hyperechoic spots. EUS-guided fine-needle aspiration can be used to rule out pancreatic cancer, but the tissue obtained is usually insufficient to make a diagnosis of AIP. A core biopsy of the pancreas is required to definitively show the typical features of AIP [37].

7   Diagnosis and differential diagnosis

7.1   Diagnostic criteria

As pathological diagnosis of AIP requires invasive procedures, alternative diagnostic criteria have been developed, so that invasive procedures are required only in the most challenging cases. At least eight sets of diagnostic criteria have been proposed since 2002, including criteria by the Japan Pancreas Society (2002 and 2006) [38], Italy (2003 and 2009), the United States (the Mayo Clinic HISORt criteria (Histology, Imaging, Serology, Other Organ Involvement and Response to Therapy), 2006), Korea (2007), the Asian consensus criteria (2008), and the International Consensus Diagnostic Criteria (ICDC 2011) [8,39–41]. These criteria use a combination of clinical, serological, pathological, and imaging findings to diagnose AIP. The earlier sets of criteria mainly aimed to avoid missing cases of resectable pancreatic cancer, rather than confirm the diagnosis of AIP. The HISORt criteria have been the most widely adopted in the literature, and can be applied in daily clinical practice because of their simplicity and clarity. However, they only describe the features of type I AIP, and may miss cases of type II AIP. The ICDC 2011 criteria are also highly recommended, and incorporate the most up-to-date knowledge on both types of AIP. The ICDC 2011 criteria are comprehensive and detailed, and can be applied to clinical research, but may be too complicated for regular use in high-volume clinics.

7.2   Differential diagnosis

AIP may be misdiagnosed as many other pancreatic diseas-

es, including pancreatic cancer. Many patients with AIP have clinical and laboratory findings that are indistinguishable from pancreatic cancer, such as painless obstructive jaundice, elevated tumor markers, focal swelling or mass in the pancreas, stenosis of the biliary and pancreatic ducts, and encasement of peri-pancreatic arteries and portal veins. This often leads to unnecessary laparotomy or surgery because pancreatic cancer has a worse prognosis than AIP.

Radiological images showing diffuse swelling of the pancreas with a long stricture of the main pancreatic duct support a diagnosis of AIP. Upstream ductal dilation is relatively rare. On diffusion weighted MRI, AIP often shows multiple diffuse hyper-intense signals, while pancreatic cancer usually shows solitary signal. Apparent diffusion coefficient values are much higher in pancreatic cancer than in AIP [35]. A low-density mass that abruptly occludes the main pancreatic duct with distal atrophy is suggestive of pancreatic cancer. Other findings, such as intrahepatic metastatic lesions, are also helpful for diagnosing pancreatic cancer [29].

Involvement of extrapancreatic organs such as the lacrimal and salivary glands, retroperitoneum, lymph nodes, and kidneys is helpful for diagnosing AIP. Although 4%–7% of patients with pancreatic cancer have an elevated serum IgG4 concentration [22,42], a serum IgG4 concentration of >280 mg dL^{-1} is highly suggestive of AIP but not pancreatic cancer [23]. A diffuse plasma cell infiltrate with >30 IgG4-positive cells per high-power field and a ratio of IgG4 to total IgG of >50%, together with the characteristic histopathological findings, supports a diagnosis of AIP. Tissues from patients with AIP often show diffuse infiltration rather than focal aggregates of IgG4-positive plasma cells.

Although most patients with AIP respond promptly to glucocorticoid treatment, a trial of glucocorticoid treatment to differentiate between AIP and pancreatic cancer should be delayed until screening for pancreatic cancer has been completed, including EUS-guided fine-needle aspiration. If the patient does not respond as well to glucocorticoid treatment as expected, re-evaluation for pancreatic cancer should be undertaken. As a few patients with AIP develop pancreatic stones or malignancy during or after glucocorticoids therapy [43], close follow-up is warranted.

Lymphoma may mimic the histopathological manifestations of IgG4-related disease, and must be ruled out by clonality study. An early clue to the diagnosis of B-cell lymphoma is a predominantly B-cell infiltration. In contrast, the lymphoid inflammatory infiltration in AIP consists mainly of T-cells.

8   Treatment

8.1   Glucocorticoids

Patients with AIP who receive glucocorticoid treatment

have significantly higher remission rates of all aspects of clinical, histopathological, and serological findings than those who do not. Glucocorticoid treatment has also been reported to reduce the time to remission and improve the exocrine function of the pancreas [44,45]. The response to glucocorticoid treatment can be useful for differentiating between AIP and other pancreatic diseases. This characteristic has been incorporated into the Korean and Mayo Clinic diagnostic criteria for AIP, even though it has not been evaluated in a randomized trial, and most of our knowledge regarding treatment responses is derived from retrospective observational case studies with insufficient follow-up time. It is emphasized that when vital organs are affected, aggressive glucocorticoid treatment is warranted, because untreated IgG4-related disease can lead to severe organ dysfunction and failure. However, not all manifestations of the disease require immediate intervention, and the implementation of treatment also depends on the significance, functional status, and disease course of the organ affected. In some cases, the extent of disease does not warrant treatment. The suggested indications for glucocorticoid treatment include obstructive jaundice, abdominal pain, back pain, and symptomatic extrapancreatic lesions.

The Mayo Clinic has proposed treatment for AIP with prednisone 40 mg d^{-1} for 4 weeks, followed by tapering of 5 mg/week. However, more than 50% of patients treated according to this regimen relapsed in a median time of 3 months (0–14 months) after discontinuing prednisone. Kamisawa et al. [25] conducted a retrospective multicenter study in Japan to evaluate the efficacy of glucocorticoid treatment for AIP, which included 17 referral centers and 563 patients. Patients were treated with prednisolone at a dose of 0.6 mg kg^{-1} d^{-1} for 2–4 weeks followed by a tapering dose over 3–6 months and then continuing with 2.5–5.0 mg d^{-1} for up to 3 years. The remission rate was significantly higher in patients who received glucocorticoid treatment than those who did not (98% vs. 74%, *P*<0.001). Only 32% of patients treated with longer-term therapy experienced disease relapse within 6 months. Both subtypes of AIP respond promptly to glucocorticoid treatment, but the relapse rate was higher in patients with type I than with type II AIP, suggesting that different glucocorticoid maintenance regimens may be appropriate for different subtypes and that addition of immunosuppressant treatment may be warranted in patients with type I AIP.

The response to glucocorticoid treatment should be comprehensively evaluated, including improvements in symptoms (jaundice and abdominal pain, but not fatigue), biochemistry (liver function tests), serology (serum IgG4 concentration), and imaging findings (bile duct strictures and abnormal appearance of the pancreas on CT). Symptoms are usually relieved within 2 weeks after the initiation of glucocorticoid treatments, but the other manifestations do not always respond as rapidly. For AIP complicated by cholan-

gitis in patients with a biliary stent, glucocorticoid treatment may expedite the removal of the stent. Patients with extrapancreatic involvement generally respond well to glucocorticoid treatment, except when there is extensive fibrosis such as in cases of Riedel's thyroiditis or end-stage retroperitoneal fibrosis.

There is concern regarding the long-term use of glucocorticoid treatment in patients with AIP, who are often elderly and have an increased risk of developing osteoporosis, glucose intolerance, and gastrointestinal complications. Long-term glucocorticoid treatment may exacerbate pre-existing glucose intolerance caused by the underlying AIP, even though treatment may initially improve glucose intolerance. Only 40% of patients who have spontaneous remission without glucocorticoid treatment subsequently relapse. Long-term glucocorticoid treatment may therefore only be necessary in patients who tend to relapse and may be used at low dose.

8.2   Immunosuppressive agents

Immunosuppressive agents have been used for the treatment of refractory or recurrent AIP. However, data about their efficacy and treatment course are limited. Azathioprine, mycophenolate mofetil, 6-mercaptopurine, cyclophosphamide, and methotrexate are the most commonly used glucocorticoid-sparing and remission-maintenance drugs, but they have not yet been evaluated in clinical trials. The Mayo Clinic has proposed the use of immunosuppressive agents only in patients who have failed prednisone tapering at least once. The first choice of drug is either azathioprine (2.0–2.5 mg kg^{-1} d^{-1}) or mycophenolate mofetil (750 mg twice daily) [46].

8.3   Biological agents

For patients with recurrent or refractory disease in spite of glucocorticoid and immunosuppressant treatment or who are intolerant to these drugs, B-cell depletion with rituximab appears to be a promising treatment [47,48]. Rapid clinical responses have been reported, with a dramatic decrease in serum IgG4 concentrations but not the concentrations of other IgG subclasses [49]. Reduction in serum IgG4 concentration correlated with clinical improvement within weeks.

Bortezomib, a proteasome inhibitor that was initially used to treat multiple myeloma because of its cytotoxicity for plasma cells, has also been reported to be successful for treating other IgG4-related diseases [50]. No data are currently available regarding the efficacy of bortezomib for treating AIP.

Large prospective studies are needed to evaluate the effectiveness of these biological agents and determine optimal treatment regimens.

9   Prognosis

Little is known about the natural history of AIP. Spontaneous remission occurs in a proportion of patients, who often have lower serum IgG4 levels, less obstructive jaundice and diabetes mellitus, and focal rather than diffuse enlargement of the pancreas on CT. Some patients relapse over time and many develop extrapancreatic manifestations.

Kamisawa et al. [27] reported a relapse rate of 56% within 1 year and 92% within 3 years. The current evidence suggests that glucocorticoid maintenance therapy may be helpful in the prevention of disease relapse, even though the relapse rate remains high [51,52]. The potential risk factors for disease relapse in AIP include obstructive jaundice [51], extrapancreatic biliary ductal strictures [45,53], failure to achieve complete remission during maintenance therapy [54], and diffuse pancreatic swelling at baseline [55]. However, large prospective studies are needed to confirm these observations.

Untreated AIP often progresses from lymphoplasmacytic inflammation to extensive fibrosis. The fibroinflammatory lesions may result in permanent organ dysfunction, and are associated with high morbidity and mortality rates. Cirrhosis and portal hypertension occur in some patients, developing over months or years after the initial onset of symptoms [45]. Patients with extensive fibrotic lesions may respond less well to glucocorticoid and rituximab, although good treatment responses have been recorded in some cases [56]. AIP generally has a benign outcome if treated promptly. A study from the United States reported that both type I and type II AIP have 5-year survival rates similar to the age- and sex-matched general population [57].

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