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*World J Gastroenterol* 2007 December 21; 13(47): 6327-6332
***World Journal of Gastroenterology*** ISSN 1007-9327


*TOPIC HIGHLIGHT*

**Michael F Byrne, MD,** *Series Editor*

# Autoimmune pancreatitis: A review

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Received: June 14, 2007 Revised: August 30, 2007

## Abstract

Autoimmune pancreatitis has emerged over the last 40 years from a proposed concept to a well established and recognized entity. As an efficient mimicker of pancreatic carcinoma, its early and appropriate recognition are crucial. With mounting understanding of its pathogenesis and natural history, significant advances have been made in the diagnosis of autoimmune pancreatitis. The characteristic laboratory features and imaging seen in autoimmune pancreatitis are reviewed along with some of the proposed diagnostic criteria and treatment algorithms.



**Key words:** Autoimmune pancreatitis; Chronic pancreatitis; Idiopathic pancreatitis; Sclerosing pancreatitis

Zandieh I, Byrne MF. Autoimmune pancreatitis: A review. *World J Gastroenterol* 2007; 13(47): 6327-6332

http://www.wjgnet.com/1007-9327/13/6327.asp

## INTRODUCTION

In a fashion similar to other solid organs, the pancreas has been linked with autoimmune disease in the form of "autoimmune pancreatitis". The concept was originally postulated by Sarles *et al*[1] over 40 years ago, when non-alcoholic pancreatitis was associated with hypergammaglobulinemia. However, only in the last 10 years has this clinical entity been firmly established in the list of diseases affecting the pancreas and thus appropriately gained significant attention. An efficient mimicker of pancreatic carcinoma on both clinical and radiologic grounds, its early and accurate diagnosis can have profound treatment and prognostic implications, distinguished by the rapid reversal of its characteristic lesions with corticosteroid therapy.

## DEFINITION AND NOMENCLATURE

With mounting evidence suggesting an underlying autoimmune mechanism, the term autoimmune pancreatitis was originally introduced by Yoshida *et al*[2] in 1995. Characterized histologically by a predominant lymphoplasmacytic infiltrate and fibrosis that can lead to both endocrine and exocrine dysfunction, autoimmune pancreatitis likely accounts for a significant proportion of cases previously classified as idiopathic pancreatitis. Various disease descriptors have been previously proposed such as chronic sclerosing pancreatitis[3], lymphoplasmacytic sclerosing pancreatitis with cholangitis[4], sclerosing pancreatocholangitis[5], non-alcoholic duct-destructive chronic pancreatitis[6], chronic pancreatitis with irregular narrowing of the main pancreatic duct[7], and pseudotumorous pancreatitis[8]. Retrospectively, these various descriptors likely describe the entity that we now refer to as autoimmune pancreatitis, however focused on its specific radiologic or histologic findings. As will be discussed further, although autoimmune pancreatitis is now the preferred term, its clinical, biochemical, radiologic, and pathologic findings are heterogeneous.

## DEMOGRAPHICS AND EPIDEMIOLOGY

Despite the increasing cases of autoimmune pancreatitis being reported around the world, its true prevalence and incidence have yet to be determined. Three case series have reported prevalence rates of 4% to 6% of all patients diagnosed with chronic pancreatitis[9,10]. The mean age of diagnosis is 55, this however can vary with cases presenting from 30 to 70 years of age[3,6,11,12]. A male predilection of 1.7:1-2:1 has been reported in three surgical series[12-14]. Considering its postulated autoimmune pathogenesis, it has been associated with Sjogren's syndrome[15,16], rheumatoid arthritis[14], primary sclerosing cholangitis[16,17], retroperitoneal fibrosis[18] and inflammatory bowel disease[19]. Although the prevalence of a concurrent autoimmune diagnosis has been reported in various series, they are likely underestimates as some diagnoses of autoimmune pancreatitis may precede the diagnosis of the concurrent autoimmune condition[9,10,20].

## PATHOGENESIS

Although the precise etiology and pathogenesis of autoimmune pancreatitis remains unknown, mounting evidence supports an autoimmune cause. Similar to other autoimmune diseases, an association of the HLA haplotype DRB1*0405-DQB1*0401 with autoimmune pancreatitis in the Japanese population has been discovered[21]. Significant autoimmune markers of the disease include its association with other autoimmune diseases, a predominant lymphoplasmacytic infiltrate on histology, hypergammaglobulinemia, elevated IgG4 levels and the presence of autoantibodies. A number of autoantibodies including antinuclear antibody (ANA), antismooth muscle antibody (ASMA), rheumatoid factor, antilactoferrin antibody (ALF) and anticarbonic anhydrase Ⅱ antibody (CA-Ⅱ) have been frequently detected in patients with autoimmune pancreatitis[22]. Both CA-Ⅱ and ALF are found in the normal pancreas, with CA-Ⅱ located in duct cells and ALF being found in the acinar cells. However, they are also distributed in the cells of several other organs including the lactating breast, biliary ducts, distal renal tubules, and salivary, bronchial and gastric glands. Thus potentially explaining some of the extrapancreatic sequelae of autoimmune pancreatitis.

As in Sjogren's syndrome or primary sclerosing cholangitis, CD4+ T-cells inducing a Th1 type of immune response are predominantly involved in the development of autoimmune pancreatitis as effector cells over Th2 type CD4+ T-cells[22,23]. Further strengthening this discovery, an animal model of autoimmune pancreatitis, using neonatally thymectomized mice immunized with CA-Ⅱ or ALF found that CD4+ Th1 cells are mainly involved in the early development of murine autoimmune pancreatitis[24]. Pancreatic specimens from this mouse model revealed histologic features consistent with those seen in autoimmune pancreatitis in humans. Therefore, an autoimmune reaction against CA-Ⅱ or ALF *via* CD4+ Th1 T-cells has a role in the early development of autoimmune pancreatitis. However many questions remain regarding the underlying triggering event and precise mechanisms leading to autoimmune pancreatitis.

## CLINICAL CHARACTERISTICS

The presenting symptoms are variable and most commonly include painless jaundice, weight loss and abdominal pain. Although common, abdominal pain tends to be mild and variable in duration, usually lasting weeks to months. Patients rarely present with acute attacks of pain, more typical of acute pancreatitis. Jaundice has been reported in up to 70%-80% of patients in some series and is usually due to an accompanying stricture in the distal common bile duct[25]. Considering the patient demographics and common presenting symptoms, it is clear why many patients are initially diagnosed with pancreatobiliary malignancies and prior to the recognition of autoimmune pancreatitis would undergo unnecessary invasive procedures.

In some series, up to 60% of patients with autoimmune pancreatitis have diabetes mellitus[26,27]. The precise pathogenesis is unclear however different theories have been proposed. The majority are felt to manifest as type 2 diabetics with a degree of impaired glucose tolerance, however a proportion have been found to have antibodies to islet cells and glutamic decarboxylase and thus can manifest as Type 1 diabetics. It has been reported that a proportion of patients with autoimmune pancreatitis associated diabetes mellitus improve following steroid therapy[28].

The presence of potential extrapancreatic target antigens in the lungs, breasts and kidneys can also lead to clinical manifestations. Breast, renal and pulmonary inflammatory masses have been detected in patients with autoimmune pancreatitis and found to be composed of a lymphoplasmacytic infiltrate containing numerous IgG4 positive plasma cells[29,30]. Cases of autoimmune pancreatitis associated with interstitial pneumonia and mild renal failure due to interstitial nephritis have also been reported[31-33].

## DIAGNOSIS-DIAGNOSTIC IMAGING

Diagnostic imaging plays a critical role in the diagnosis of autoimmune pancreatitis. It is often the first investigative modality that raises the possibility of autoimmune pancreatitis, based on characteristic imaging features. As a result, both radiologists and non-radiologists need to be familiar with its unique features on ultrasound, computed tomography and endoscopic retrograde cholangio-pancreatography.

### *Ultrasound*

Although abdominal ultrasonography is a commonly ordered initial radiologic investigation for painless jaundice, overlying bowel gas and obesity greatly limit its ability to accurately visualize the pancreas. Furthermore, ultrasound findings in patients with autoimmune pancreatitis are non-specific and include many features commonly seen in other types of acute and chronic pancreatitis. The role of contrast-enhanced ultrasonography is evolving and may prove to be an important modality in the differentiation of pancreatic lesions[34].

### *Computed tomography (CT)*

In patients with diffuse pancreatic involvement, the findings on CT usually consist of a diffusely enlarged pancreas, commonly referred to as 'sausage-like' or 'bulky', which correlates with the pathologic finding of marked stromal edema on gross examination (Figure 1). Focal involvement typically appears as a mass, most commonly involving the head of the pancreas, with low attenuation or isoattenuation. Peri-pancreatic fat infiltration is uncommon. Pancreatic parenchymal calcification and intraductal stones, commonly seen in chronic pancreatitis, are also rarely observed in autoimmune pancreatitis. Mild peri-pancreatic lymphadenopathy and loss of parenchymal lobularity are commonly seen.

Another distinguishing feature of autoimmune pancreatitis is delayed enhancement of the pancreatic parenchyma. The pancreas tends to appear hypodense in comparison to the spleen on the arterial enhanced

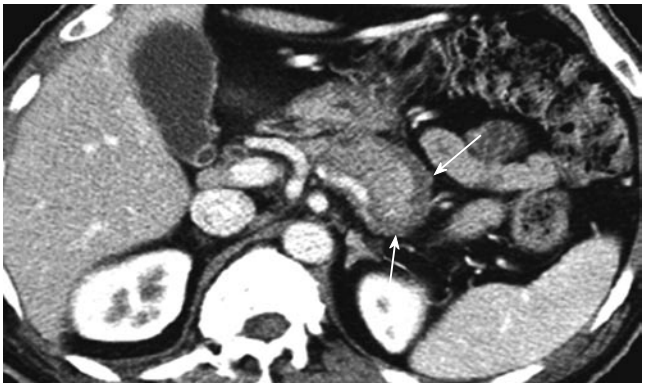

**Figure 1** Contrast enhanced CT showing sausage-like swelling of the pancreatic tail along with a surrounding low attenuation rim (arrows).

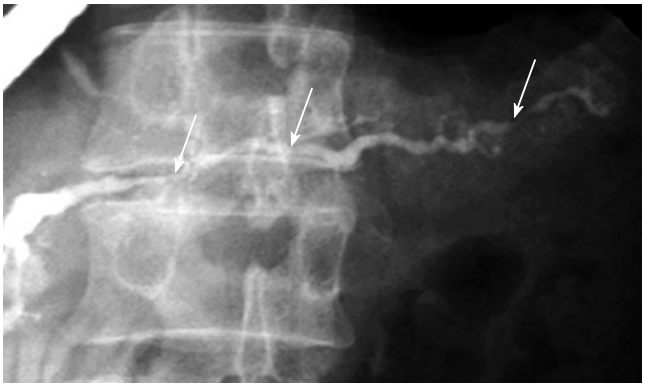

**Figure 2** Direct pancreatography delineating a pancreatic duct with multiple segments of narrowing (arrows).

phase with increasing attenuation in the delayed phase images. It has been proposed that delayed enhancement is a reflection of the heterogeneous lymphoplasmacytic infiltrate and fibrosis observed on histologic examination of the pancreas[35]. Finally, a capsule-like low density rim can also be seen surrounding the pancreas on both arterial and delayed images. This may represent clear demarcation of the inflammatory process in autoimmune pancreatitis from the surrounding peripancreatic fat, due to the absence of peripancreatic fat infiltration.

### *Magnetic resonance cholangio-pancreatography (MRCP)*

The role of MRCP continues to evolve, especially as a non-invasive modality in assessing pancreatobiliary ductal anatomy. Its role however in autoimmune pancreatitis remains limited, primarily because the lack of exogenous contrast and lower resolution compared to ERCP, greatly limit its ability to detect the characteristic pancreatic duct changes.

### *Endoscopic retrograde cholangio-pancreatography (ERCP)*

The hallmark findings on direct pancreatography are focal, segmental, or diffuse narrowing of the main pancreatic duct (Figure 2)[36]. The pattern and degree of ductal narrowing is a direct result of ductal compression due to the heterogenous lymphoplasmacytic infiltrate and fibrosis affecting the gland. Although uncommon, the focal variant of autoimmune pancreatitis represents a diagnostic challenge because its findings are quite similar to those expected in pancreatic cancer. Usually associated with a mass in the head of the pancreas on CT, the focal type of autoimmune pancreatitis results in localized stenosis of the main pancreatic duct and upstream dilatation.

In the 'segmental' variant, multiple strictures affecting different sections of the pancreatic dust are visualized with intervening duct that appears non-dilated. In the 'diffuse' form, the entire pancreatic duct is narrowed. Rather than representing distinct variants of autoimmune pancreatitis, some reports have documented progression of the segmental form to a more diffuse appearance on ERCP without therapy[12]. Thus suggesting that the different patterns of ductal narrowing are primarily a result of the timing of ERCP and represent the spectrum of the disease rather than distinct entities[20,36].

Other potential ERCP findings in autoimmune pancreatitis include narrowing of the intrapancreatic portion of the common bile duct and irregular narrowing of extrahepatic bile ducts. Although uncommon, dilatation of the intrahepatic bile ducts has also been reported[36].

### *Endoscopic ultrasonography (EUS)*

Due to its ability to accurately visualize the pancreas and perform fine needle aspiration, EUS is a crucial modality in the diagnosis of autoimmune pancreatitis. The absence of exogenous contrast makes it an important diagnostic test, even prior to CT, especially in women of child-bearing age. The findings seen in autoimmune pancreatitis closely resemble those found on CT, including a hypoechoic gland with focal or diffuse parenchymal swelling. Above all, the ability to perform tissue acquisition either by fine needle aspiration or core biopsy further strengthens the role of EUS in the diagnosis of this elusive entity.

## DIAGNOSIS-PATHOLOGY

The hallmark histologic finding of autoimmune pancreatitis includes a dense lymphoplasmacytic infiltrate and fibrosis (Figure 3). The infiltrate is often heterogeneous in its distribution throughout the gland and its degree of cellularity. Although consisting predominantly of lymphocytes, the cellular infiltrate also contains neutrophils and eosinophils. Studies using immunohistochemistry have further defined that the lymphocyte population consists predominantly of CD4+ T lymphocytes with a smaller but detectable population of CD8+T cells and B cells[24].

Another important histologic finding is the presence of periductal inflammation, usually involving medium-sized and large interlobular ducts (Figure 4)[37]. Sometimes referred to as a 'collar' of inflammation, it consists predominantly of plasma cells and lymphocytes, sometimes forming germinal centers. The infiltrate is primarily subepithelial, with the epithelium only rarely being infiltrated by lymphocytes. It completely encompasses the duct leading to luminal narrowing by way of epithelial infolding and gives the lumen a star-like appearance[24]. Periphlebitis and perineural inflammation are also often

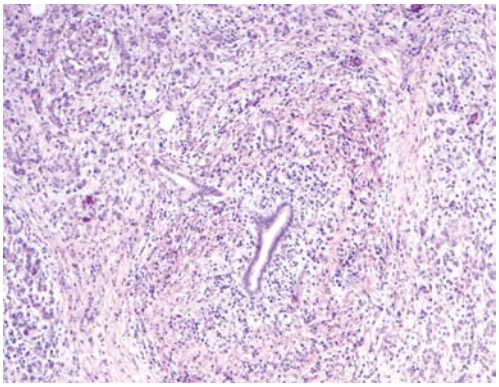

**Figure 3** Diffuse pancreatic lymphoplasmacytic infiltrate with early fibrosis and atrophy.

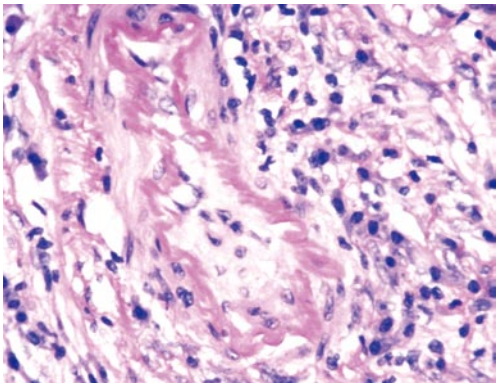

**Figure 5** Medium sized artery with infiltration of the vessel wall by lymphocytes and plasma cells.

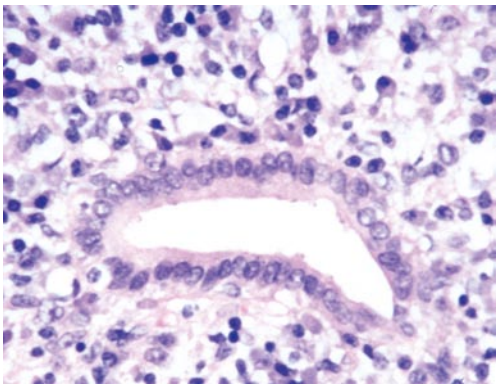

**Figure 4** Small pancreatic duct surrounded by a cuff of lymphocytes and plasma cells that is extending into the atrophic pancreatic parenchyma.

**Table 1 Diagnostic criteria for autoimmune pancreatitis proposed by the Japanese Pancreas Society**

| |
|---|
| A Imaging criterion: Diffuse narrowing of the main pancreatic duct with an irregular wall (more than 1/3 the length of the entire pancreatic duct) and enlargement of the pancreas |
| B Laboratory criterion: Abnormally elevated levels of serum gamma-globulin and/or IgG, or the presence of autoantibodies |
| C Histopathologic criterion: Marked lymphoplasmacytic infiltration and dense fibrosis |
| For the diagnosis, criterion A must be present together with criterion B and/or C |

observed (Figure 5)[12,30].

Finally, an important histologic observation in the pathologic diagnosis of autoimmune pancreatitis is the absence of ductal dilatation, calcifications and proteinaceous plugs, commonly found in chronic pancreatitis.

## DIAGNOSTIC CRITERIA

Considering the difficulty in accurately differentiating autoimmune pancreatitis from other forms of chronic pancreatitis and pancreatic carcinoma, a number of diagnostic criteria have been proposed. The earliest was proposed by the Japanese Pancreas Society and is outlined in Table 1[38]. It is based on three criteria encompassing imaging, laboratory and histopathologic findings. The mandatory imaging findings include diffuse narrowing of the pancreatic duct involving at least one third of the entire length along with pancreatic enlargement. One of the two 'minor' laboratory or pathologic criteria also needs to be present for the diagnosis. Aparisi *et al*[39] proposed a different scoring system based on clinical presentation, laboratory parameters and morphologic findings. More recently, investigators have specifically included an elevation in the IgG4 level and response to steroids as supporting criteria for the diagnosis of autoimmune pancreatitis[11,40].

Kim *et al*[11] retrospectively applied the original diagnostic criteria of the Japanese Pancreas Society to a series of 28 patients diagnosed with autoimmune pancreatitis who had responded to steroid therapy. The original diagnosis required the presence of diffuse enlargement of the pancreas and diffuse or segmental irregular narrowing of the main pancreatic duct. Supporting criteria included elevated levels of IgG and/or IgG4, the presence of autoantibodies and histopathologic findings. Despite the absence of laboratory abnormalities or histopathologic findings in some patients, steroid therapy was initiated if the imaging criteria were met. The authors concluded that had they strictly applied the diagnostic criteria of the Japanese Pancreas Society, 9 of 28 patients would have not been diagnosed with autoimmune pancreatitis and appropriately treated. Seven of the 9 patients would have been missed because the extent of ductal narrowing was less than one third of the entire length of the main pancreatic duct. Another two patients had normal IgG levels, absence of autoantibodies and non-diagnostic pancreatic histopathology. As a result, the authors revised the diagnostic criteria by including the response to steroids and association with other autoimmune diseases as supporting criteria. They also abolished the need for more than one third of the pancreatic duct to be affected.

Although none of the proposed diagnostic criteria have been validated, they underscore the highly characteristic

imaging findings in autoimmune pancreatitis. Finally, the histopathologic findings which have previously been felt to represent the gold standard for the diagnosis can be absent on specimens due to the patchy distribution of the disease and have also been seen in patients with alcohol induced chronic pancreatitis[30].

## TREATMENT AND PROGNOSIS

Corticosteroids are the first line therapy in the treatment of autoimmune pancreatitis, often providing dramatic and rapid results. The role of other immunosuppressive agents in this patient population remains largely undefined.

Prednisone is usually initiated at a dose of 0.4-0.6 mg/kg per day for a period of months. Although a detailed steroid schedule has not yet been fully defined, most patients are usually treated for a period of 2-3 mo, with a tapering schedule of 5 mg every 1-2 wk.

From a laboratory perspective, hypergammaglobulinemia and elevated IgG4 levels can resolve and previously identified autoantibodies can become undetectable[41]. Marked changes are also observed in the pretreatment findings of CT and ERCP[20]. The diffuse enlargement of the gland, characteristic pattern of enhancement and capsule-like low density rim seen on CT revert to normal. ERCP findings of focal, segmental or diffuse pancreatic duct narrowing also disappear. Narrowing of the distal common bile duct normalizes. Since almost all patients undergo ERCP prior to the initiation of steroid therapy, the finding of distal common bile duct narrowing is often treated with stent placement. The rapid reversal of biliary narrowing with steroid therapy usually allows for stent removal within 1-2 mo.

These radiologic changes closely parallel the clinical improvement that patients experience, specifically regarding the most common presenting symptoms of abdominal pain or painless jaundice. They are often observed within 2-4 wk of corticosteroid initiation and serve to further confirm the diagnosis of autoimmune pancreatitis.

In terms of prognosis, although the majority of patients achieve a sustained clinical remission with a tapering course of corticosteroid therapy, a subset may go on to require chronic maintenance dosing of 5-10 mg/d. The long term prognosis of autoimmune pancreatitis remains as yet undefined considering its recent discovery. Two different cohorts involving 23 patients followed for a mean of 56 mo and 17 patients followed for 16 mo, each had 1 patient relapse[9,35]. In both cases the patient was successfully treated with a second course of corticosteroids and maintained on low dose steroid therapy.

## CONCLUSION

In the last 40 years autoimmune pancreatitis has gone from a proposed concept to a well-recognized clinical entity. Despite the fact that our understanding regarding its pathogenesis, presentation, diagnosis and treatment have evolved, many questions remain unanswered. Its relationship to other autoimmune diseases, precise pathogenesis, accurate diagnosis and long-term prognosis require further clarification.

Above all, as an efficient mimicker of pancreatic carcinoma, the accurate and timely diagnosis of autoimmune pancreatitis can have drastic consequences on therapy and prognosis. Thereby underlining the critical importance of its awareness among internists, gastroenterologists, radiologists, pathologists and surgeons.

## ACKNOWLEDGMENTS

We wish to acknowledge Dr. David Owen, Department of Pathology, University of British Columbia, Vancouver, British Columbia, Canada for providing histology images.

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