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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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Recent Advances in Autoimmune Pancreatitis

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Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis that is characterized clinically by frequent presentation with obstructive jaundice, histologically by a dense lymphoplasmacytic infiltrate with fibrosis, and therapeutically by a dramatic response to corticosteroid therapy. Two distinct diseases, type 1 and type 2 AIP, share these features. However, these 2 diseases have unique pancreatic histopathologic patterns and differ significantly in their demographic profiles, clinical presentation, and natural history. Recognizing the popular and long-standing association of the term "AIP" with what is now called "type 1 AIP," we suggest using "AIP" solely for type 1 AIP and to acknowledge its own distinct disease status by using "idiopathic duct-centric chronic pancreatitis" (IDCP) for type 2 AIP. AIP is the pancreatic manifestation of immunoglobulin G4–related disease (IgG4-RD). The etiopathogenesis of AIP and IgG4-RD is largely unknown. However, the remarkable effectiveness of B-cell depletion therapy with rituximab in patients with AIP and IgG4-RD highlights the crucial role of B cells in its pathogenesis. IDCP is less commonly recognized, and little is known about its pathogenesis. IDCP has no biomarker but is associated with inflammatory bowel disease in ~25% of patients. Recently, the international consensus diagnostic criteria for AIP identified combinations of features that are diagnostic of both diseases. Both AIP and IDCP are corticosteroid responsive; however, relapses are common in AIP and rare in IDCP. Therefore, maintenance therapy with either an immunomodulator (eg, azathioprine, 6-mercaptopurine, or mycophenolate mofetil) or rituximab is often necessary for patients with AIP. Long-term survival is excellent for both patients with AIP and patients with IDCP.

Keywords: Lymphoplasmacytic Sclerosing Pancreatitis; Idiopathic Duct-Centric Chronic Pancreatitis; IgG4-Related Disease; Rituximab.

Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis that is characterized clinically by frequent presentation with obstructive jaundice, histologically by a dense lymphoplasmacytic infiltrate and fibrosis, and therapeutically by a dramatic response to corticosteroid therapy.[1,2] When thus defined, there are at least 2 distinct steroid-responsive pancreatitides under the rubric of AIP, currently referred to as type 1 and type 2 AIP.

Subtypes of AIP: History and Nomenclature

The term "AIP" was used by Yoshida et al to describe a corticosteroid-responsive disease associated with features of autoimmunity.[3] The association of AIP and elevated serum immunoglobulin (Ig) G4 levels was recognized by Hamano et al.[4] The observation by Kamisawa et al that not only the pancreas but also the extrapancreatic organs involved in AIP had abundant infiltration with $IgG4^+$ plasma cells led to the notion that AIP was part of a multiorgan disease, recently named IgG4-related disease (IgG4-RD).[5]

Studies from Europe and the United States have highlighted 2 histopathologic patterns, both called AIP, in patients with chronic pancreatitis who underwent pancreatic resection for presumed pancreatic cancer. Lymphoplasmacytic sclerosing pancreatitis (LPSP) matched Japanese descriptions of histology in AIP, and idiopathic duct-centric pancreatitis (IDCP) or granulocytic epithelial lesion (GEL) plus pancreatitis resembled "duct destructive pancreatitis" as reported earlier in Europe.[6–8] Patients with LPSP and IDCP also had distinct clinical profiles. Thus, in 2009, 2 subtypes of AIP (defined by their histopathology), called type 1 (LPSP) and type 2 (IDCP) AIP, were formally recognized.[8,9] It was decided to call both "AIP" because of the many similarities between the 2 entities (discussed later in this review).

However, despite the distinction of subtypes, the term "AIP" continues to be equated with type 1 AIP and elevated serum IgG4 levels, a feature typically absent in IDCP. Therefore, IDCP remains underrecognized and is often inappropriately treated on the mistaken belief that the treatments for the 2 diseases must be the same. Providing distinct disease names will help minimize confusion between the 2 diseases. Recognizing the popular and long-standing association of the term "AIP" and elevation of serum IgG4 levels with what is now called type 1 AIP, we

Abbreviations used in this paper: **AIP, autoimmune pancreatitis; Breg, regulatory B cell; CFTR, cystic fibrosis transmembrane conductance regulator; GEL, granulocytic epithelial lesion; IDCP, idiopathic duct-centric pancreatitis; Ig, immunoglobulin; IgG4-RD, immunoglobulin G4–related disease; IL, interleukin; LPSP, lymphoplasmacytic sclerosing pancreatitis; Treg, regulatory T cell.**

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suggest using "AIP" solely for type 1 AIP and "IDCP" for type 2 AIP.

Before the use of the term "type 2 AIP," the entity had been called "nonalcoholic duct destructive pancreatitis,"[10] "GEL-positive pancreatitis,"[7] and "IDCP."[6] All 3 terms highlight the "duct-centric" nature of the disease. Because the etiology is still unknown, IDCP appears to be a reasonable choice. Rather than suggesting a new title to replace IDCP, we chose to retain this. It is fitting to retain this title because the histology is its defining feature. In the future, biomarkers will hopefully make it possible to more accurately distinguish AIP and IDCP without the need for histopathology.

AIP (IgG4-Related Pancreatitis)

Definition. AIP is the pancreatic manifestation of IgG4-RD; using currently proposed nomenclature, it is also called IgG4-related pancreatitis.[11] IgG4-RD is a multiorgan syndrome characterized by typical histology (see the description of LPSP) in affected organs, frequent elevations of serum IgG4 levels, abundant $IgG4^+$ plasma cells in affected organs, and dramatic response to corticosteroid therapy.[12] An individual patient with IgG4-RD may not exhibit all features and patients without IgG4-RD may have some features; however, a cohort of subjects with a particular clinical phenotype of IgG4-RD (eg, AIP) would meet all criteria.

Pathogenesis. The pathogenetic mechanisms of AIP are incompletely understood. Studies have identified genetic predisposing factors and unique immunologic features of AIP, raising the possibility that the process is multifactorial. As with most immune-mediated conditions, a likely pathogenetic mechanism is that the disease develops in genetically susceptible people after exposure to environmental factors. This section covers potential contributions to the development of AIP from (1) genetic predisposition, (2) possible immunologic triggers, and (3) subsequent immune reactions. Although experimental AIP is beyond the scope of this review, new insights recently obtained from animal models of AIP are briefly described. Assuming that IgG4-RD at various anatomic sites shares pathogenetic mechanisms, several studies on the extrapancreatic manifestations are also mentioned.

Genetic predisposition. A potential genetic predisposition was first recognized in 2002, when HLA serotypes DRB1*0405 and DQB1*0401 were found to increase the susceptibility to AIP in Japanese populations.[13] Efforts to validate these findings in a Korean population were unsuccessful, but instead identified the absence of aspartic acid at position 57 of DQβ1 as a genetic factor significantly associated with disease relapse.[14] Four non-HLA genes, single nucleotide polymorphisms, that have been associated with AIP encode cytotoxic T lymphocyte–associated antigen 4, tumor necrosis factor α, Fc receptor-like 3, and cationic trypsinogen (PRSS1).[15–18] Although growing evidence has highlighted underlying genetic risks of AIP, more comprehensive analyses such as genome-wide association studies will be needed to fully understand the genetic aspects of this condition. Unfortunately, the large sample size needed to attain adequate statistical analysis for this type of study would be impossible, aside from a large-scale, multinational collaborative effort.

Immunologic trigger. *Autoimmunity.* The fact that approximately 40% of patients with AIP have antinuclear antibodies prompts us to suspect that autoimmunity may be an initial immunologic stimulus in this condition.[19,20] Patients with AIP often have autoantibodies against carbonic anhydrase II (55% of patients), lactoferrin (75% of patients), and/or pancreatic secretory trypsin inhibitor (33% of patients).[19] A German study identified that patients with AIP have high titers of autoantibodies against trypsinogens PRSS1 and PRSS2 but not against PRSS3.[21] An interesting aspect is that all autoantibodies identified in patients with AIP are against enzymes. This may explain why pancreatic acini are more deeply involved in the inflammatory process than pancreatic ducts. Some of these enzymes are also expressed in other exocrine organs (eg, salivary amylase), which may potentially explain the association with other organ involvement. However, whether the production of these antibodies directed against pancreatic enzymes occurs primarily or secondarily to the inflammation remains to be clarified. Another caveat is these antibodies are not entirely specific for AIP and are sometimes detected in other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.[22]

Bacterial infection/molecular mimicry. Because substantial homology between human carbonic anhydrase II and α–carbonic anhydrase of *Helicobacter pylori* was identified, the possible involvement of *H pylori* in the pathogenesis of AIP has been investigated.[23] More recently, additional homology was recognized between the plasminogen-binding protein of *H pylori* and the ubiquitin-protein ligase E3 component n-recognin 2, an enzyme expressed in acinar cells of the pancreas.[24] The investigators speculated that *H pylori* infection initiates an immune reaction and the production of antibodies against the plasminogen-binding protein of *H pylori* and may lead to autoimmune response against the pancreatic acinar cells via molecular mimicry. However, the homologous amino acid sequence is not entirely specific for these 2 proteins, and similar peptide sequences exist in other human proteins (eg, transforming growth factor β regulator 1) as well as proteins derived from other microbes.[25] Thus, the possibility of molecular mimicry in AIP has drawn interest but remains to be validated.

Environmental factors. Serum IgG4 concentrations increase in subjects with repeated exposure to antigens.[26] For example, beekeepers develop elevated serum IgG4 levels in the absence of elevation of IgE levels.[26] Given that occupational exposure to other antigens leads to the same phenotype, a European group investigated a possible role of occupational exposures in a group of patients with AIP and/or IgG4-related sclerosing cholangitis (previously referred to as IgG4-associated cholangitis).[27] Of 25 patients in The Netherlands, 88% of these patients were blue-collar workers compared with only 14% of those with primary sclerosing cholangitis. This observation was validated by a