REVIEW ARTICLE

Review Article: Diagnosis and Management of Igg4 Autoimmune Pancreatitis

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ABSTRACT

Autoimmune pancreatitis is a rare form of chronic pancreatitis that has only recently been recognized as a separate type of pancreatitis in the last two decades. The histopathological features of this distinct form of pancreatitis was first described as early as 1961 when the French Henry Sarles.

INTRODUCTION

Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis that has only recently been recognized as a separate type of pancreatitis in the last two decades. The histopathological features of this distinct form of pancreatitis was first described as early as 1961 when the French Henry Sarles [1] described a type of sclerosing pancreatitis associated with hypergammaglobulinemia. Subsequently, most of the early literature about AIP came from Japan where the concept of Autoimmune Pancreatitis (AIP)was first proposed in 1995 by Yoshida *et al.* [2] after many authors had reported a form of chronic pancreatitis associated with Sjögren's-like syndrome. The definition of AIP was widely accepted and AIP was differentiated from other types of chronic pancreatitis. An increasing awareness and further research of AIP has found it is a heterogeneous disorder with variations in pathophysiology, genetic predisposition and extra-pancreatic manifestations compared to chronic pancreatitis [3, 4].

Asian and European observations were reported differently. Reports from Asia described a disease affecting elderly males with pancreatic histology showing lymphoplasmacytic sclerosing pancreatitis (LPSP) [5], later called type 1 AIP. Reports from Europe and US described a disease that affects both genders equally with pancreatic histology characterized by granulocytic epithelial lesions (GEL) [6], later called idiopathic duct-centric chronic pancreatitis (IDCP) or type 2 AIP.

In 2001, Hamano *et al.* [7] reported increased serum levels of IgG4 in patients with AIP. Subsequently in 2004 a critical milestone was reached when Kamisawa *et al.*

[8] found intensely positive IgG4 cells in extrapancreatic organ systems in AIP patients. Thus, the concept of IgG4-related systemic disease emerged. Type 1 AIP is now considered to be a pancreatic manifestation IgG4-related disease whereas type 2 AIP appears to be a pancreas specific disorder.

EPIDEMIOLOGY

Up till now the true incidence of AIP is in the United States is unknown with reports limited to case series and descriptions of tertiary referrals. The estimated prevalence in Japan, where AIP was first described, is 0.82 per 100,000 persons [9]. Japanese series have estimated the prevalence of autoimmune pancreatitis in patients with chronic pancreatitis to be between 5% and 6%. Several series in the United States have reported that 2% to 3% of pancreatic resections had evidence of autoimmune pancreatitis at pathologic analysis [10-12]. AIP was diagnosed in approximately 2%-6% of patients that underwent pancreatic resection for suspected pancreatic cancer [13, 14].Type 1 AIP is the most common form worldwide, accounting for almost all cases in Japan and Korea and more than 80% of cases in Europe and the United States [15, 16]. Type 1 AIP has a peak incidence in the sixth or seventh decade of life [9, 16] and is at least twice as common in men as in women. It is frequently associated with sclerosing extra-pancreatic lesions such as sclerosing cholangitis, retroperitoneal fibrosis and sclerosing sialadenitis [17, 19]. On the other hand, Type 2 AIP seems to affect a younger subset of patients with a peak incidence typically about a decade younger than those with type 1 AIP with no gender preponderance [16]. There also appears to be an association between type 2 AIP and inflammatory bowel diseases especially ulcerative colitis [20-22].

CLINICAL PRESENTATION

The presentation of AIP can be variable [23]. It can be divided into an acute and a sub-acute phase. In the acute phase, the most common clinical presentation for both subtypes of AIP is obstructive jaundice, typically painless

or with mild epigastric pain. The jaundice of type 1 typically has a fluctuating course and spontaneous resolution has been reported [13, 24]. Features suggestive of acute pancreatitis such as abdominal pain and elevation of serum pancreatic enzymes greater than three times upper limit of normal are more often observed in type 2 AIP [15, 24-28]. Another key feature that can characterize type 1 AIP is other organ involvement (OOI) [21]. As previously mentioned, type 1 AIP is considered to be part of systemic IgG4-related disease, therefore, other organs can be involved prior, concomitant, or subsequent to pancreatic involvement. Thus type 1 patients can also present with manifestations , such as biliary disease, symptoms of Sjogren's disease, lung nodules, interstitial nephritis, retroperitoneal fibrosis, orbital pseudotumors, and diffuse or focal lymphadenopathy among others [29, 30].

In the subacute phase, after initial treatment, AIP can present with pancreatic atrophy leading to steatorrhea resembling chronic pancreatitis [21]. Diabetes mellitus (DM) or impaired fasting glucose is seen in up to 50% of patients with AIP. Interestingly, glycemic control improves in a subset of AIP patients following the treatment with corticosteroid therapy [31, 32].

PATHOPHYSIOLOGY

The exact pathophysiology of AIP has yet to be fully elucidated. It is an inflammatory and fibrosing disease marked by pancreatic lymphoplasmacytic infiltrates. An autoimmune cause of AIP has been inferred due to the profound response to steroid therapy and the pancreatic infiltrates of various types of immune cells, including CD4-positive T-cells, IgG4-producing plasma cells (in type 1 AIP), and granulocytes (in type 2 AIP)[21, 33-35]. Thus, the pathogenesis of AIP has been studied mainly from an immunological approach and focused mainly on type 1 AIP. The most striking observation is the association between serum IgG4 and AIP [7]. In healthy subjects, IgG4 constitutes the smallest fraction of total IgG in plasma (usually less than 5%) [36, 37] and elevation in serum IgG4 is seen in only a limited number of autoimmune and parasitic diseases [37-41]. It has been demonstrated that IgG4 antibodies are unable to activate the classical complement pathway and have limited binding to Fc-gamma receptor [42]. This can be explained by the fact that IgG4 antibodiesare involved in a continuous process referred to as 'Fab-arm exchange' or "half antibody exchange" by swapping a heavy-light chain pair with a heavy-light chain pair from another molecule . This results in a bispecific (two different Fab arms),but functionally monovalent, IgG4 that is unable to bind antigensand form immune complexes [43]. Therefore, most experts considered increased IgG4 levels to be an epiphenomenon rather than the cause of AIP. Some studies even suggested that they may be protective [44, 45] since IgG4 levels typically rise after prolonged exposure to a particular allergen and reduce the degree of chronic inflammation caused by the stimulating antigen.

Further evidence suggesting an autoimmune pathophysiology is the variety of autoantibodies against carbonic anhydrase, antinuclear antibody, rheumatoid factor, lactoferrin, trypsinogen and pancreatic secretory trypsin inhibitor [31, 46-48], although none of these are exclusive to AIP. Animal models of AIP have been limited, but have suggested AIP may be T-cell mediated since agents that increase regulatory T-cell population and activity (sirolimus, rapamycin) had significant benefits [4]. One proroposed mechanism for the pathogenesis of AIP is molecular mimicry in genetically predisposed persons [31, 46].

DIAGNOSIS

An accurate diagnosis of AIP remains challenging. The clinical and radiographic findings of AIP and pancreatic malignancy have a significant overlap and frequently AIP is misdiagnosed as pancreatic cancer and only realized after pathology from Whipple surgery returns as lymphoplasmotic infiltrates and no sign of carcinoma. More concerning though, is mistaking a diagnosis of pancreatic malignancy for AIP as delay in diagnosis is likely to close the already narrow window of curative surgical options in these patients [50]. Many diagnostic criteria have evolved over the last 15 years and reflected different approaches of medical practice between East and West. The first sets of diagnostic criteria were established by the Japanese Pancreatic Society in 2002 and 2006 (JPS 2002, 2006) [51, 52] and consisted of three main items: characteristic radiographic findings (including endoscopic retrograde pancreatocholangiography), serology tests, and histopathological findings .IgG4 was added to the serological evaluation in JPS 2006. In the United States and Europe diagnostic ERCP is used less commonly due to the risk of pancreatitis, therefore a different diagnostic approach (HISORt) was proposed by Chari et al.. of the Mayo Clinic in 2006 [53] . HISORt criteria (Figure 1) consisted of five cardinal features of AIP in histology, imaging and serology, other organ involvement, and response to corticosteroid therapy and newly introduced other organ involvement (OOI) and response to steroid (Rt) as diagnostic parameters whereas ERCP was excluded as a major factor.

Subsequently in 2010 during the 14th Congress of the International Association of Pancreatology, the International Consensus Diagnostic Criteria (ICDC) [21] were proposed in attempt to globally unify the AIP diagnostic criteria. ICDC were similar to the original HISORt five cardinal features proposed by Mayo clinic with the exception of steroid responsiveness considered optional in the ICDC criteria. ICDC also focused on the distinction between Type 1 and Type 2 AIP, and for four of the five criteria there are two levels of evidence according to their diagnostic reliability, For example, a greater than 2-fold elevation of IgG4 is considered a level 1 criteria; a lesser elevation level 2. Further specification is given for pancreatic ductal and parenchymal appearances, histology and response to steroids. With this stratification, Type 1

Criterion H-Histology (at least one of the following)	1. Periductal lymphoplasmacytic infiltrate, obliterative phlebitis, storiform fibrosis 2. Lymphoplasmacytic infiltrate, storiform fibrosis, abundant IgG4+ cells (≥10 HPF)
Criterion I-Imaging of pancreas	1. Typical-diffusely enlarged gland with delayed (rim) enhancement; diffusely irregular, attenuated main pancreatic duct 2. Others-Focal pancreatic mass/enlargement; focal pancreatic duct stricture; pancreatic atrophy; pancreatic calcification; pancreatitis
Criterion S-Serology	Elevated serum IgG4 (normal: 8-140 mg/dL)
Criterion O-Other organ involvement (can be confirmed by biopsy or resolution/ improvement with steroid therapy)	Hilar/intrahepatic biliary strictures; persistent distal biliary stricture; parotid/lacrimal gland involvement; mediastinal lymphadenopathy; retroperitoneal fibrosis
Criterion R-Response to steroid therapy	Resolution or marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy
Diagnostic of autoimmune pancreatitis when any of the following is fulfilled	1. Criterion H 2. Criterion I+S 3. Strong clinical suspicion of autoimmune pancreatitis (idiopathic pancreatic disease+Criterion S and/or O)+Criterion R

Figure 1. HISORt criteria for the diagnosis of autoimmune pancreatitis

AIP can be confirmed with a variety of combinations of level 1 and level 2 evidence, whereas by ICDC recommendations, a definitive diagnosis of Type 2 AIP requires histology. In late 2011, the Japanese Pancreatic Society released a revised criteria (JPS 2011) [54] which were more similar to ICDC with a notable difference of ERCP classified as indeterminate imaging evidence. An important goal of each of these diagnostic criteria was to avoid misdiagnosing pancreatic cancer which is much more common.

Serology

Given the presumed autoimmune etiology, numerous autoimmune antibodies have been reported to be elevated in AIP. Hamano *et al.*. was one of the first to report elevated serum IgG4 levels and IgG4-positive plasmacytic pancreatic infiltration in AIP patients [7]. Hamano *et al.* recommended a cut-off value of 135 mg/dL for serum IgG4 concentration to differentiate AIP from pancreatic cancer, which had an accuracy of 97%, a sensitivity of 95% and specificity of 97%. More recent studies reveal a much lower sensitivity and specificity. A Mayo Clinic cohort study including 45 AIP patients and 465 controls used a cut-off value of 140 mg/dl for IgG4 serum levels which gave a sensitivity, specificity and positive predictive value of 76%, 93% and 36% respectively [55]. A meta-analysis of seven studies, evaluating the usefulness of serum IgG4 in diagnosing AIP, showed variation in sensitivity and specificity ranging from 67–94% and 89–100%, respectively [56]. Type 1 AIP almost always has an elevated serum IgG4, whereas type 2 AIP most often does not have an elevated serum IgG4 level. It is important to keep in mind that up to 5% of control subjects and 10% of patients with pancreatic cancer may have elevated IgG4 [55, 57, 58]. Notably, some patients with type 1 AIP are seronegative for IgG4 [21]. IgG4 levels between 135 – 200 mg/dl should be interpreted with caution. Serum IgG4 levels were found to be elevated in cholangiocarcinoma and some had a more than 2-fold rise [59]. Also, CA 19-9 levels may be elevated in AIP [34,

56, 60-62]. Hence, elevated IgG4 alone cannot be used to make the diagnosis of AIP [62] and patients who are seronegative should not be assumed to have type 2 AIP. Though, elevated IgG4 cannot be used to make the diagnosis of AIP, twice-the-upper-limit-of-normal elevation markedly increased its specificity [55] and can be helpful to guide the diagnosis especially when combined with other features of AIP. IgG4 levels are frequently used to monitor AIP disease activity as steroids cause a decline in IgG4 relative to the clinical improvement.

Other antibodies have been associated with AIP but are not diagnostic and include antibodies to anti-plasminogen-binding protein peptides, carbonic anhydrase antigens, lactoferrin, pancreatic secretory trypsin inhibitor, anti-plasminogen-binding peptide antibody (PSTI or SPINK) as well as rheumatoid factor, antinuclear antibody, and anti-smooth muscle antibody [50, 63]. Although there are some preliminary strengths of association with these antibodies, none of these biomarkers appears to be sensitive or specific enough to serve as distinctive evidence of AIP. For now, elevation of IgG4 serum levels to greater than two fold the upper limit of normal remains the most reliable and reproducible indicator that a patient has AIP [64].

IMAGING

Pancreatic imaging is essential in the diagnosis of AIP. It can be subdivided into pancreatic parenchymal imaging and pancreatic ductal imaging. Parenchymal imaging by computed tomography (CT) or magnetic resonance imaging (MRI) is usually performed as part of initial work up of obstructive jaundice. Though MRI and CT have comparative results, the lower cost and more availability of CT has made it rapidly the imaging modality of choice to diagnose AIP. Three different forms of the disease process can be seen diffuse, focal or multifocal disease, with the diffuse form being the most common. The classic features of diffuse disease on a pancreas protocol abdominal CT are a diffusely enlarged, sausage-shaped pancreas with

featureless borders, a low-density rim surrounding the pancreas, and delayed enhancement of the pancreas in the late arterial phase [65, 66, 67]. This enhancement pattern is distinct from that of pancreatic cancer and is applied to contrast-enhanced EUS for the differentiation of AIP and cancer by analyzing time-intensity curves [68, 69]. Peripancreatic stranding is usually minimal in AIP, unlike other forms of pancreatitis [70]. On MRI, the pancreas appears diffusely hypointense on T1weighted images, is slightly hyperintense on T2weighted images and exhibits heterogeneously diminished enhancement during the early phase and delayed enhancement during the late phase of contrast enhancement . The rim is hypointense on both T1and T2 weighted images, and has delayed enhancement on contrastenhanced MRI [71, 72]. Focal disease also called "mass-forming autoimmune pancreatitis" is less common than diffuse disease and manifests as a focal mass, often within the pancreatic head that is typically isoattenuating or hypoattenuating to the spared, non-enlarged segment of pancreatic parenchyma making it indistinguishable from pancreatic cancer[11, 59, 73]. Sometimes however focal AIP may involve the dorsal pancreas or the pancreatic tail [33]. Multi-focal involvement is also evident a can also mimic multifocal pancreatic cancer [74]. Although exact estimates vary, it is more common for type 2 autoimmune pancreatitis to present with focal pancreatic involvement relative to type 1[13, 75, 76].

Pancreatic duct imaging with endoscopic retrograde pancreatography (ERP) can be a useful adjunct in the diagnosis of AIP, especially in patients with non-classic CT abdominal features for AIP. ERCP features of AIP include the presence of a long narrow stricture (more than one third of the main pancreas duct), the lack of upstream dilation from the stricture, side branches arising from the strictured portion of the duct, and multiple noncontiguous strictures longer than 3 cm in the diffuse form of AIP [77]. MRCP is a less invasive with fewer adverse events, but MRCP cannot completely replace ERCP for diagnosing AIP, since experts believe main pancreatic ductal narrowing may best be visualized with ERCP [78, 79].

Endoscopic ultrasound (EUS) classically exhibits a diffusely hypoechoic gland. However, the greatest advantage of EUS is the ability to obtain tissue. Tissue sampling via fine-needle aspiration is sufficient for diagnosing pancreatic cancer, but a core biopsy of the pancreas is likely to have all the features of LPSP and diagnose AIP [80]. Though there might be some technical limitations for using EUS-TCB needles especially in pancreatic head lesions, is an accurate procedure for the diagnosis of AIP and can serve as a rescue technique in cases of AIP lacking typical imaging or serological findings. Furthermore, EUS-TCB can provide histological diagnosis of AIP regardless imaging or serological findings [81].

Histology

The traditional 'gold standard' for the diagnosis of autoimmune pancreatitis is characteristic histology.

AIP shows well-defined histopathological changes in the pancreas that are easily differentiated from changes occurring in other types of pancreatitis. Some of these types are common findings for type 1 and type 2 and others are used to differentiate both groups. Common histologic features for both subtypes include (periductal lymphoplasmacytic infiltrate and an inflammatory cellular stroma), which can positively differentiate it from other types of chronic pancreatitis [3, 21, 82, 83]. Other features serve as the basis for distinguishing the two clinical phenotypes of AIP. Differentiated by expert pathologists. The histopathological pattern of type 1 AIP is called lymphoplasmacytic sclerosing pancreatitis (LPSP). It is characterized by a periductal lymphoplasmacytic infiltrate, peculiar storiform fibrosis and obliterative phlebitis, and abundant IgG4 immunostaining (>10/ high power field IgG4-positive cells [21]. When most, if not all, of these features are present, they substantiate the diagnosis of type 1 AIP. In this context, it is important to point out that the presence of IgG4-positive cells is just one of the features of LPSP and that the histologic diagnosis of type 1 AIP should not be made or excluded solely on the presence or absence of this one feature alone. Similar histological features might also be seen in other organs involved in type 1 AIP.

The histological hallmark of type 2 AIP is the presence of granulocytic epithelial lesions (GEL) in pancreatic ducts, which can lead to duct destruction [6, 82, 84] .Obliterative phlebitis is uncommon in type 2 AIP, and there are scant to no IgG4-positive cells. Although type 2 AIP also has storiform fibrosis and a lymphoplasmacytic infiltrate, these features are less prominent than in type 1 AIP. In both forms of AIP, there is a conspicuous absence of intraductal protein plugs, stones, and pseudocysts; the usual features of other types of chronic pancreatitis.

Other Organ Involvement (Extra Pancreatic Manifestations)

As mentioned above, Type 1 AIP is the pancreatic manifestation of a multisystem disease. Thus, the well-described pattern of the multiple other organs involved is an important clue to the diagnosis [3, 85-89]. The most common extrapancreatic site of involvement is the biliary tree [85]. This condition has been termed IgG4-associated cholangitis (IAC), sometimes called IgG4 sclerosing cholangitis (IgG4-SC) and has been reported to occur in 20%-88% of cases of AIP [90]. A possible overlap between IAC and primary sclerosing cholangitis (PSC) is also suggested by the finding that 9%-36% of patients with PSC have increased serum IgG4 levels, compared with less than 1% in other liver diseases [60, 91]. Cholangiograms may be able to distinguish between these two entities by highlighting the short band-like biliary strictures, with diverticulum formation and a beaded appearance typical of PSC, compared with the longer, segmental strictures with pre-stenotic dilation found in IAC. Strictures of the distal common bile duct are also more common in IAC than in PSC [92].

Other affected organs include salivary glands(sialadenitis), chest (including mediastinal fibrosis and adenopathy), retroperitoneum (chronic periaortitis, idiopathic retroperitoneal fibrosis), kidneys (tubulointerstitial nephritis) and orbits (IgG4-associated pseudolymphoma) [30]. There are other organs that have been less frequently reported, such as aorta, prostate, breast, meninges, thyroid, pericardium and skin [30]. Extrapancreatic lesions have been reported as showing pathological findings similar to the pancreas, including massive lymphoplasmacytic infiltration and fibrosis, obliterating phlebitis, and presence of prominent IgG4 positive plasma cells [93]. These lesions can be detected incidentally in cross-sectional images and whole body imaging such as 18F-Fluoro-deoxyglucose positron emission tomography (PET) [94, 95] and Gallium scintigraphy [96].

Extrapancreatic disease can be a useful factor in the diagnosis of AIP, distinguishing it from pancreatic cancer, and forms part of the HISORt and ICDC criteria. It also provides collateral evidence for AIP, according to the IAP diagnostic guidelines.

A Practical Approach to Diagnose AIP

There is no single diagnostic test for AIP and there is significant variation in clinical practice worldwide. The complexity of the criteria used in the ICDC is necessary due to the protean disease presentations. Applying ICDC strictly is necessary to avoid misdiagnosing pancreatobiliary malignancies and AIP diagnosis can't be established without exluding maliganacy first. Thus, the responsibility of the clinician is primarily to exclude malignancy rather than to establish an AIP diagnosis. As mentioned above, pancreatic enlargement can be focal or diffuse based on pancreatic parenchymal imaging. When typical imaging (e.g., diffuse pancreatic enlargement with delayed enhancement of the parenchyma, with or without presence of a capsule sign) is present any non-ductal imaging collateral evidence (i.e. elevated serum IgG4 OR presence of OOI) will establish an AIP diagnosis. In these patients a diagnostic steroid trial and core biopsy of pancreas are unnecessary to support the diagnosis.

On the other hand, if the pancreatic imaging shows focal/segmental enlargement particularly in the presence of a low-density pancreatic mass at imaging, the first diagnostic goal is to exclude pancreatic cancer, even if the presence of clinical (young age, other organ involvement), radiological (perfusion of the pancreatic mass suggestive of inflammation, no or mild dilation of the main pancreatic duct) and serological (high level of IgG4, presence of autoantibodies, low serum levels of Ca 19-9) findings are suggestive of AIP. Therefore, pancreatic biopsy is mandatory. EU-FNA provides a sensitive modality for detecting pancreatic cancer.

TREATMENT AND RELAPSE

Unlike other forms of pancreatitis, AIP is very responsive to steroid therapy, therefore making therapy a component of the diagnostic criteria. For now, steroids remain the mainstay treatment of AIP, although the relapse rate is significant. Steroids have been shown not only to improve AIP symptoms, labs and radiographs, but also possibly prevent further complications such as sclerosing cholangitis, bile duct stenosis and retroperitoneal fibrosis [97]. A large multicenter, Japanese, retrospective trial from Kamisawa *et al.* in 2009 identified 563 patients with AIP and found that 98% responded to steroid therapy versus 74% that improved without [98]. Another recent large multinational analysis of data obtained from 23 institutions from 10 different countries and included 1064 patients meeting the ICDC diagnostic criteria for either type 1 or type 2 AIP, showed that 99% of type 1 AIP patients and 92% of type 2 AIP patients went into clinical remission with steroid therapy [16]. A wide variety of steroid regimens were employed for induction and maintenance of remission. Most experts use an initial weight-based (0.6 mg/kg/d) or fixed-dose (30-40 mg/d) regimen [15, 16]. Currently, there is no consensus on the definition of 'clinical remission, the degree of radiological improvement needed prior to initiating steroid taper, or what constitutes 'radiological remission'. Clearly defining remission is an important issue in the treatment of AIP sincepatients who experience relapse during the course of steroid taper or while on steroid maintenance might represent a recrudescence of residual disease which is not yet in remission [99]. Due to a lack of consensus on when to initiate a tapering regimen, most experts rely on objective data such as radiologic evidence of a dramatic decrease in the pancreatic mass or other organ involvement, resolution of the obstructive jaundice without biliary stenting, and normalization of liver function tests. It is also important to keep in mind that changes in serum IgG4 levels vary with treatment and should not be used as a criterion to determine response to therapy. Moon *et al.* have suggested that two weeks may be sufficient to determine the response [60] and if there is no improvement or if the CA 19-9 level is rising, then the diagnosis of AIP should be reconsidered and further efforts to rule out pancreatic cancer should be pursued [3, 73].

Multiple tapering regimens have been also advocated. Asian centers use a maintenance strategy of low-dose (2.5–5 mg/day) prednisolone, which is continued for anywhere from 6 months to 3 years [98, 100]. The main purpose of maintenance therapy here is to prevent relapses which can be evident in up to 30% to 50% of AIP type 1 patients after the first course of corticosteroid therapy [16, 25]. In contrast, American and European centers do not typically use maintenance steroids. Based on The Mayo Clinic's experience, more than half of patients do not relapse within 3 years after induction therapy with steroids [25, 101]. Therefore, they suggested that maintenance therapy is not warranted in all patients since risks of long term steroid use outweighs the benefits [15]. A recent small series by The Mayo Clinic attempted to employ steroid-sparing immunomodulators (IMs) such as azathioprine in a maintenance regimen in AIP patients, but the relapse-free survival was similar to those treated with steroids.

A report from the Mayo Clinic outlining their experience treating relapsed type 1 AIP demonstrated that steroids plus IM were equivalent to steroids alone [102]. This study also reported on 12 patients that received Rituximab, an anti-CD20 antibody,for treatment of refractory AIP or steroid/IM intolerance. Ten of the 12 patients achieved complete remission, one patient had a partial response and was then found to have cholangiocarcinoma, and the last patient had a symptomatic improvement, but continued to require steroid therapy [103].

A wide range of relapse rates after an initial course of steroids have been reported [104]. This variation may be due to the heterogeneity of AIP, the lack of a uniform definition of disease relapse, various study designs, short follow-up times, ethnic variability, and differences in steroid regimens. Relapses are generally more common in type 1 AIP than in type 2 AIP. A large recent multinational analysis reported relapses in 31% of patients with type 1 AIP and 9% of patients with type 2 AIP after steroid discontinuation [16]. Higher serum IgG4 levels and extra-pancreatic involvement have been found to be associated with higher relapse rates [105]. Whereas most experts agree that an isolated serologic relapse (repeat elevation in serum IgG4) does not necessitate maintenance therapy, clinical relapse (obstructive jaundice, recurrence of OOI, weight loss)or radiological relapse (enlarged pancreas, presence of new duct strictures) will often necessitate a second course of corticosteroid therapy [90, 102, 106]. Treatment of relapse is usually achieved with the same initial dose of corticosteroids, though the Japanese consensus guideline recommend to a more gradual taper [102].

Conflicting Interest

The authors had no conflicts of interest

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