

## Autoimmune pancreatitis

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### Abstract

Since the autoimmune pancreatitis was introduced in 1995, it has been recognized as a form of chronic pancreatitis, which is always associated with autoimmune manifestations. As the improvement of technical and instrumental made in ultrasonography, computed tomography and magnetic resonance imaging, the diagnoses of autoimmune pancreatitis is no longer such difficult. Even though the treatment of autoimmune pancreatitis is available with a conservative therapy, there are many points that are still unclearly. These have stimulated widespread interest in this disease from gastroenterologists, endoscopists, pathologists, and prevalent research. The present article provides with our better understanding of the diagnosis and treatment of autoimmune pancreatitis.

**Keywords:** autoimmune pancreatitis, diagnosis, treatment, chronic.

### Introduction

Autoimmune pancreatitis (AIP) was first described by Yoshida et al [1] in 1995, and introduced to be a form of chronic pancreatitis associated with autoimmune manifestations. Today it has been known that the disease represents a systemic autoimmune condition that involves not only the pancreas but also a variety of other organs such as bile duct [2], the retroperitoneum [3], and lymph nodes [4]. AIP is also known by other names including lymphoplasmacytic sclerosing pancreatitis with cholangitis, idiopathic duct destructive pancreatitis, primary inflammatory pancreatitis, non-alcoholic duct destructive chronic pancreatitis, tumefactive pancreatitis, and destructive pancreatitis depending on the specific tissue changes found on biopsy or the predominant and accompanying symptoms.

As significant improvement of technical and instrumental made in ultrasonography, computed tomography and magnetic resonance imaging, autoimmune pancreatitis is no longer a rare disease, but is an increasingly recognized clinical condition [5]. However, both the diagnosis of autoimmune pancreatitis at an early stage and the differential diagnosis between the pancreatitis and small pancreatic

cancers are still difficult to make [6]. Some patients with autoimmune pancreatitis may present with diseases in other parts of the body. The purpose of this article, therefore, is to review the advances in the diagnosis and treatment of autoimmune pancreatitis.

### Diagnosis

*For the purpose of correct diagnosis, patients should be evaluated by an experienced team of specialists in autoimmune pancreatitis, including gastroenterologist, endoscopist, a pathologist and a radiologist.*

Autoimmune pancreatitis occurs in twice as many men as women. The initial presentation usually occurs between ages 50-60, but patients can also develop autoimmune pancreatitis as early as age 30 as well as late in life [7].

The disease can occur as alone or in association with other autoimmune disorders including sclerosing cholangitis, primary biliary cirrhosis, inflammatory bowel disease, rheumatoid arthritis, hypothyroidism, sarcoidosis, and Sjogren's syndrome. In addition, autoimmune pancreatitis has been seen in association with retroperitoneal fibrosis and lung nodules.

Common symptoms of autoimmune pancreatitis include jaundice, weight loss, and mild abdominal pain. Severe abdominal pain or other symptoms of acute pancreatitis are unusual [8]. However, autoimmune pancreatitis can also cause a wide variety of symptoms that tend to occur as a relapsing-remitting type of disease, with periods of symptoms alternating with periods of remission.

As the number of published cases of AIP is increasing, efforts have been focused on defining AIP as a distinct clinical and pathologic entity and toward developing some generally agreed upon diagnostic criteria and nomenclature. Typical immunological abnormalities in autoimmune pancreatitis are increased levels of serum gammaglobulin, IgG, or IgG4, and the presence of autoantibodies. The histopathological findings show storiform fibrosis with infiltration of lymphocytes and IgG4-positive plasmacytes. Recently, it has been reported that regulatory T cells are involved in both the development of various autoimmune diseases and the shift of B-cell toward IgG4 producing plasmacytes. To clarify the role of CD4+CD25<sup>high</sup> Tregs in pathophysiology of autoimmune pancreatitis, it was now studied the number of regulatory T cells in the pancreas by immunohistochemistry and IL-10 producing cells in the peripheral blood lymphocytes by flowcytometry in 37 patients with autoimmune pancreatitis. IL-10 producing CD4+CD25<sup>high</sup> Tregs were analyzed from peripheral blood by flow cytometry. There were no significant differences in CD3+, CD4+, or CD79+ cells between the AIPs and control sections. On the other hand, CD4+ Foxp3+ cells were significantly increased in the pancreas with AIP compared with Control. In patients with the untreated AIP, the numbers of CD4+CD25<sup>high</sup> Tregs and IgG4 are positively correlated. IL-10 producing CD4+CD25<sup>high</sup> cells and IgG4 also positively correlated. This means that increased numbers of CD4+CD25<sup>high</sup> Tregs may influence IgG4 production in AIP [9].

However, a study compared four groups of patients with gastric, duodenal, ileal and/or colonic biopsies, and concluded that IgG4+ plasma cells are not more numerous in the digestive mucosa of AIP patients than in controls. Plasma and IgG4+ cell infiltration is more abundant in the colon of IBD patients than in AIP patients. Therefore, the authors believed that IgG4 immunostaining of the digestive mucosa is not helpful for AIP diagnosis [10].

Because certain markers of autoimmune pancreatitis, such as IgG4 positive plasma cells can be detected in other tissues besides the pancreas in affected patients [2], some researchers believe that autoimmune pancreatitis may be a systemic autoimmune disease affecting multiple organs besides the pancreas, including the gallbladder, bile ducts,

salivary glands, lungs, biliary tree, and the kidney's renal tubules.

On the other hand, diagnostic criteria for AIP are controversially reported [4]. To identify the frequency of autoimmune pancreatitis in patients with a first episode of acute pancreatitis suggestive of underlying chronic disease or with chronic pancreatitis in Germany, 545 patients from one clinic collected 1997-2008 were reviewed. "Definite autoimmune pancreatitis" was diagnosed in patients with Mayo HISORt or Asian AIP criteria, or in patients simultaneously presenting with pancreatic disease, other autoimmune disease and/or elevated autoantibodies, and response of pancreatic disease to steroids. "Probable AIP" was diagnosed in patients with pancreatic disease, elevated IgG4 and/or other autoantibodies, and other autoimmune disease. "Possible AIP" was diagnosed in patients with pancreatic disease and either elevated IgG4 and/or other autoantibodies, or other autoimmune disease. Non-alcoholic pancreatitis was found in 228/545 patients (42 %). Among this group, it was detected AIP in 35/228 patients. Other autoimmune diseases were found in 26/35 patients. Steroids were given to 21/35 patients. Surgery was performed in 3/35 patients. The authors, therefore, concluded that definite autoimmune pancreatitis or pancreatitis associated with autoimmune features is found in a significant amount of patients with non-alcoholic pancreatitis. However, established diagnostic criteria of AIP do not reflect the entire spectrum of the disease [4].

Image reveals that the pancreas is enlarged [11] and is surrounded by a halo of lymphocytes and plasma cells. Over 90% of the 33 CP-SjS cases also presented pancreatic enlargement on initial examination with ultrasonography or computed tomography [6]. Granulomas may also be present around the ducts of the pancreas, and a mass may obstruct the ducts. Cross-sectional imaging shows diffuse gland enlargement and a long attenuated segment of the pancreatic duct. A favorable response to corticosteroids also differentiates autoimmune pancreatitis from alcohol-induced pancreatitis. Because a mass obstructing the biliary ducts is often seen in autoimmune pancreatitis, autoimmune pancreatitis must be differentiated from pancreatic cancer with fine needle aspiration biopsy and tissue studies of the pancreas.

Overview, if an elevated IgG, positive antinuclear antibodies, enlargement of the pancreas on ultrasonography or computed tomography, and/or irregular narrowing of the main pancreatic duct on ERP or MRI are found, autoimmune pancreatitis should be suspected when pancreatic cancer and other neoplastic pancreatic disease can be ruled out [6].

## Differential Diagnosis

Pancreatic cancer is the most common condition that should be differentiated from local forms of autoimmune pancreatitis [12, 13]. Differentiation from pancreatic carcinoma and normal pancreas on the basis of enhancement characteristics at dual-phase CT demonstrated that the mean CT attenuation value of the pancreatic parenchyma in patients with autoimmune pancreatitis was significantly lower than that in patients with a normal pancreas, the mean CT attenuation value of the mass in autoimmune pancreatitis was not significantly different from that of carcinoma, but in the hepatic phase, the value was significantly higher than that of carcinoma [14].

## Treatment

The disorder can be treated with steroids and doesn't require surgery [15]. Since its characters are very similar to the malignancy, therefore, the failure to differentiate autoimmune pancreatitis from malignancy may lead to unnecessary pancreatic resection, and the characteristic lymphoplasmacytic infiltrate of AIP has been found in about 1/3 of patients undergoing pancreatic resection for suspected malignancy who are ultimately found to have benign disease. In this subset of patients, a trial of steroid therapy may have prevented a Whipple procedure or complete pancreatectomy for a benign disease which responds well to medical therapy [16].

The evaluation of the therapy effect includes the improvement of clinical signs and symptoms: 1) decreased jaundice, abdominal and back pain, 2) decreased pancreatic size on imaging, 3) decreased levels of pancreatic enzymes, hepatobiliary enzymes and total bilirubin, and 4) recovery of blood glucose and insulin level.

## Conclusions

Autoimmune pancreatitis is an increasingly recognized clinical condition. There has been significant progress in understanding the clinical profile of AIP, but the pathogenesis of AIP remains unclear. Even though a large number of reports on increased serum IgG4 levels and IgG4-positive cells in bile duct biopsy specimens are related the disease, established diagnostic criteria of autoimmune pancreatitis do not reflect the entire spectrum of the disease. Autoimmune pancreatitis is steroid-responsive, but maintaining remission continues to remain challenging.

## References

1. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality: proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 1995; 40:1561-1568.
2. Webster GJM, Pereira SP, Chapman RW. Autoimmune pancreatitis/IgG4-associated cholangitis and primary sclerosing cholangitis – Overlapping or separate diseases? *J Hepatology*. 51; (2): 398-402.
3. Kamisawa T, Matsukawa M, Ohkawa M. Autoimmune Pancreatitis Associated with Retroperitoneal Fibrosis. *JOP. J Pancreas* 2005; 6(3):260-263.
4. Schneider A, Steih J, Mosler D, Pfutzer RH, Lohr JM, Singer MV. Frequency of autoimmune pancreatitis (AIP) in Patients with acute and chronic pancreatitis from Germany. *Pancreatology* 2009; 9: 454-455 (abstract).
5. Okazaki K. Autoimmune pancreatitis is increasing in Japan. *Gastroenterology* 125; 5: 1557-1558.
6. Hayakawa T, Naruse S, Kitagawa M, Kondo T. Clinical Aspects of Autoimmune Pancreatitis in Sjogren's syndrome. *JOP. J Pancreas* 2001; 2(3):88-92.
7. Zamboni G, Luttges J, Capelli P, Frulloni L, Cavallini G, Pederzoli P, Leins A, Longnecker D, Kloppel G. Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. *Virchows Arch* 2004; 445:552-563.
8. Yadav D, Notahara K, Smyrk TC, Clain JE, Pearson RH, Farnell MB, Chari ST. Idiopathic tumefactive chronic pancreatitis: clinical profile, histology, and natural history after resection. *Clin Gastroenterol Hepatol* 2003; 1:129-135.
9. Uchida K, Miyoshi H, Kusuda T, Koyabu M, Fukata N, Sakaguchi Y, Ikeura T, Fukui T, Matsushita M, Takaoka M, Okazaki K. Regulatory T cells in patients with autoimmune pancreatitis. *Pancreatology* 2009; 9: 458 (abstract).
10. Le Baleur Y, Rebours V, Cazals-Hatem D, Bouhnik Y, Bedossa P, Ruzsniwski P, Levy P, Couvelard A. IgG4 positive plasma cell infiltration in the digestive tract mucosa of patients with autoimmune pancreatitis is neither abundant nor specific. *Pancreatology* 2009; 9: 460 (abstract).
11. Nishimori I, Suda K, Oi I, Ogawa M. Autoimmune pancreatitis. *Nippon Shokakibyo Gakkai Zasshi*. 2000; 97:1355-1363.
12. Cavallini G, Frulloni L. Autoimmunity and chronic pancreatitis A concealed relationship. *JOP. J Pancreas* 2001; 2:61-68.
13. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001; 120:682-707.
14. Takahashi N, Fletcher JG, Hough DM, Fidler JL, Kawashima A, Mandrekar JN, Chari ST. Autoimmune Pancreatitis: Differentiation From Pancreatic Carcinoma and Normal Pancreas on the Basis of Enhancement Characteristics at Dual-Phase CT. *Am J Roentgenol* 2009; 193:479-484.

15. Finkelberg D, Sahani D, Deshpande V, Brugge W. Autoimmune Pancreatitis. *N Eng J Med* 2006; 355:2670-2676.
16. Pezzili R, Casadei R, Calculli L, Santini D. Autoimmune Pancreatitis. A Case Mimicking Carcinoma, *Clinical Imaging, JOP. J Pancreas* 2004; 1; 5: 527-530.