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Autoimmune Pancreatitis-What is Known, What Needs to be Known

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Introduction

Autoimmune Pancreatitis (AIP) is an emerging clinical entity found in 4.6-6 percent of patients with chronic pancreatitis [1]. It was first reported as an idiopathic chronic pancreatitis associated with hypergammaglobulinemia by Sarles et al. [2], with the term AIP being first used by Yoshida et al. [3]. In 2003, Notohara and coworkers described two types of AIP: Lymphoplasmacytic Sclerosing Pancreatitis (LPSP) termed "type 1 AIP" and idiopathic duct-centric chronic pancreatitis with Granulocyte Epithelial Lesion (GEL) termed "type 2 AIP" [1] (Table 1).

It is the histopathological findings observed on pancreatic biopsies that seem to separate AIP into two discrete disease entities. In type 1 AIP there is abundant infiltration of Immunoglobulin G4 (IgG4) positive plasma with CD4+ and CD8+ lymphocytes. Storiform fibrosis (fibrosis in a swirling pattern) around main and interlobular ducts that spares the duct epithelium and lumen is a typical feature. Similar infiltration is observed near the pancreatic veins leading to obliterative phlebitis [4]. This type of AIP often presents in men in the 5-6th decade of life as painless jaundice mimicking pancreatic cancer and patients experience frequent relapses despite treatment. Very soon, patients diagnosed with AIP were being reported with extra-pancreatic manifestations such as biliary, retroperitoneal, renal, and salivary gland disease. Similar pathologic features were found in affected organs, and type 1 AIP began to be recognized as the pancreatic manifestation of a systemic auto-inflammatory syndrome now known as IgG_4-related disease [5].

The exact pathogenic mechanisms behind type 1 AIP remain unclear. Although some mechanisms have been proposed, no genetic markers have been confirmed as susceptibility factors and no specific antibodies have been identified. It has been observed that T helper 1 (Th1) cells predominate over T helper 2 (Th2) cells in the peripheral blood while Th2 cells dominate over Th1 within the involved organs, and circulating levels of regulatory T cells (T-regs) are increased while naïve T-reg cells are decreased. This has led some researchers to suggest a biphasic mechanism by which cytokines produced by Th1 cells induce AIP, and Th2 cytokines contribute to disease progression [6]. The initial "induction" phase involves response to self-antigens induced by decreased levels of naive T-reg cells which causes a Th1 type immune response and release of pro-inflammatory cytokines. This eventually leads to upregulation of Th2 cells and memory T-reg cells during the "progression" phase inducing the maturation and proliferation of local B cells. During this phase, the overproduction of IL-10 leads to expansion of IgG_4-producing plasma cells and the elevated levels of transforming growth factor beta induce fibrosis [6]. As Th2 and T-reg cells are known to contribute to pathogenesis of allergic disorders, this would explain the elevated serum IgE and peripheral eosinophilia often observed in these patients [6]. It has also been observed that increased peripheral inducible memory T-reg cells correlate with serum levels of IgG_4, suggesting that the elevated IgG_4 level does not act as a pathogenic factor in this disease but rather as an anti-inflammatory factor. This would explain why serum IgG_4 level is not universally increased in these patients and the observation that lower IgG_4 levels are sometimes discovered further in disease course and in more severe presentations [7].

Type 2 AIP is considered to be a solely pancreatic disease predominantly seen in younger Caucasian patients with no sex predilection. It usually presents as obstructive jaundice with abdominal pain mimicking acute pancreatitis, and has a low relapse rate. Histologically, there is neutrophilic infiltration and granulocytic lesions that damage the duct epithelium itself, but no obliterative phlebitis or IgG_4-positive plasma cells. It tends to be associated with inflammatory bowel disease, but no other extra-pancreatic manifestations have been observed with this type of AIP [6].

Both types of AIP are known to respond quickly to systemic steroids [8] and these agents can be used for both initial attacks and first or second relapses. However, further relapses (as is typical of type 1 AIP), can be treated with immunomodulator drugs such as azathioprine, mycophenolate mofetil [9,10] or cyclophosphamide. In patients intolerant to steroids or immunomodulatory therapy, Rituximab, the B cell depleting monoclonal antibody against CD-20 [11], has demonstrated efficacy.

AIP is evidenced as a diffusely enlarged pancreas demonstrating a sausage–like appearance on computed tomography (Figure 1). MRI of our patient with AIP type 1 demonstrates diffuse swelling of pancreatic body and tail which resolved with a 2 month course of steroids (Figure 1A and 1B).

Diagnostic Criteria for AIP

There have been several criteria proposed for diagnosis of AIP.

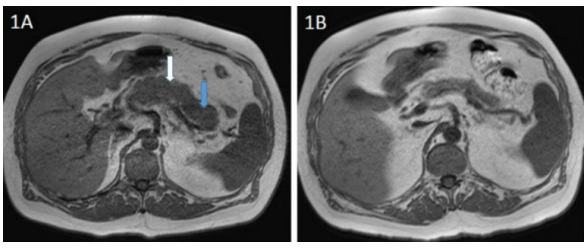

Figure 1: 1A-Non-contrast T1 MRI showing diffuse pancreatic body (white arrow) and tail (blue arrow) enlargement in patient with type 1 autoimmune pancreatitis. **1B**-Improvement in pancreatic morphology following glucocorticoid therapy.

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Feature	Type 1 AIP	Type 2 AIP
Demographic Factors		
Race	More common among Asians	More common among Caucasians
Age	Elderly	Young adult- middle age
Sex	Male>Female	Male=Female
Clinical Factors		
Presentation	Painless obstructive jaundice	Painless jaundice or acute pancreatitis
Serum IgG4	Elevated	Normal
Extra-Pancreatic	Various other organ involvement	Inflammatory bowel disease
Response to steroids	Excellent	Excellent
Recurrence	Common	Rare
Pathologic features		
Infiltrating cellLymphocytes and IgG_4+plasma cellsNeutrophil		
Fibrosis	Storiform pattern	none
Obliterative phlebitisCommon		None
Duct epithelial cells	Sparing	Destruction and obliteration

AIP-Autoimmune Pancreatitis

Table 1: Differences between 2 subtypes of AIP.

The first diagnostic criteria was proposed by The Japanese Pancreas Society in 2000, and subsequently revised in 2006 and 2011. Another criteria that had been proposed is the HISORt-(Histology, Imaging, Serology, Other organ involvement and Response to glucocorticoids) by Mayo clinic in 2006. Another diagnostic approach was taken by the International Consensus Diagnostic Criteria (ICDC) proposed in 2011 [12]. ICDC uses five features to diagnose AIP: Pancreatic imaging, serology, other organ involvement, histology and immunostaining and optional criteria for steroid responsiveness [13]. Each feature is characterized as level 1 or 2 depending on the diagnostic reliability. The ICDC criteria had 98.4% sensitivity and 100% specificity whereas the Japanese Pancreas Society Classification had 84.4% sensitivity and 100% specificity for diagnosis of AIP [13].

Still Unfolding

As this is a relatively rare condition that has only become identified in recent decades, there is still much that needs to be learned. The role of IgG_4 as a bystander or as a participant is still controversial. No clear genetic markers or antibodies can be identified as markers of the disease. Different diagnostic criteria are proposed but they are still in the process of evolution, as is the disease. Further investigations are needed to determine the exact pathophysiology of this condition. Hopefully with deeper insight into the origins of the disease and studies performed on larger pools of diagnosed patients, more exact diagnostic criteria can be developed and more comprehensive treatment protocols can be recommended.

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