IgG4 Related Autoimmune Pancreatitis: An Overview and the Emerging Role of Serum Eotaxin as a Potential Treatment Target

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ABSTRACT: Autoimmune pancreatitis (AIP) is a rare disease that has been classified into two subtypes. Type 1 is believed to be mediated by immunoglobulin G4 (IgG4) and type 2 is related to granulocytic epithelial lesions, but the pathogenetic mechanisms in both are still unknown. The patho-mechanism of AIP type 1 is suggested to be secondary to autoimmunity or allergy due to the increased serum IgG4 and immunoglobulin E levels, abundant infiltration of IgG4, plasmacytes and lymphocytes in the pancreas, and fibrosis. Both types of AIP respond to steroid treatment. The relapse rate after remission is high and reaches 30–50% within 6–12 months in AIP type 1; however, in AIP type 2 relapse is rare. The maintenance therapy and therapeutic strategy for relapsing patients with type 1 is managed with low dose steroids, however there are no consensus guidelines. In this review we discuss the current understanding of AIP, highlighting the emerging potential role of eotaxin in pathogenesis, classification, and management of the disease.

IMAJ 2019; 21: 620–623

KEY WORDS: autoimmune pancreatitis (AIP), eotaxin, immunoglobulin G4-related disease, therapy

The first observations of pancreatitis with elevated immunoglobulin levels were described in 1961 by Sarles and colleagues [1]. However, the concept of autoimmune pancreatitis (AIP) was proposed by Yoshida and co-authors in 1995 [2]. Recently, the International Consensus Diagnostic Criteria for AIP classified two distinct subtypes: type 1 and type 2 [3]. Type 1 AIP is an autoimmune disease with systemic organ involvement mediated by immunoglobulin G4 (IgG4), whereas type 2 AIP is a specific pancreatic disease occasionally associated with inflammatory bowel disease [4,5]. Type 1 AIP typically affects males, generally older than 50 years [6]. Incidence and prevalence rates are very difficult to determine; however, a prevalence rate of 4.6 per 100,000 individuals and annual incidence rate of 1.4 per 100,000 individuals was reported in 2011 in Japan [6].

In this review we discussed the current research on AIP, highlighting the emerging potential role of eotaxin in pathogenesis and management.

AUTOIMMUNE PANCREATITIS SUBTYPES

AIP can be classified into two specific subtypes: type 1 and type 2 [5,7] [Table 1]. Type 1 AIP is considered an IgG4-related disease connected to diseases such as sclerosing sialadenitis, sclerosing cholangitis, and retroperitoneal fibrosis. There are several histopathological features in type 1 AIP, including abundant infiltration of plasma cells and lymphocytes as well as fibrosis and perivenular infiltration, which may lead to obliterative phlebitis [8,9]. The clinical presentation differs between the two types of AIP. AIP type 1 patients present with obstructive jaundice while type 2 patients present with a special type of pancreatitis named idiopathic duct-centric pancreatitis or AIP with granulocytic epithelial lesion mostly associated with destruction of the pancreatic duct [5,7]. AIP type 2 patients do not show serum IgG4 or IgG elevation. Furthermore, there are no extra-pancreatic organ involvements, except for inflammatory bowel disease (IBD) in about 30% of the cases. Although type 1 AIP has no serological autoimmune markers, C3 complement and IgG are deposited at the basement membrane of pancreatic ducts and acini suggesting immune complex-mediated destruction of ducts and acini in AIP [9].

PATHOGENESIS: IGG4 AND HUMORAL IMMUNITY

The classification of AIP as an autoimmune disease depends on the presence of pancreatic tissue infiltration by circulating immune cells and the profound response to steroids. Although both subtypes of AIP respond well to steroid treatment [10,11], the pathophysiological process underlying AIP is not well established. Most of the immunological studies focused on type 1 AIP since very few abnormal immunological indices have been reported in type 2 AIP. Moreover, there is inadequate evidence to support T cell lymphocytes and granulocytes in type 2 AIP pathogenesis [12]. Apart from the anticipated elevation of serum IgG4 antibodies, there are other several non-specific antibod-

Table 1. Features of type 1 and type 2 autoimmune pancreatitis

Subtypes of autoimmune pancreatitis	Type 1	Type 2
Nomenclatures	Lymphoplasmacytic sclerosing pancreatitis or IgG4 associated	Idiopathic duct-centric pancreatitis
Average age at presentation	60–70 years	40–50 years, but may present in younger adults and even children
Gender predominance	Male	Equal
Clinical presentation Obstructive jaundice Acute pancreatitis	 Frequent Rare	 Frequent Common
Pancreatic imaging	Diffuse\focal enlargement	Diffuse\focal enlargement
IgG4 level	Elevated in serum, positive staining in involved tissue	Normal
Extra-pancreatic organ involvement	Present	None
Associated disease	Retroperitoneal fibrosis, Sclerosing sialoadenitis, Sclerosing cholangitis, Others	Inflammatory bowel disease
Steroids	Responsive	Responsive
Relapse	Frequent	Rare or no relapse

IgG4 = immunoglobulin G4

ies that are present in type 1 AIP, such as antinuclear antibody, hypergammaglobulinemia, anti-smooth muscle antibodies, and rheumatoid factor [12-15]. In healthy people, IgG4 comprises approximately 4–6% of the total IgG pool and elevated serum IgG levels are mainly reported in allergic diseases, parasitic infection and dermatological conditions [16]. Roughly 5% of normal healthy individuals have elevated IgG4 without any clinical symptoms or radiological abnormalities [17]. Type 1 AIP is part of a systemic disease which can involve multiple organs, thus there may be common target antigens in the involved organs such as the pancreas, biliary tract, kidneys, lungs, and salivary glands. Despite the identification of IgG4 in type 1 AIP as a main immunological derangement, disease specific antibodies have not yet been identified. However, autoantibodies against lactoferrin, carbonic anhydrase-II (anti-CA-II) [15,18-20], CA-IV, pancreatic secretory trypsin inhibitor (anti-PSTI), amylase-α, heat shock protein 10, and plasminogen-binding protein peptide [21] have been detected in type 1 AIP. Despite the identification of these antibodies, IgG4 has the highest diagnostic accuracy and is considered as the sole serological diagnostic immunological test in type 1 AIP. Studies have reported a high diagnostic accuracy, with specificity and sensitivity of 97% and 95% respectively when a cut-off value for serum IgG4 concentrations of 135 mg/dl was used for differentiating AIP from pancreatic cancer [22]. A subsequent study reported 76% sensitivity, 93% specificity, and 36% positive predictive value for elevated serum IgG4 (> 140 mg/dl) in AIP [23].

Imaging is crucial for the diagnosis of AIP. Three classical radiologic features of the disease can be observed, including diffuse, focal, or multifocal involvement. An enhanced computed tomography (CT) scan is a fundamental modality for diagnosis as it is crucial to exclude pancreatic tumors since AIP can be mistakenly diagnosed as pancreatic tumors. Characteristic features of type 1 AIP on CT include a diffusely enlarged or sausage-shaped pancreas and delayed peripheral rim enhancement. Generally there is minimal involvement of the peripancreatic soft tissue and the mesentery. Other less common, possible features are local peripancreatic lymphadenopathy, pancreatic calcification, and pseudocyst formation.

Type 1 autoimmune pancreatitis (AIP) is mediated by IgG4 and is an autoimmune disease with systemic organ involvement, whereas type 2 AIP is a specific pancreatic disease associated with Inflammatory Bowel Disease

IGG4 RELATED AUTOIMMUNE PANCREATITIS AND ATOPY

Several studies have assessed the association between IgG4 related autoimmune pancreatitis and allergic symptoms. Della Torre and colleagues [21] observed a high atopy prevalence of 31% among patients with IgG4-related autoimmune pancreatitis associated with elevated serum IgE levels and peripheral blood eosinophilia. Moreover, this study showed a subset of non-atopic IgG4 related AIP patients who exhibit peripheral blood eosinophilia and elevated IgE, suggesting that processes inherent to IgG4-related AIP itself rather than atopy per se contribute to the eosinophilia and IgE elevation observed in the absence of atopy.

ROLE OF EOTAXIN IN AUTOIMMUNE PANCREATITIS

AIP is characterized by an enhanced T helper type 2 (Th2)-dominant immune response [24]. Peripheral eosinophilia is present in 15.6% of patients with chronic pancreatitis, and their incidence is significantly higher in patients with AIP [25]. Furthermore, studies reported that mild to moderate eosinophilic infiltrates are present in 70–80% of patients with type I AIP [26]. Chemokines are a large family of chemically related chemoattractant cytokines that have a role in orchestrating inflammation and directing leukocytes migration toward the

inflammatory sites [27,28]. The eotaxin subfamily of CC chemokines is composed of eotaxin-1 (CCL11), eotaxin-2 (CCL24), and eotaxin-3 (CCL26), which have a similar function of attracting eosinophils to sites of inflammation by binding to the CC chemokine receptor [29-31]. Moreover, studies have shown an essential role of eosinophils in pancreatic diseases such as AIP and eosinophilic pancreatitis [30,31] and pancreatic eosinophilic infiltration can be used as an additional histological criterion for the diagnosis of both subtypes of AIP [29]. In addition, AIP is often confused with eosinophilic pancreatitis which is another rare entity characterized by eosinophil infiltration that is frequently diagnosed after pancreatic resection for suspected pancreatic tumors [32]. Most patients with eosinophilic pancreatitis have systemic manifestations such as peripheral eosinophilia, elevated immunoglobulin E, and eosinophilic infiltration of the gastrointestinal tract [33]. Thus, eosinophils may play a role in the pathophysiology of certain disorders of the pancreas, especially in AIP. Recently, several studies have suggested Th2 immune response as main mechanism in the pathophysiology of AIP. The Th2 response is mediated mainly by induction of IL-4, IL-5, and IL-13, which leads to eotaxin-3 expression via the STAT6 pathway activation. STAT6 binds to a single specific regulatory motif located upstream of the transcription initiation site of the eotaxin-3 gene [32]. In human pancreatic myofibroblasts there is an overexpression of eotaxin-3 induced by Th2 cytokines IL-4 and IL-13 suggesting that Th2 cytokine-induced eotaxin-3 may participate in the pathophysiology of pancreatic disorders such as AIP and eosinophilic pancreatitis. While eotaxin induction is mediated by Th2 immune cells, the Th1 cytokine, interferon-gamma (IFN-γ) was shown to suppress eotaxin-3 expression via STAT6 silencing.

Autoimmune pancreatitis disease specific antibodies have not been identified

Eotaxin is a major mediator of inflammation and plays a role in the pathophysiology of autoimmune pancreatitis

TREATMENT

Steroids are the recommended treatment for both types of AIP. A study of 563 patients in 17 centers in Japan reported a remission rate of 98% for patients with AIP who were treated with steroids [34]. An additional multicenter study including 10 different countries and involving 1064 patients with both subtypes of AIP (978 patients with type 1, and 86 patients with type 2) who were treated with steroids achieved a remission rate of 99% and 92% in patients with type 1 and type 2, respectively [35]. Steroid therapy has been shown to improve all the symptoms of AIP including jaundice, abdominal pain, abnormal imaging, and other organ involvement (retroperitoneal fibrosis, salivary gland enlargement, IgG4-related renal disease, lymphadenopathy, and inflammatory bowel disease) [36]. The relapse rate was more common in type 1 AIP patients than in type 2 (31% vs. 9%, respectively). The relapses more commonly occurred in the pancreas and biliary tract, specifically with the presence of IgG4-related sclerosing cholangitis (56% vs. 26%). To date, restoration with steroids is the preferred and efficient treatment for induction of maintenance [37]. The relapse-free survival of AIP patients treated with steroid-sparing immunomodulators (IMs) such as azathioprine was similar to those treated with steroids. Rituximab, an anti-CD20 antibody, was used for treatment 12 patients with refractory AIP or steroid/IM intolerance. Complete remission was achieved in 10 of the 12 patients. Bertilimumab, a fully human anti-eotaxin-1 antibody, is in clinical development for patients with high eotaxin-1 levels presenting with IBD and bullous pemphigoid. Recently evidence has been accumulating on the role of chemokines and specifically eotaxin-1 in various autoimmune diseases [38]. Furthermore, it was shown that blockage of specific chemokine CXCR3+ has led to alleviation of autoimmune hepatitis.

CONCLUSION

Eotaxins are major mediators of inflammation and increased evidence is accumulating on their role of in the pathophysiology of AIP. This emerging role should broaden the treatment options for anti-eotaxin targeted therapy, which will enable avoiding the hazardous side effects of chronic use of steroids. It is necessary to establish the exact pathogenesis of AIP, including genetic backgrounds and disease specific antigens, as well as to define the role of eotaxins in inducing and perpetuating the course of AIP. Randomized controlled trials are required to examine the effect of specific antibodies targeting eotaxins family in in AIP patients.

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Capsule

Neuronal vulnerability and multi-lineage diversity in multiple sclerosis

Multiple sclerosis (MS) is a neuroinflammatory disease with a relapsing–remitting disease course at early stages, distinct lesion characteristics in cortical grey versus subcortical white matter and neurodegeneration at chronic stages. **Schimer** and co-authors used single-nucleus RNA sequencing to assess changes in expression in multiple cell lineages in MS lesions and validated the results using multiplex in situ hybridization. The authors found selective vulnerability and loss of excitatory *CUX2*-expressing projection neurons in upper-cortical layers underlying meningeal inflammation; such MS neuron populations exhibited upregulation of stress pathway genes and long non-coding RNAs. Signatures of stressed oligodendrocytes, reactive astrocytes and activated microglia mapped most strongly to the rim of MS plaques. Notably, single-nucleus RNA sequencing identified phagocytosing microglia and/or macrophages by their ingestion and perinuclear import of myelin transcripts, confirmed by functional mouse and human culture assays. These findings indicate lineage- and region-specific transcriptomic changes associated with selective cortical neuron damage and glial activation contributing to progression of MS lesions.

Nature 2019; 573: 75

Eitan Israeli

"I have never met a man so ignorant that I couldn't learn something from him"

Galileo (1564–1642), Italian physicist, mathematician, astronomer, and philosopher