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REVIEW

Autoimmune pancreatitis: Cornerstones and future perspectives

Camilla Gallo, Giulia Dispinzieri, Nicola Zucchini, Pietro Invernizzi, Sara Massironi

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Abstract

Autoimmune pancreatitis (AIP) is an autoimmune subtype of chronic pancreatitis resulting from the aberrant immune response against the pancreas, leading to inflammation and fibrosis. Although AIP is rare, its incidence is increasing and is often misdiagnosed as other pancreatic diseases. AIP is commonly classified into two types. Type 1 AIP (AIP-1) is typically associated with elevated serum immunoglobulin G4 (IgG4) levels and systemic manifestations, while type 2 AIP is typically a more localized form of the disease, and may coexist with other autoimmune disorders, especially inflammatory bowel diseases. Additionally, there is emerging recognition of a third type (type 3 AIP), which refers to immunotherapy-triggered AIP, although this classification is still gaining acceptance in medical literature. The clinical manifestations of AIP mainly include painless jaundice and weight loss. Elevated serum IgG4 levels are particularly characteristic of AIP-1. Diagnosis relies on a combination of clinical, laboratory, radiological, and histological findings, given the similarity of AIP symptoms to other pancreatic disorders. The mainstay of treatment for AIP is steroid therapy, which is effective in most cases. Severe cases might require additional immunosuppressive agents. This review aims to summarize the current knowledge of AIP, encompassing its epidemiology, etiology, clinical presentation, diagnosis, and treatment options. We also address the challenges and controversies in diagnosing and treating AIP, such as distinguishing it from pancreatic cancer and managing long-term treatment, highlighting the need for increased awareness and knowledge of this complex disease.

Key Words: Autoimmunity; Pancreatitis; Autoimmune pancreatitis; Immunoglobulin G4; Steroids; Relapse

Core Tip: Autoimmune pancreatitis (AIP) is rare and often misdiagnosed. The lymphoplasmacytic sclerosing form, type 1 AIP (AIP-1), represents the pancreatic manifestation of immunoglobulin G4-related disease, while the idiopathic ductal centric form, type 2 AIP (AIP-2), is often associated with inflammatory bowel disease. AIP-1 presents with obstructive jaundice or abnormalities in exocrine and endocrine pancreatic function; AIP-2 usually shows abdominal pain and acute pancreatitis. The atypical mass-forming abnormality of the pancreas implies the need to histologically distinguish AIP form pancreatic ductal adenocarcinoma. Steroids are the first-line therapy for both AIP-1 and AIP-2, rituximab is a good alternative for AIP-1. Given the high relapse rate, long-term maintenance therapy is recommended. Scientific efforts are focusing on target therapies.

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INTRODUCTION

Definition

Autoimmune pancreatitis (AIP) is a relatively rare, specific form of chronic benign pancreatic disease characterized by obstructive jaundice, with or without pancreatic masses, histologic evidence of a specific lymphoplasmacytic infiltrate and fibrosis, and a dramatic response to steroid therapy[1].

Two main forms of AIP have been described: Type 1 AIP (AIP-1), known as lymphoplasmacytic sclerosing pancreatitis, and type 2 AIP (AIP-2), known as idiopathic ductal centric pancreatitis[2], which differ mainly in epidemiology, pathogenesis, clinical presentation, histologic pattern, and natural history.

AIP-1 predominantly affects men in their sixth to seventh decade of life, and is usually painless, although mild epigastric pain may occur in about one third of patients[3]. It represents the pancreatic manifestation of immunoglobulin G4 (IgG4)-related disease (IgG4-RD), a rare, immune-mediated, systemic fibro-inflammatory multi-organ disease that often determines the growth of inflammatory pseudotumors in the affected organs. IgG4-RD usually affects two or more organs, with AIP-1 and IgG4-related cholangitis (IRC) being the most common manifestations (45% of cases overall). However, other possible typical localizations of the disease include retroperitoneal fibrosis, sialadenitis and dacryoadenitis (Mikulicz disease), Riedel's thyroiditis, mediastinal lymphadenopathy, aortic and/or renal involvement, and interstitial lung disease[4]. Based on the distribution of organ involvement, four characteristic IgG4-RD phenotypes can be distinguished: Pancreatic-hepatobiliary disease, which is the most common; retroperitoneal fibrosis and/or aortitis; disease confined to the head and neck; Mikulicz syndrome with systemic involvement[5]. IgG4-RD is characterized by the following histologic features: lymphoplasmacytic infiltrates rich in IgG4+ plasma cells [> 10 per high-power field (HPF)], storiform fibrosis, and obliterative phlebitis. Circulating IgG4 levels may vary, but the ratio of circulating IgG4 to IgG levels is typically > 10%[6].

AIP-2 usually affects younger subjects without sex differences. It manifests as acute symptomatic pancreatitis, with specific involvement of a single organ. AIP-2 is caused by dysimmune fibro-inflammatory infiltration of the middle and small pancreatic ducts (PDs) and pancreatic acini, leading to the formation of pathognomonic granulocytic epithelial lesions (GELs)[7]. In 15%-30% of cases, AIP-2 is associated with inflammatory bowel disease (IBD), typically ulcerative colitis (UC). For this reason, anti-neutrophil cytoplasmic antibodies (p-ANCA and c-ANCA) can often be detected in patients with AIP-2[8], although no specific serological markers are currently available: Serum IgG4 Levels are usually normal or only slightly elevated.

A third type of AIP has recently been described: Type 3 AIP (AIP-3) is a mostly asymptomatic or rarely paucisymptomatic form of pancreatic injury that exclusively affects patients with advanced malignancies. It is an iatrogenic entity caused by a non-specific, inflammatory T-cell mediated immune response against PDs and acini, triggered by immune checkpoint inhibitors (often anti-PD-1 and anti-CTLA4). The disease typically occurs 4-6 months, rarely more than 12 months, after the start of therapy. It is not characterized by pathognomonic histopathologic lesions, and it is usually seronegative, although elevated IgG4 levels have been occasionally described[9].

Epidemiology

Few data are available on the overall prevalence and incidence of AIPs. Among the possible immune-mediated pancreatic disorders, AIP-1 is the most common and accounts for the vast majority of cases[10]; it is more common in Asia than in the United States and European Union[11]. Regarding AIP-1, thanks to the increasing awareness of IgG4-RD and the dissemination of diagnostic guidelines, large-scale epidemiological data have recently been published, mainly from Japan. According to a nationwide epidemiological survey conducted in 2016, AIP-1 showed an incidence of 1-3 cases per 100,000 adults and a prevalence of approximately 10 cases per 100000 adults; compared with previously published data, these results have more than doubled in less than 5 years. The reported male-to-female sex ratio was 2.94:1, and the mean age at diagnosis was 64.8 years[12]. The first raw data published in Italy showed that AIP-1 affects approximately 6% of the general population, and accounts for 61% of AIP cases[3].

On the other hand, AIP-2 is more prevalent in Western countries than in Asia[13], with an estimated prevalence rate of 4.6–6% in acute and chronic pancreatitis and about 1-4 cases per 100000 adults in the general population[2-14]. Only two Asian studies investigated the epidemiology of AIP-2 in IBD patients and reported a prevalence of 0.3%-0.5%[15,16], which is approximately 100-fold higher than in the general population, and may even be underestimated due to the difficulty of diagnosing AIP-2, which often requires histological confirmation. On the other hand, 49%-67% of AIP-2 patients have concomitant IBD, which means that AIP-2 patients have a 12-15-fold higher risk of having a concurrent IBD compared to the general population[17]. According to an Italian multicenter study, AIP-2 accounts for 28% of all AIP cases. Compared to AIP-1, younger people are more likely to be affected, with no significant gender difference between men and women[3].

According to a recent American review on AIP-3, the incidence of AIP-3 among all immune-mediated adverse events with immune checkpoint inhibitors is between 0.6% and 4%[9].

Etiopathogenesis

Despite numerous attempts, the pathogenesis of AIP-1 is still unclear. As it is the pancreatic manifestation of IgG4-RD, it is a multifactorial disease in which both genetic and environmental factors play a pivotal role. Genome-wide association studies in IgG4-RD-affected patients revealed a significant association between mutations in human leukocyte antigen *DRB1* genes encoding macrophage-type toll-like receptors (TLRs) II major histocompatibility complex (MHC)[4]. The overexpression of certain types of TLRs in the pancreas highlights the central role of the innate immune system in the development of AIP-1. Plasmacytoid dendritic cells (pDCs) may also play a key role in the pathogenesis of AIP: They are involved in host defense against microbial infections and are the major source of type 1 interferons (IFN-I)[18]. The unregulated production of IFN-I and, consequently, of interleukine (IL)-33 by pDCs could underlie AIP-1. IL-33, which is also produced by overexpression of certain types of TLRs, may promote activation of mainly Th2 cells and regulatory T cells that produce IL-4 and IL-10, respectively, which in turn are responsible for switching immunoglobulins to the IgG4 subclass[19]. The role of IgG4 in the development of AIP-1 and IgG4- RD is still unclear, but it is hypothesized that IgG4 may play a role in the activation of the complement system after the presence of immune complexes has been demonstrated in IgG4-RD-affected tissues[20].

In addition to the activation of T helper and T reg CD4+ lymphocytes that follows the interaction between TLRs and MHC-II, also the interaction between T follicular helper (Tfh) cells, especially circulating type 1 Tfh cells, and SLAMF7, a member of the Signaling Lymphocyte Activation Molecule family receptors, promotes IgG4 release[21]. SLAMF7 is implicated in homotypic interactions with activated B cells and, thus, it is involved in disease immunopathogenesis. SLAMF7+ CD4+ cytotoxic T cells (CTLs) are unusual CD4+ cells, which have been shown to express cytotoxic mediators that are typically expressed by CD8+ cells, and have been shown to have the potential to both stimulate fibroblast activation and interact with antigen-presenting B cells[22]. Recent studies have shown that SLAMF7+ CD4+ CTLs are increased in the peripheral blood of subjects with active IgG4-RD, and thus represent a key pathological factor in the disease[23].

Furthermore, cellular components that form the fibro-inflammatory pancreatic aggregate include eosinophils, which are attracted to the pancreatic site primarily by the chemotactic action of eotaxin. It is noteworthy that elevated levels of circulating eotaxin-1 and 3 have been detected in AIP-1 patients[24]. The presence of elevated levels of circulating IgE and IgG4 in IgG4-RD and AIP-1 and the presence of eosinophilic infiltrates in the pancreas suggest that, in addition to genetic predisposition, environmental factors play an important role in the development of AIP-1. Prolonged exposure to certain exogenous antigens and molecular mimicry between these antigens and some autoantigens may lead to overactivity of specific types of TLRs that trigger a dysimmune response directed against the endogenous autoantigens[4].

Regarding the pathogenesis of AIP-2, the Th-17 subset of CD4+ effector T cells plays a crucial role in infiltrating the periductal pancreatic tissue, where they release inflammatory cytokines, mainly IL-17, IL-21, IL-22, and IL-23[25]. The reasons leading to this hyperactivation of Th-17 cells and their migration into pancreatic tissue are not yet clear. However, there may be a link with genetic mutations in the genes for multiple endocrine neoplasia 1 and polycystic kidney and liver disease 1, which are frequently found in AIP-2 patients[26]. Moreover, the pathognomonic AIP-2 GELs consist not only of lymphocytes but mainly of neutrophils that migrate and aggregate in the periductal pancreatic tissue, attracted by the chemotactic function of IL-8, which in turn is stimulated by IL-17[27]. IL-8 was overexpressed not only in AIP-2 cases but also in UC patients, suggesting that it is an immunological biomarker for the coincidence of AIP-2 and UC[28].

The increasing awareness of the relationship between specific alterations in the composition of the gut microbiota and the innate immunological response, and thus the development of autoimmune diseases, led to the hypothesis of a possible role of the microbiota in the etiopathogenesis of AIP, particularly *K. Pneumoniae*[29]. This possible gut-pancreas axis could apply not only to AIP-2, for which the correlation data between IBD and changes in the gut microbiota are strong but also to AIP-1[30].

Finally, the etiopathogenesis of AIP-3 is closely related to the administration of checkpoint inhibitors, which trigger a non-specific inflammatory immune response mediated by T cells, mainly CD8+ T cells, resulting in an increased ratio of CD8+/CD4+ T lymphocytes[31,32]. In Figure 1, a concise overview of the etiopathogenetic mechanisms underlying AIP-1, AIP-2, and AIP-3 is provided.

CLINICAL AND SEROLOGICAL FEATURES

The two main forms of AIP described, AIP-1 and AIP-2, have two distinct clinical phenotypes. AIP-1 occurs mainly in older men and is usually painless. According to an international multicenter study, the most common symptom is

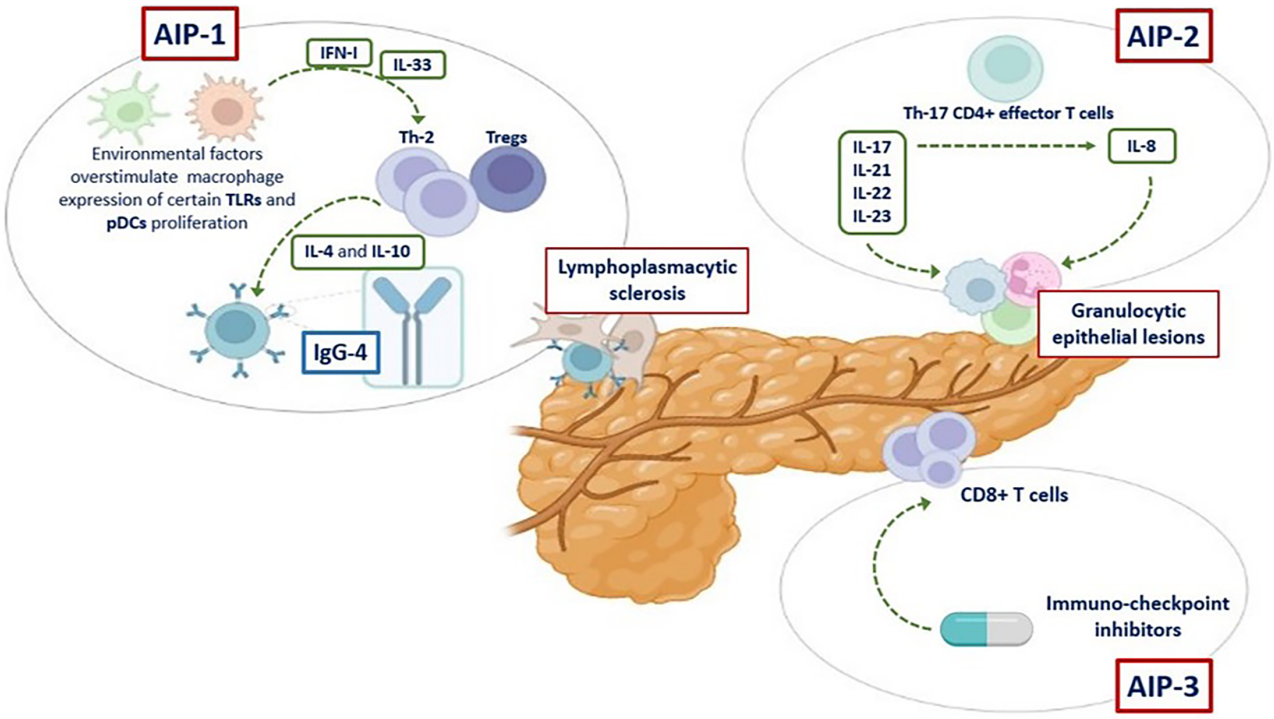

Figure 1 Ethiopathology of different types of autoimmune pancreatitis. Ethiopathological mechanisms of type 1 autoimmune pancreatitis, type 2 autoimmune pancreatitis, and type 3 autoimmune pancreatitis. AIP: Autoimmune pancreatitis; IFN: Interferon; IL: Interleukine; TLRs: Toll-like receptors; pDCs: Plasmacytoid dendritic cells; IgG4: Immunoglobulin G4; AIP-1: Type 1 autoimmune pancreatitis; AIP-2: Type 2 autoimmune pancreatitis; AIP-4: Type 3 autoimmune pancreatitis.

obstructive jaundice, which occurs in 75% of cases[10] and is thought to be due to compression of the common bile duct by the mass/swelling of the pancreatic head or by direct infiltration of biliary wall with lymphocytes and plasma cells [33]. Less commonly, AIP-1 manifests with abdominal symptoms (in nearly 40% of patients), such as abdominal pain or malaise, and more rarely with acute pancreatitis. Other clinical manifestations include weight loss and abnormalities of exocrine and endocrine pancreatic function, with diabetes mellitus that may occur before (33%), concurrently (52%), or after steroid treatment[6]. It may also manifest as diffuse, focal, or segmental enlargement of the pancreas, mimicking PD adenocarcinoma (PDAC), from which it must be differentiated. As it is the pancreatic manifestation of IgG4-RD, AIP-1 usually occurs with the involvement of other organs, such as biliary stricture, renal involvement, orbital pseudotumor, extensive lymphadenopathy, and retroperitoneal fibrosis. The most common clinical presentation of IgG4-RD sees the involvement of the bilio-pancreatic district, such that AIP-1 and IRC occur together in 80% of cases. It should be noted that although the involvement of other organs supports the diagnosis of AIP, the absence of involvement of other organs does not exclude AIP-1, and isolated pancreatic involvement is seen in approximately 50% of patients[34]. IgG4-RD is a multisystemic fibroinflammatory disease characterized by elevated serum concentration of IgG4 and accumulation of IgG4-expressing plasma cells in the affected organs[35]. However, serum IgG4 plays an increasingly minor role in the diagnosis of AIP-1 and IgG4-RD. Recent studies have shown that up to half of patients with biopsy-proven and clinically active IgG4-RD may have normal serum IgG4 concentrations[36]. Furthermore, only 10% of patients with elevated serum IgG4 levels were diagnosed with IgG4-RD, underscoring the lack of specificity of this test[37].

While AIP-1 has a mostly asymptomatic clinical course, AIP-2 manifests more frequently with abdominal pain and acute pancreatitis. Acute pancreatitis occurs in nearly 50% of patients[28]. Other manifestations include painless obstructive jaundice, focal pancreatic masses, and symptomatic PD strictures[38], similar to AIP-1 patients. Compared with AIP-1, AIP-2 typically affects younger patients, with an average age of 40 years, and has no gender predilection. Although AIP-2 can also occur with exclusive pancreatic involvement, a strong association between AIP-2 and concurrent IBD, especially UC, has been reported, as mentioned previously[17]. In most cases, the diagnosis of IBD precedes the diagnosis of AIP-2, but it is unclear whether active IBD plays a role in the development of AIP-2. According to an Italian retrospective study at IBD-AIP, 68% of patients had a prior or concomitant diagnosis of UC, but only 44% had active disease[39]. However, a French study with a similar group of patients shows that 80% of patients had a previous or concomitant diagnosis of IBD, and about 70% had active disease at the onset of AIP[40]. Table 1 resembles the differential characteristics between AIP-1 and AIP-2.

RADIOLOGICAL PRESENTATION

Contrast-enhanced (CE)-computed tomography (CT) and magnetic resonance imaging (MR) (MRI) have proven useful in the imaging diagnosis of AIP. Imaging abnormalities of the pancreas are virtually indistinguishable between AIP-1, AIP-

Table 1 Differential characteristics between type 1 and type 2 autoimmune pancreatitis

	AIP-1	AIP-2
Gender (M:F)	3:1	1:1
Mean age at disease onset	60-70 yr	40-60 yr
Epidemiology	Asia > Western Countries	Western Countries > Asia
Main clinical manifestations	Painless jaundice (75%); Abdominal symptoms (40%)	Abdominal pain and acute pancreatitis (50%)
	Weight loss	
	Diabetes and exocrine pancreatic insufficiency	
Extrapancreatic manifestations	IgG4-related disease extrapancreatic manifestations (50%)	IBD (49%-67%)
	Hepatobiliary disease	
	Retroperitoneal fibrosis and/or aortitis	
	Head and neck involvement	
	Mikulicz syndrome	
Serum IgG4 levels	Elevated (circulating IgG4 to IgG levels typically > 10%) (50%)	Normal (p-ANCA and c-ANCA autoantibodies often positive)
Histologic features	Lymphoplasmacytic infiltrates rich in IgG4+ plasma cells	Granulocytic epithelial lesions
	Storiform fibrosis	
	Obliterative phlebitis	
Steroid therapy	Responsive	Responsive
Relapse	High rate (39%)	Rare

AIP: Autoimmune pancreatitis; IBD: Inflammatory bowel disease; ANCA: Anti-neutrophil cytoplasmatic antibodies; IgG: Immunoglobulin G; AIP-1: Type 1 autoimmune pancreatitis; AIP-2: Type 2 autoimmune pancreatitis.

2, and AIP-3[9,41]. The differential diagnosis between these three different nosographic entities is mainly based on the combination of history, clinical presentation, histopathologic findings, and, in the case of IgG4-RD-involvement of the pancreas, the possible presence of combined characteristic radiologic findings reflecting coexisting pathologies in other affected organs[42]. Furthermore, CE-CT and MRI scans do not always allow a correct differential diagnosis between mass-forming AIP and PDAC, which is challenging because of their common epidemiologic and clinical manifestations [43].

Typical CT features of AIP include focal or diffuse sausage-like swellings of the parenchyma with straight margins, rectangular shape of the tail (cut-tail sign), and consequent loss of the typical lobular structure[44] (Figure 2). An exception is elderly patients, in whom the age-related reduction in pancreatic volume may mask the presence of inflammatory swelling of the organ[45].

Due to the presence of fibrosis, the arterial or pancreatic phase of the CE-CT scan typically shows a homogeneous reduced enhancement of the affected areas compared with the normal pancreatic parenchyma, whereas a gradually increasing enhancement is detectable in the delayed phases of the dynamic scan[46,47]. Small areas of normal pancreatic parenchyma may remain focal in association with the affected lesions: such areas maintain normal arterial blood flow and may therefore be visualized as punctate, speckled, or dotted contrast enhancement in the arterial phase[45]. These findings help to distinguish AIP from PDAC[48].

As a result of the physio-pathological accumulation of the fibrotic component at the periphery of the inflammatory areas (be it the pancreas as a whole or the intrapancreatic pseudotumor lesions), a capsular rim demarcates the swollen pancreas and/or the pseudotumoral affected areas, with a typical reduced enhancement in the arterial phase and a progressively increasing enhancement in the delayed phases[49]. PDAC may sometimes have a peripheral rim, but unlike the rim detectable in AIP, it is usually early enhanced in the arterial phase[50]; therefore, the CE behavior of the perilesional rim of AIP with mass-forming AIP may help distinguish AIP from PDAC.

As a consequence of inflammatory involvement of the main PD (MPD), the arterial phase of the CE-CT scan may show a marked hyperdense demarcation of the MPD walls, which are often also thickened (enhanced duct sign)[51].

In particular, the capsular rim and thickened and hyper-enhanced MPD are usually less common in AIP-2, but these differences are not sufficient to make a differential diagnosis with AIP-1 based on radiologic presentation alone[41].

The typical appearance of AIP at CE-MRI is characterized by a diffuse or focal signal of lower intensity on unenhanced T1-weighted MRI images, with an even more hypointense signal in line with the border delineating the entire pancreas or the affected pseudotumoral areas, which are heavily composed of fibrosis. On T2-weighted images, the areas affected by AIP show moderately higher signal intensity, still demarcated by a low-intensity fibrotic rim (Figure 3). The contrastographic behavior of AIP on MRI is the same as that described for CE-CT (Figure 2)[46,47].

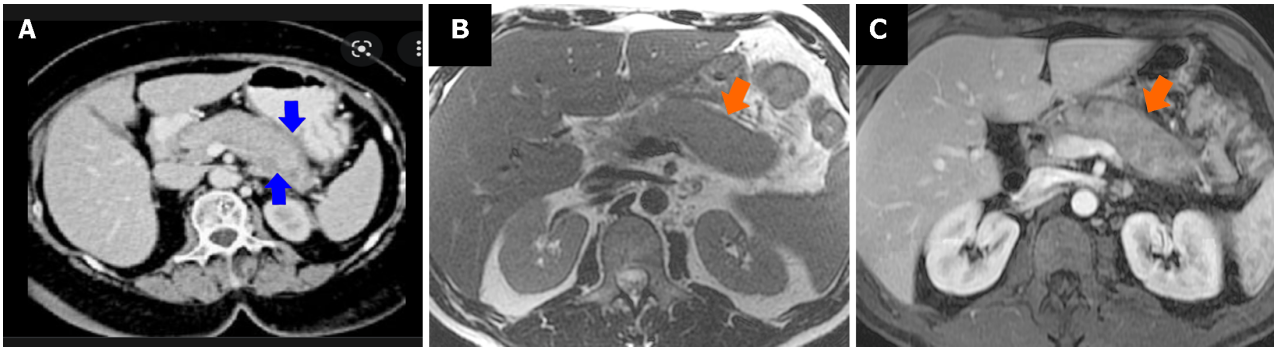

Figure 2 Radiological appearance of autoimmune pancreatitis-part 1. A: Unenhanced computed tomography scan appearance of a diffuse autoimmune pancreatitis (AIP): Sausage-like swelling of the parenchyma, with straight margins, and consequent loss of the typical lobular structure. A hypodense fibrotic capsule-like rim demarcates the swollen pancreas (blue arrow); B: Unenhanced T1 weighted magnetic resonance imaging (MRI) appearance of a diffuse AIP: Sausage-like swelling of the parenchyma, with straight margins, and rectangular shape of the tail (cut-tail sign) (orange arrow); C: Arterial phase of the contrast-enhanced T1 weighted MRI: Homogeneous reduced enhancement of the pancreatic parenchyma, with a more hypointense fibrotic capsule-like rim that demarcates the swollen pancreas (orange arrow).

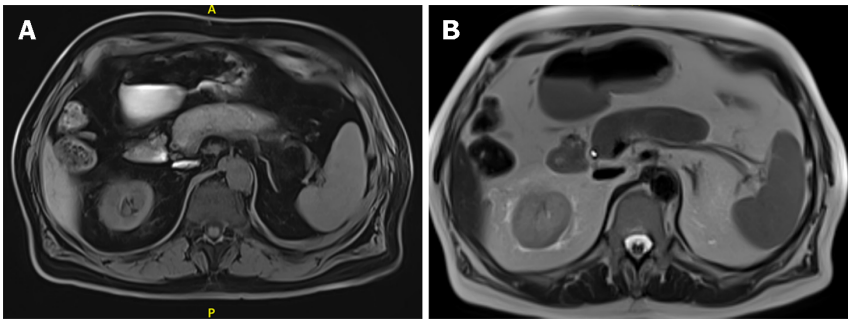

Figure 3 Radiological appearance of autoimmune pancreatitis-part 2. A: Unenhanced T1 weighted magnetic resonance imaging (MRI) images of autoimmune pancreatitis (AIP): Diffuse hypointense pancreas, with an even more hypointense fibrotic capsule-rim; B: Unenhanced T2 weighted MRI images of diffuse AIP: The affected parenchyma shows a moderately higher intensity signal, with a persistently low-intensity fibrotic rim.

On diffusion-weighted images, the presence of highly cellular plasmocyte proliferation is reflected in a homogeneously hyperintense signal of the affected areas, with the mean apparent diffusion coefficient of the lesions being significantly lower in mass-forming AIP than in PDAC[52-54].

Magnetic resonance cholangiopancreatography images show typical multiple and long MPD skip narrowings without upstream dilatation but with prominent side branches of the PD[55], producing a characteristic radiological sign (icicle sign). In the case of mass-forming AIP, the MPD may penetrate the lesion without complete occlusion (the sign of ductal penetration)[56].

MR elastography results vary considerably depending on the pathological phases of AIP: Recent edematous inflammation is associated with lower stiffness values, whereas chronic fibrotic inflammation is associated with higher stiffness values. However, AIP is generally associated with lower median pancreatic stiffness values than PDAC[57,58].

Concerning the MRI differential diagnosis between mass-forming AIP and PDAC, a multicenter nationwide study highlighted the following features of AIP as the most reliable among all those mentioned above: The presence of long and multiple MPD strictures, the absence of upstream dilatation of the stricture, and the detection of PD side branches originating from a strictured segment (sensitivity 44%-71%, specificity 92%-$P < 0.05$)[50]. According to a recent Korean meta-analysis, the absence of MPD dilation has the highest pooled sensitivity (87%, 95%CI = 68%-96%), whereas the presence of a peripancreatic rim has the highest pooled specificity (100%, 95%CI = 88%-100%) in distinguishing the two diseases[43].

According to the results of a recent comparative meta-analysis between CT and MRI in terms of diagnostic accuracy in AIP, MRI had significantly higher summary sensitivity than CT (84% *vs* 59%, $P = 0.02$) but similar specificity (97% *vs* 99%, $P = 0.18$). In the subgroup analysis for mass-forming AIP, sensitivity for discriminating between mass-forming AIP and PDAC was higher for MRI than CT (76% *vs* 50%, $P = 0.28$), but specificity was similar for both methods (97% *vs* 98%, $P = 0.07$)[59].

On 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT, AIP usually shows markedly increased diffuse uptake, which is different from the typical focal PDAC uptake[60]. Some other 18F-FDG parameters, including the SUV_{max} ratio between the pancreatic lesion and liver and uptake outside the pancreas in other organs, might help to distinguish the two diseases. Indeed, the SUV_{max} ratio between the pancreas and liver in delayed scans is usually higher in PDAC. On the contrary, the presence of increased uptake in the salivary glands, prostate (with a typical "V" shape), and mediastinal, hilar, and para-pancreatic lymph nodes are likely concomitant signs of IgG4- RD with pancreatic

involvement[61,62].

Furthermore, since fibrosis is an important feature of IgG4-RD, 68Ga-fibroblast activation protein inhibitor-PET, which uses a recently introduced agent targeting fibroblast activation protein, proved to have high sensitivity in detecting IgG4-related pancreatic, biliary and lacrimal gland involvement, with significantly higher uptake than 18F-FDG-PET[63].

According to a very recent study focusing on the radiological appearance of AIP-3[32], it is consistently associated with acinar injury and pancreatic volume loss. The parenchymal loss is directly proportional to pancreatic enzyme elevation: higher pancreatic enzymes correspond to major parenchymal loss, while near-normal pancreatic enzymes are associated with near-normal radiological pancreatic aspect. These distinct radiological features suggest AIP-3 to be sustained by a novel mechanism of chronic pancreatic injury.

ENDOSCOPIC ULTRASOUND PRESENTATION AND ENDOSCOPIC ULTRASOUND-GUIDED TISSUE SAMPLING

In the complex scenario of AIP diagnosis, the role of endoscopic ultrasound (EUS) so far can be seen mainly in its ability to biopsy the affected pancreatic parenchyma and thus make a definite AIP diagnosis, which is also different from PDAC. The endoscopic approach of first choice for obtaining pancreatic specimens for histopathological evaluation should be EUS fine-needle biopsy (FNB): According to a recent meta-analysis, FNB needles seem to be more accurate than fine-needle aspiration (FNA) needles in diagnosing AIP, as they guarantee a core biopsy[64,65]. However, the diagnosis of AIP is challenging, even by using EUS and FNA/FNB. The sonographic and cross-sectional findings of AIP closely mimic PDAC, and tissue sampling techniques for diagnosis of AIP still remain suboptimal[66]. Although the diagnostic consistency of histologic diagnosis of type 1 AIP based on the findings obtained by an EUS-guided FNA/FNB is feasible, it remains a challenge and not conclusive[67].

The main EUS findings may be divided into diffuse and focal pictures of AIP. EUS characteristics suggestive of diffuse AIP included diffuse pancreatic enlargement with echo-poor echo texture, hyperechoic foci/stands or lobularity (parenchymal heterogeneity), loss of connection to the splenic vein, hyperechoic MPD walls thickening and peripancreatic hypoechoic margin; stones and cysts similar to those described in chronic alcoholic pancreatitis may occur in the late stages of AIP. In mass-forming AIP, EUS features included focal hypoechoic mass, absence of parenchymal heterogeneity, eventually PD dilation, and vessel involvement. In a recent retrospective study, these pictures were used to construct a prediction diagnostic model, that showed an area under the receiver operating characteristic curve of more than 0.95, with a good capability to distinguish focal AIP from PDAC. By using the optimal cutoff value, the efficacy of the model for diagnosing PDAC showed 83.7%-91.8% sensitivity and 93.3%-95.6% specificity[68]. It is likely that the use of EUS-based convolutional neural networks can help, showing in a recent study, a sensitivity of 99% and a specificity of 98% for distinguishing AIP from normal pancreas, a sensitivity of 94% and a specificity of 71% for distinguishing AIP from chronic pancreatitis, and a sensitivity of 90% and a specificity of 93% for distinguishing AIP from PDAC[66].

EUS elastography may show increased stiffness of the parenchyma. EUS is extremely useful in detecting other typical findings of IgG4- RD AIP, such as changes in the common bile duct and lymphoadenomegaly (Figure 4)[69].

Finally, regarding the natural history of the disease, the typical picture of AIP described above usually improves after steroid treatment: the swelling of the pancreas decreases, the capsular rim disappears, the multiple MPD stenoses improve, and the enhanced duct sign also disappears. Nevertheless, the global CE of the previously affected parenchyma may not completely normalize[54,70]. Table 2 resembles the main radiological features of AIP.

HISTOPATHOLOGICAL CHARACTERISTICS

The main morpho-histological features of AIP-1 are dense lymphoplasmacytic infiltrate of the affected areas, distributed mainly lobule-centered but sometimes involving the periductal areas with a resulting slit-like obstruction of the PD; storiform fibrosis composed of spindle-shaped cells and inflammatory cells on a background of delicate collagen; luminal obliteration of the interlobular vein by the lymphoplasmacytic infiltrate, forming obliterative phlebitis. Interobserver variability in the interpretation of storiform fibrosis and obliterative phlebitis is not negligible; additional elastic staining, such as Elastica van Gieson staining, should be considered because it may help reduce interobserver variability[71]. In contrast to the findings typical of AIP-2, organs affected by AIP-1 do not usually show neutrophilic infiltration or abscess formation.

In addition to these typical morphologic features, which have historically been the primary histologic diagnostic criteria for AIP-1, biopsy or resection specimens of AIP-1 exhibit a highly pathognomonic immunohistochemical pattern: Diffuse and massive IgG4+ plasma cell infiltration with > 10 per HPF in biopsy specimens and > 50 per HPF in surgical specimens. For diagnostic purposes, to date, minimally invasive small biopsies have largely replaced surgical resections, and although this development is an achievement for the field, it represents a major challenge for the surgical pathologist. In fact, according to recent studies, around one-half of all small biopsies do not usually meet the pathological criteria for IgG4-RD, being the lack of both storiform-type fibrosis and obliterative phlebitis the most common reason for diagnostic failure. However, despite the lower pathological quality of biopsy samples, which is mainly due to their smaller size, the IgG4/total IgG ratio on biopsy samples proved the same high diagnostic accuracy when compared to the one on resection specimens. Immunohistochemistry (IHC) for IgG4 and total IgG, and the evaluation of IgG4/total IgG ratio is thus mandatory for IgG4-RD diagnosis, being it the most sensitive tissue-based feature of IgG4-RD[72]. According to a recent

Table 2 Main radiological features of autoimmune pancreatitis

CT scan	**Diffuse or focal sausage-like swelling**
	Cut-tail sign
	Homogeneous reduced enhancement with dotted contrast enhancements of normal parenchyma
	Hypo-enhanced capsule-like rim with delayed enhancement
	Thickened hyperdense MPD walls
MRI	Diffuse or focal lower intensity signal on T1-weighted MRI images, with an even more hypointense capsule-rim
	Moderately higher intensity signal on T2-weighted images, still with a low-intensity fibrotic rim
	DWI homogeneously hyperintensity
MRCP	Multiple and long MPD skip narrowings
	No upstream dilatation
	Side PD branches (icicle sign)
	Duct-penetrating sign, in case of mass-forming AIP
18F-FDG PET-CT	Diffused or focal increased uptake
EUS	Diffuse pancreatic enlargement, with echopoor echotexture, loss of interface with the splenic vein, concomitant intraparenchymal hyperechoic foci and strands
	Hyperechoic MPD walls
	Solitary, irregular, hypoechoic mass, in case of mass-forming AIP, generally in the head of the pancreas, without upstream dilatation of the MPD
Elastography	Magnified parenchymal stiffness

AIP: Autoimmune pancreatitis; CT: Computed tomography; MPD: Main pancreatic duct; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography; FDG: Fluorodeoxyglucose; PET: Positron emission tomography; EUS: Endoscopic ultrasound.

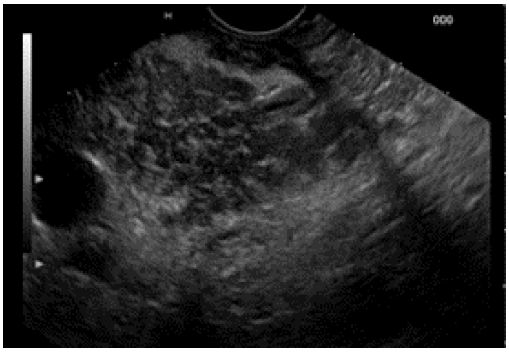

Figure 4 Endoscopic ultrasound appearance of autoimmune pancreatitis. Endoscopic ultrasound aspect of a mass-forming autoimmune pancreatitis: Solitary, irregular hypoechoic mass, located in the head of the pancreas, without upstream dilatation of the main pancreatic duct.

meta-analysis, in fact, the use of IHC for IgG4 in the diagnosis of AIP-1 has a sensitivity and specificity of approximately 70% and 92%, respectively[73].

Although the IgG4/total IgG ratio is emphasized in most diagnostic algorithms, the optimal cutoff has not yet been shared univocally; to date, most studies have utilized a cutoff ranging from 30% to 40% with a higher cutoff corresponding to higher specificity, but proportionally lower sensitivity[74,75].

Of note, treatment can interfere with histological findings and cell counts; on the other hand, also prolonged disease can lead to possible false negative immunohistochemical patterns.

Currently, there are no specific serological markers for AIP-2, so the diagnosis is made based on histology[7]. AIP-2 is characterized by a large inflammatory infiltrate in the pancreas composed mainly of neutrophils but also containing lymphocytes and plasma cells. This inflammation occurs primarily in the PD area, where it forms structures known as GELs[7,76]. AIP-2 can also cause clusters of neutrophils to form inside the ducts. Unlike AIP-1, which is characterized by obliterative phlebitis and storiform fibrosis, these features are less common in AIP-2. In addition, the number of IgG4+ plasma cells is usually not significantly increased in AIP-2, although small pockets of these cells may be present[74].

The absence of established histologic patterns for AIP-3 raises questions about its categorization, even if it is important to consider that the field of AIP is still evolving, and our understanding of the disease continues to expand. Therefore, at this stage, referring to this subtype as AIP-3 allows for the recognition of a distinct subgroup within the spectrum of AIP, even in the absence of well-defined histologic patterns. However, it is crucial to continue research efforts to establish clearer diagnostic criteria and classification systems for AIP-3 and other potential subtypes to improve the accuracy of diagnosis and guide appropriate treatment strategies. Figure 5 Histological samples of AIP-1.

DIAGNOSIS

According to the International Consensus Diagnostic Criteria for AIP, a definitive diagnosis of AIP-1 can be made in diffuse pancreatitis based on clinical, radiological, and serological features. In the presence of atypical mass-forming imaging and concomitant absence of other diagnostic criteria (mainly IgG4-RD extrapancreatic involvement or elevated IgG4+ plasma cells count), histologic evaluation by surgical or EUS-FNB tissue sampling is mandatory to make the definitive diagnosis and differentiate AIP from PDAC. In the latter scenario, the AIP-1 diagnosis can be definitively established if three or more of the following four histologic features are present: lymphoplasmacytic cell infiltration, > 10 per HPF IgG4+ plasma cells (in case of biopsy sampling, otherwise > 50 per HPF in case of surgical specimen), storiform fibrosis, or obliterative phlebitis. In the presence of fewer than three of these histologic features, increased plasma IgG4 cell counts, along with typical imaging features, may help determine the diagnosis: (1) Serum IgG4 level has proven to be a valuable tool in the diagnosis of AIP and it is one of the five cardinal features of Mayo's HISORt criteria for the diagnosis of AIP-1[77], which are based on 5 main diagnostic criteria: Histologic findings, imaging, serology, involvement of other organs, and response to steroid therapy. Indeed, in most cases, AIP patients exhibit significantly elevated levels of serum IgG4, typically exceeding a defined threshold of 135 mg/dL. However, it is important to note that elevated IgG4 levels alone are not sufficient for an AIP diagnosis, as they may also be observed in other conditions, such as IgG4-RD involving multiple organ systems. Therefore, a comprehensive diagnostic approach combining clinical presentation, radiologic imaging, serologic markers (including IgG4 levels), and histopathologic evaluation is critical for accurate diagnosis and differentiation of AIP from mimicking diseases.

With the exact purpose of excluding disease mimics, in 2019 the ACR/EULAR diagnostic criteria were developed. They consist of a three-step classification process: first, at least one of 11 possible organs must be involved in a manner consistent with IgG4-RD; second, 32 clinical, serological, radiological, and pathological exclusion criteria must be verified; third, eight weighted inclusion criteria domains, addressing clinical findings, serological results, radiological assessments, and pathological interpretations, have to be applied. A case meets the classification criteria for IgG4-RD if the entry criteria are met, no exclusion criteria are present, and the total points is ≥ 20[5].

In the case of an uncertain histologic diagnosis, systems for grading the likelihood of AIP (highly suggestive, probable, inconclusive) based on various combinations of features have been proposed, but they remain to be clinically validated [78-81]. A biopsy showing little or no evidence of AIP cannot exclude AIP with certainty unless a positive alternative diagnosis can be made[75].

Ongoing research in the field of AIP is investigating potential future markers for diagnosis. These markers include subclass analysis of IgG4, serum cytokines [such as IL-6 and tumor necrosis factor (TNF)-alpha], serum microRNAs (*e.g.*, miR-21 and miR-375), autoantibodies targeting pancreatic antigens and advanced imaging techniques (*e.g.*, EUS and MRI). However, further research is needed to validate their clinical utility in routine AIP diagnosis. Integration of these markers with existing diagnostic criteria may improve accuracy in diagnosing AIP.

Definitive AIP-2 diagnosis is histologic and requires the presence of GELs; lobular neutrophil infiltration strengthens the diagnosis[41].

AIP-3 can be diagnosed in the presence of a compatible drug history and by excluding other causes of pancreatitis.

INDUCTION THERAPY FOR AIP

According to recent literature data, approximately 25% of cases of AIP show spontaneous resolution of symptoms without medical treatment, with some case series reporting resolution rates up to 55%[82]. Nevertheless, experts from different countries have proposed detailed treatment criteria for acute AIP. A consensus statement published in 2016 stated that therapy is recommended for symptomatic disease (abdominal pain, back pain, fever, obstructive jaundice) or in the case of AIP-1, for asymptomatic patients with persistent pancreatic mass on imaging or persistent liver test abnormalities in case of concomitant IRC[82]. In addition to the above criteria, following the latest United European Gastroenterology (UEG) recommendations, treatment is indicated for subclinical conditions that may lead to severe or irreversible organ failure[75].

Steroids are the first-line therapy for patients with active AIP-1 and 2[75,82]. They inhibit dendritic cell maturation and downstream signal transduction of TLRs; they also inhibit the expression of many proinflammatory cytokines involved in AIP pathogenesis. Based on UEG and Swedish Society of Gastroenterology recommendations, the initial dose of prednisone should be 0.6-0.8 mg/kg per day (typically 30-40 mg/d). The treatment duration at the full dose is one month, with an initial assessment of response to treatment approximately 2 wk after initiation (especially in cases of a diagnostic steroid study). Thereafter, treatment should be gradually tapered by 5 mg/wk to a maintenance dose of 2.5-5 mg/d over 2-3 months[83].

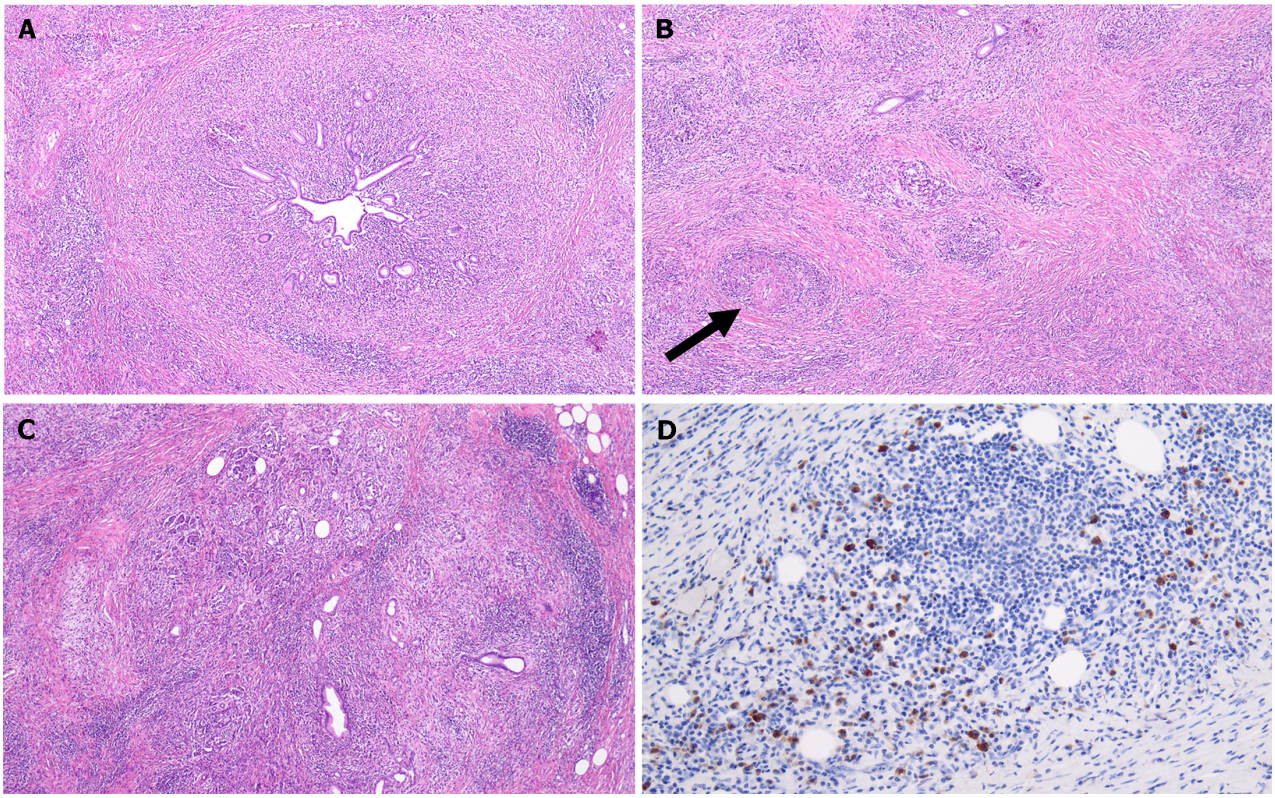

Figure 5 Histology of autoimmune pancreatitis. A: Histological samples of type 1 autoimmune pancreatitis. Hematoxylin eosin (HE) 4, Duct centric lymphoplasmacytic infiltrate; B: HE 10, storiform fibrosis with intense lymphoplasmacytic infiltrate and obliterative phlebitis (arrow); C: HE 4, lobule complete effacement by inflammatory cells and fibrosis; D: Immunoglobulin G4 (IgG4) IIC 20, moderate increase of IgG4+ plasma cells.

Up to 97%-100% of AIP, patients respond to steroid treatment[84,85]. Clinical complete remission is defined as the disappearance of symptoms, normalization of IgG or IgG4 serum levels, and disappearance of typical AIP features on imaging, *i.e.*, mainly shrinkage of the enlarged pancreatic parenchyma and regression of the narrowing of the multistrictured MPD. Incomplete remission is achieved only when one or 2 of these 3 categories are met. Imaging response to steroids is an optional diagnostic criterion, as mentioned earlier. In a small proportion of cases, AIP patients do not show any steroid response[84,85]. Furthermore, some comorbidities may contraindicate long-term steroid treatment[86]. In such cases, rituximab, a monoclonal antibody directed against CD20 B-cell-specific antigen, is the second-line good alternative therapeutic choice for acute AIP-1[75,87], whether monotherapy with immunomodulators (such as azathioprine, 6-mercaptopurine, mycophenolate mofetil, cyclosporine A, tacrolimus, methotrexate, and cyclophosphamide) did not prove sufficient efficacy, but reliable data specifically on AIP-2 are lacking[88].

If rituximab therapy is required for induction remission, the most common regimen includes 1 g of intravenous rituximab on days 0 and 14[75], and it has been shown to guarantee complete remission in up to 83% of patients[89,90]. On the other hand, given their low efficacy as monotherapy, immunomodulators steroid-sparing agents are used mainly in combination with low-dose steroids in steroid-refractory conditions[91].

Minipulse steroid therapy (two administrations of methylprednisolone 500 mg/day for three days with an interval of four days) was described in several Japanese protocols[92].

Specifically concerning AIP-2, colchicine has recently been reported to be a successful treatment option: it inhibits neutrophils and thus reduces the formation of the pathognomonic GELs[93]. There is also emerging evidence suggesting the potential use of biologic medications in the treatment of AIP-2. While corticosteroids remain the first-line therapy for AIP-2, there have been reports of cases where biologic agents, such as anti-TNF-alpha and ustekinumab, have shown promise in managing steroid-refractory or steroid-dependent AIP-2. These patients have often been effectively treated with anti-TNF-alpha agents, which are also indicated for frequent concomitant IBD[7]. In a recent letter by Lauri, two cases of AIP-2 were reported to have been safety and successfully treated with ustekinumab, a monoclonal antibody that targets interleukin-12 and interleukin-23, used for concomitant IBD. This treatment option highlights the potential efficacy of ustekinumab in managing AIP-2, although further research and clinical trials are needed to validate its effectiveness in a larger patient population[94].

AIP-3 therapy is essentially based on the discontinuation of immune checkpoint inhibitors and supportive therapy. Indeed, the role of corticosteroids and immunosuppressants is not well understood. A retrospective study of 82 patients with AIP-3 found no statistically significant differences in the duration of symptoms or hospitalization between patients treated with corticosteroids and patients not treated with them[95]. Furthermore, steroid use in these immunocompromised patients with advanced malignancies carries a significantly increased risk of infectious events[96].

DISEASE RELAPSES

Relapses are significantly more common with AIP-1 (nearly 60% of cases) than with AIP-2 (9%-25%); the relapse rate in AIP-IBD patients appears to be similar to that of isolated AIP-2[97].

The main factors predicting relapse are young age, high serum IgG4 levels at disease onset, persistently high serum levels after treatment, diffuse enlargement of the pancreas, concurrent evidence of IRC, especially if proximal, or extensive multiorgan involvement[98]. Also, elevated levels of circulating IgE and/or eosinophils, and the presence of rich-in-eosinophils pancreatic infiltrate at histology represent other risk factors for disease relapse that need to be considered. Lastly, prolonged exposure to certain exogenous antigens may lead to overactivity of specific types of TLRs that may perpetuate a dysimmune response[4].

Given the high relapse rate in AIP-1, long-term maintenance therapy is recommended, especially for patients with a known high risk of relapse. Current guidelines recommend low-dose (5 mg/d) maintenance treatment with steroids for 2-3 years[99]. To reduce the risk of adverse events and lifetime cumulative steroid dose, the use of steroid-sparing agents is an alternative treatment strategy. According to a recent meta-analysis, nearly 40% of the cases relapse on immunosuppressive agents (azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide). To date, no study that compares the efficacy of different immunosuppressive has been published and the interpretation of the efficacy of conventional immunosuppressive medications is hampered by concomitant glucocorticoid use[100]. Also in the case of maintenance therapy, rituximab with the same induction scheme proved to be superior to immunomodulatory drugs in terms of efficacy[101]: 100% rituximab *vs* 81% azathioprine *vs* 72% other immunosuppressant[100].

In AIP-2, maintenance therapy is unnecessary in most patients unless certified risk factors are present; in the latter case, anti-TNF-alpha agents have been shown to be effective[7].

In cases of proven recurrent AIP, re-administration of a high dose of glucocorticoids with a slow steroid taper is effective[99].

Concerning AIP-3, it is not appropriate to refer to the risk of disease recurrence but rather to emphasize that after the acute event has resolved, the disease evolves in up to 36% of cases to a treatment-emergent stage of glandular atrophy with endocrine and exocrine insufficiency, associated with markedly reduced overall survival[102].

CONCLUSION

Given the multitude of mechanisms that explain the etiopathogenesis of AIP, great scientific efforts are being made to find new effective target therapies. As mentioned earlier, given the chemotactic role of eotaxin on inflammatory cells, attention is being paid to the development of targeted anti-eotaxin therapy[24]. Because increased production of IFN-I and IL-33 by pDCs promotes the chronic inflammation and fibrosis characteristic of AIP and IgG4- RD, neutralization of IFN-I and IL-33 may represent a new therapeutic option for these diseases. The anti-IFN-I therapeutics anifrolumab and sifalimumab and the anti-IL-33 therapeutic etokimab have been successfully used in systemic lupus erythematosus, but reliable data are not yet available for AIP in humans[35].

In addition, targeted therapies against B-cell lineage plasmablasts and CD4+ T cells (such as anti-CD19 inebilizumab, an inhibitor of B-cell activating factor ianalumab, anti-CD80/86 abatacept, anti-LOX2 simtuzumab, anti-SLAMF7 elotuzumab, or anti-CD38 daratumumab) have recently been proposed[103].

Finally, regarding the possible role of the microbiota in the etiopathogenesis of AIP, manipulation of the gut microbiota through prebiotics, probiotics, symbiotics, and fecal microbiota transplantation may represent a future prophylactic perspective, possibly targeting IgG4-RD and/or IBD patients. Indeed, early studies in mice have shown that sterilization of the gut leads to a significant reduction in the accumulation of pDCs in the pancreas that produce IFN-I and IL-33[104].

FOOTNOTES

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