Autoimmune pancreatitis: negotiating the labyrinth of terminology, diagnosis and differential diagnosis

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Abstract

Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis that typically affects adults with a male predilection. Jaundice, weight loss, anorexia and abdominal pain are the most common presenting symptoms. Serum IgG and IgG4 are frequently elevated. Imaging studies show diffuse enlargement of the pancreas with diffuse or segmental narrowing of the main pancreatic duct. When pancreatic involvement is focal, it can mimic adenocarcinoma on imaging. Histologically, the disease is characterized by a duct-centric fibroinflammatory process, dense lymphoplasmacytic infiltrates and phlebitis. High numbers of IgG4-positive plasma cells are frequently present. The absence of duct dilatation, pseudocyst, fat necrosis or calcification aids in the distinction from alcoholic pancreatitis. AIP can involve other sites in the pancreaticobilairy tree and is frequently associated with other autoimmune and fibrosclerosing diseases. This has led to the concept that AIP is the pancreatic manifestation of systemic IgG4-related immunological disease. The prognosis is generally favourable with an excellent response to steroids.

Keywords autoimmune; IgG4; lymphoplasmacytic; pancreatitis; sclerosing

Autoimmune pancreatitis (AIP) is a distinct form of chronic pancreatitis with characteristic clinical, radiological and pathological features. The disease was first described nearly 50 years ago,[1] but has evolved into a definite diagnostic entity only in the last 10 years. AIP accounts for 2–6% of cases of chronic pancreatitis[2] and for nearly one-quarter of cases of Whipple resections that show benign pathology.[3,4] A plethora of terms have been used to describe this disease, including idiopathic chronic pancreatitis, primary inflammatory pancreatitis, nonalcoholic duct-destructive pancreatitis, inflammatory pseudotumour, lymphoplasmacytic sclerosing pancreatitis and chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct. Laboratory data and animal models indicate that the disease is immunologically mediated and the term autoimmune pancreatitis has been advocated over other more descriptive terms.[5] This review first describes the clinical, radiological and pathological features, and then focuses on the common diagnostic problems encountered by pathologists.

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Autoimmune pancreatitis: clinical and pathological characteristics

Clinical features

The disease generally affects adults with a mean age of 56 years, but a wide age range from teens to 80s has been reported.[4,6] Males are twice as commonly affected as females.[4,6,7] Jaundice is the most common symptom and is present in two-thirds of subjects; it results from fibroinflammatory involvement of the common bile duct (Table 1). Weight loss, anorexia and mild abdominal pain are also commonly present. The duration of symptoms is typically 3–4 weeks.[7]

Immunological features

Serum γ-globulin and IgG are elevated in the majority of AIP patients. Increased serum IgG4 (>140 mg/dl), a minor component of the IgG subclass, is a characteristic feature of AIP. The sensitivity of elevated serum IgG4 for the diagnosis of AIP is approximately 70% in most series, while the specificity is around 90%.[8–10] Mild elevations (less than two-fold) in serum IgG4 are seen in up to 10% of subjects without AIP, including some with pancreatic cancer or alcoholic pancreatitis.[10–12] If more than twice normal serum levels of IgG4 (>280 mg/dl) are used as a cut-off value, the specificity for AIP diagnosis rises to 99%, but sensitivity falls to around 50%.[10] Most patients with primary sclerosing cholangitis, primary biliary cirrhosis and Sjögren syndrome have normal serum IgG4 levels.[13]

A variety of autoantibodies have been described in AIP patients, including antinuclear, antismooth muscle, antimitochondrial, antimicrosomal, antineutrophilic cytoplasmic (p-ANCA), antithyroglobin and rheumatoid factor.[9] Antibodies directed against antigens present on ductal and acinar cells like carbonic

Clinical features of autoimmune pancreatitis

Symptoms	Obstructive jaundice most common
	Weight loss, mild abdominal pain
Immunological	Increased serum γ-globulins and IgG
	Elevated IgG4 highly characteristic
	Variety of autoantibodies often present
Imaging	Diffuse enlargement of pancreas
	Diffuse or focal narrowing of main pancreatic duct
	Stricture of distal common bile duct
	Mass-like lesion often present
Extrapancreatic disease	Gallbladder, common bile duct, salivary gland
	Association with other fibrosclerosing disorders (retroperitoneal fibrosis)
	Association with other immunological diseases (Sjögren, rheumatoid arthritis and inflammatory bowel disease)
	Extrapancreatic pseudotumours (liver, lung)
Therapy	Excellent response to steroids

Table 1

anhydrase II (30–60%) and lactoferrin (50–75%) are often present.[11] However, none of these antibodies is consistently present. In approximately 5% of patients, autoantibodies can be present despite normal IgG and IgG4 levels,[14] indicating that measurement of both IgG4 and autoantibodies can be complementary for diagnosis.[9]

Radiological features

The characteristic features are diffuse enlargement of the pancreas with diffuse or segmental narrowing of the main pancreatic duct.[15,16] When present together, these features have high specificity for the diagnosis of AIP.[9] Pancreatic enlargement can be visualized with computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS). The irregular narrowing of the main pancreatic duct can be demonstrated on endoscopic retrograde cholangiopancreatography (ERCP) and is often accompanied by stricture of the distal common bile duct. The latter feature can mimic primary sclerosing cholangitis.[17] In some cases, pancreatic involvement is focal rather than diffuse, resulting in the radiographic appearance of a mass lesion. In these cases, the imaging findings can be indistinguishable from pancreatic adenocarcinoma. Irregular hypoechoic masses have been reported by EUS in 25–40% of cases.[2,16] Calcifications, pseudocysts, atrophy and calculi are more characteristic of alcoholic pancreatitis, but some of these features may be seen in late stages of AIP.[9,18]

Pathological features

Gross features

The pancreas is firm and diffusely enlarged. When there is focal involvement, the head is usually affected and may form one or more mass-like lesions. Focal involvement can be associated with stricture of the main pancreatic and common bile duct, and has been referred to as 'tumefactive' AIP, as it is commonly mistaken for pancreatic adenocarcinoma.[7]

Microscopic features

The histological features of AIP have been well characterized and include a duct-centric fibroinflammatory process, dense lymphoplasmacytic infiltrate and phlebitis (Table 2).[4,6,7,19] Extensive destruction of exocrine pancreatic tissue can occur.

Morphological features of autoimmune pancreatitis

Typical features

- Duct-centric inflammation
- Lymphocytic exocytosis
- Dense lymphoplasmacytic infiltrate
- Phlebitis
- Storiform fibrosis
- High (> 10/high power field) number of IgG4-positive plasma cells on immunohistochemistry

Features that can be present

- Mass-like fibroinflammatory lesion (pseudotumour)
- Neutrophilic infiltration of ducts
- Duct-centric granulomas

Table 2

Inflammation

- *Dense lymphoplasmacytic infiltrate*. Inflammation around interlobular ducts is the hallmark of AIP (Figure 1). The infiltrate is usually dominated by lymphocytes and plasma cells, but eosinophils can be numerous. The lymphocytes often extend into the duct epithelium, a feature referred to as lymphocytic exocytosis, but the epithelial cells are usually preserved (Figure 2). The inflammation and fibrosis often extend into the peripancreatic tissue. Lymphoid follicles with prominent germinal centres can be present in the pancreas and peripancreatic tissue. The peripancreatic and peribiliary lymph nodes are enlarged and show follicular hyperplasia and plasma cell infiltration. Immunohistochemistry shows that the pancreatic lymphocytic population is predominantly composed of T cells, but B lymphocytes are also present.[20] Increased IgG4-positive plasma cells are a characteristic feature of AIP (see below).[9,20,21]
- *Intraductal neutrophils* are present in around 40% of cases (Figure 3) and have been referred to as granulocytic epithelial lesions (GEL).[4,19] Neutrophilic infiltration can also be seen in the lobule and can form microabscesses.[19] It is not clear whether these cases represent a distinct subset of AIP. GELs tend to occur in younger patients and are associated with inflammatory bowel disease.[4,5,19]
- *Granulomas* are uncommon in AIP, but were seen in 32% of cases in one series.[2] When present, they are ductocentric. The characteristic location and absence of nodal granulomas help in distinction from other granulomatous diseases like sarcoidosis and infections.

Fibrosis

The inflammation is accompanied by fibroblastic/myofibroblastic proliferation, often arranged in a storiform pattern. In some cases, the inflammation may be less conspicuous and the fibrous tissue can become hyalinized and keloid-like. The stromal proliferation can form a radiographically and grossly detectable solid mass that can be confused with pancreatic adenocarcinoma (Figure 4). These pseudotumours may be present independently or accompanied by other features of AIP. It is likely that most cases reported as inflammatory pseudotumours in the

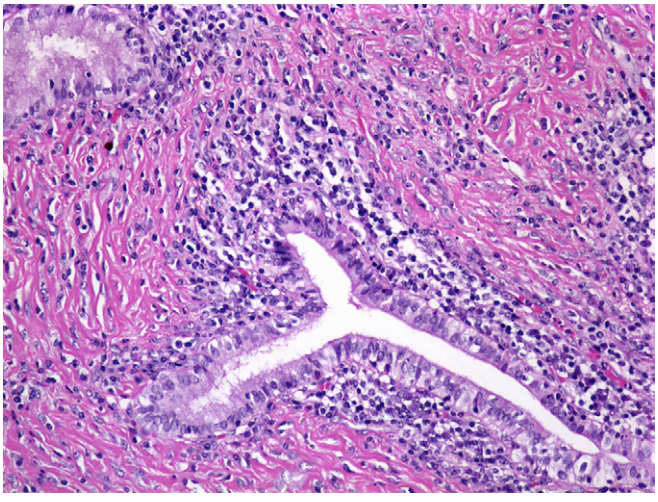

Figure 1 Periductal lymphoplasmacytic infiltrate in autoimmune pancreatitis.

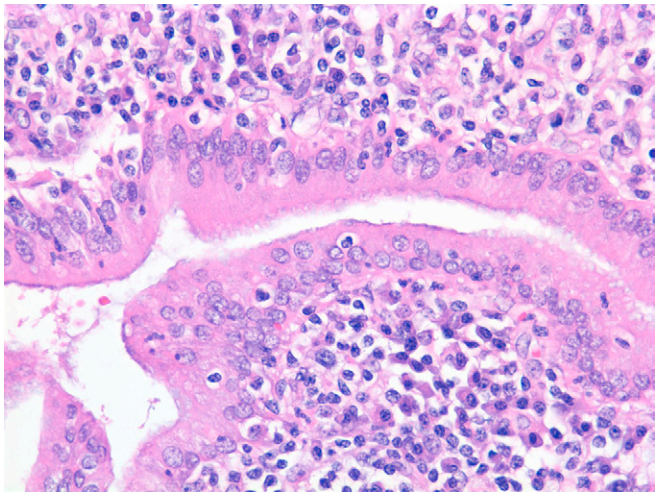

Figure 2 Lymphocytic infiltration into the duct (exocytosis) with little epithelial injury.

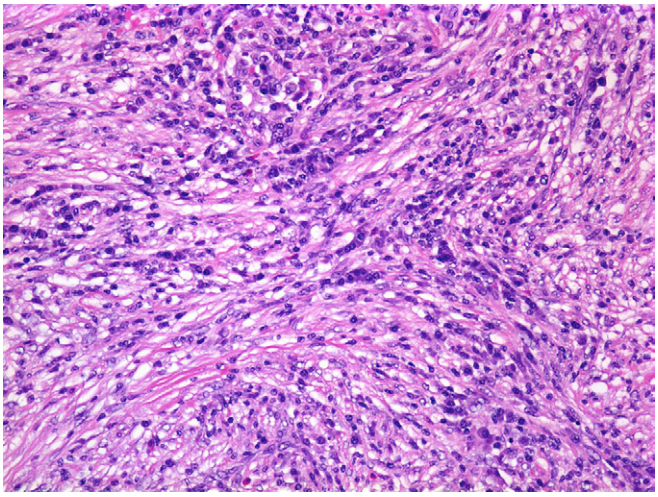

Figure 4 Focal pancreatic involvement can lead to inflammatory pseudotumours characterized by marked fibrosis and plasma cell-rich inflammation.

literature would be currently categorized as AIP.[22] Other less common causes of pseudotumour in the pancreas include paraduodenal pancreatitis, fungal or mycobacterial infections. The rare inflammatory myofibroblastic tumour, a true neoplasm, has some morphological overlap with AIP.[23,24] Immunohistochemical expression of ALK1 and absence of increased IgG4-positive plasma cells can help in the distinction.

Ductal involvement

Involvement of pancreatic ducts is typically patchy, and can be missed on limited biopsy material. The process involves medium-sized and large ducts, and extends to small ones in later stages. Although lymphocytic exocytosis is common, damage to duct epithelium is not a typical feature. The ducts can be compressed by fibrosis, leading to stenosis in contrast to the duct dilatation commonly seen in other types of chronic pancreatitis such as alcoholic pancreatitis. The fibroinflammatory process can also lead to stricture of the common bile duct.

Phlebitis

Venular involvement is almost always present and is a useful diagnostic feature.[4,6,7] Perivenular inflammation around the vein is an early lesion, followed by eventual destruction of vein wall and obliteration of the lumen (obliterative phlebitis). The invariable presence of companion arteries (Figure 5) and elastic stain (Figure 6) can be helpful in the identification of obliterated veins. Periarterial adventitial inflammation can be seen, but arterial wall involvement is rare.

Histological subtypes

Based on the distribution of the fibroinflammatory process, two histological subtypes of AIP have been proposed, lymphoplasmacytic sclerosing pancreatitis (LPSP) and idiopathic duct-centric chronic pancreatitis (ICP).[7] The former involves pancreatic lobules and ducts with frequent involvement of the common bile duct. ICP is characterized by more prominent inflammation in the lobules compared to the interlobular areas. Granulocytic

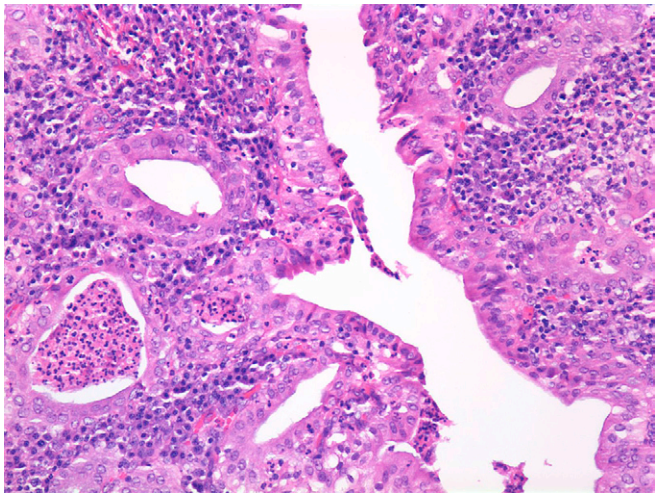

Figure 3 Neutrophilic infiltration around and into the duct epithelium (granulocytic epithelial lesion).

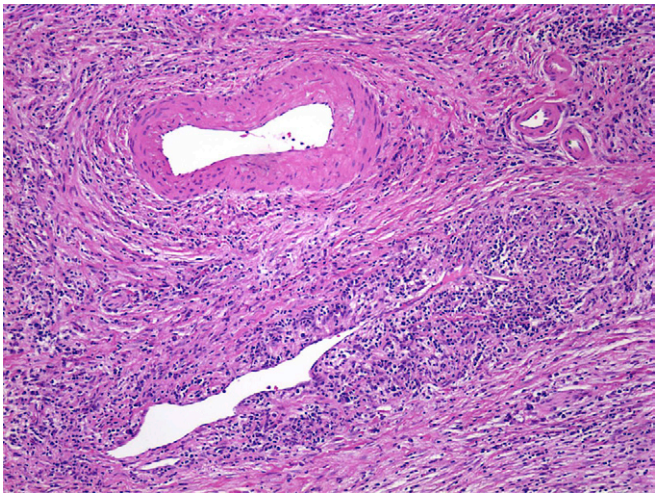

Figure 5 Marked inflammation of the vein (phlebitis). The presence of companion arteries is helpful in locating the damaged veins.

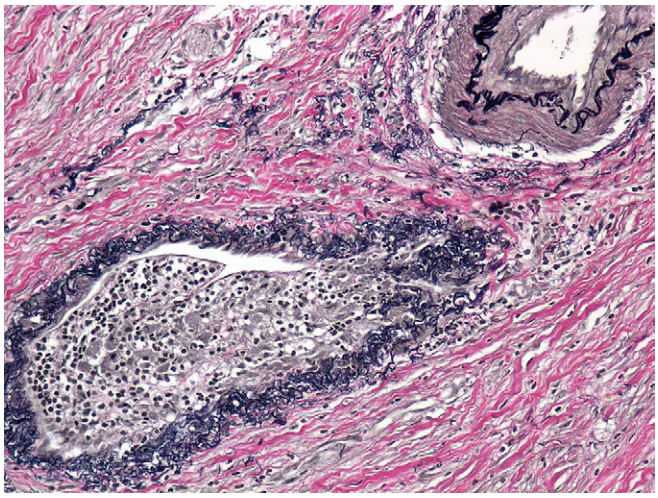

Figure 6 Elastic stain can be helpful in demonstration of phlebitis.

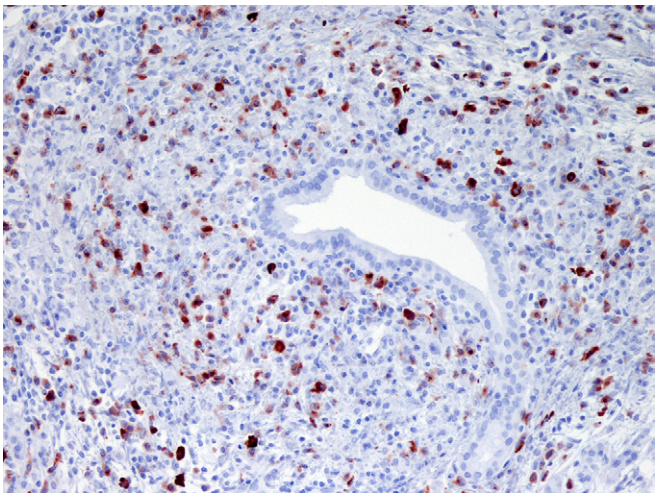

Figure 7 Immunohistochemistry demonstrates numerous IgG4-positive plasma cells around the involved duct.

epithelial lesions and duct epithelial damage are more often seen in ICP. Clinically, these two types are largely similar, but LPSP tends to occur in older individuals and is more likely to present with obstructive jaundice; ICP is more often associated with inflammatory bowel disease. High numbers of IgG4-positive plasma cells are typically associated with LPSP subtype. Some investigators have divided AIP into predominantly ductal and predominantly lobular subtypes, which roughly correspond to LPSP and ICP respectively.[2] The significance of histological subtyping is not clear and some authors have not been able to replicate these findings in their series.[4]

Treatment and prognosis

The prognosis of AIP is better than for other forms of chronic pancreatitis as nearly all patients respond favourably to steroids within a few weeks.[25–28] Pancreatic enlargement and narrowing of the pancreatic duct resolve in almost all patients. Serum IgG4 levels decrease in the majority of cases,[25] while endocrine and exocrine functions improve in some patients.[26] Regression of histological findings like inflammation and even fibrosis has been reported.[29] Deformities of pancreatic and bile ducts can persist in some patients, especially those with persistently elevated serum IgG4 levels.[25] Recurrence rates of 6–26% have been reported.[27,28] Most recurrences also respond to high-dose steroid therapy.[27] Steroid therapy also leads to improvement in extrapancreatic manifestations, including salivary gland enlargement and retroperitoneal fibrosis.[25]

Autoimmune pancreatitis: challenges for the surgical pathologist

IgG4 immunohistochemistry

Immunohistochemical studies have demonstrated high numbers of IgG4-positive plasma cells (> 10/high power field) in 27–100% of AIP (Figure 7).[9,20] These cells are more likely to be present with lymphoplasmacytic sclerosing histological subtype.[21] The number of IgG4-positive plasma cells does not correlate with serum IgG4 levels[9]; in fact, some patients with normal serum IgG4 levels have increased IgG4-positive plasma cells in tissue. Demonstration of IgG4-positive cells in tissue is a helpful confirmatory test in resection specimens and is a key diagnostic feature for AIP in needle biopsies. Rare cases of alcoholic pancreatitis and pancreatic adenocarcinoma may also have > 10 IgG4-positive cells/high power field.[21]

Differential diagnosis

Pancreatic adenocarcinoma

The presence of obstructive jaundice, mass lesion and localized strictures of main pancreatic duct and distal common bile duct can strongly mimic pancreatic adenocarcinoma. Normal serum CA19-9 and elevation of serum IgG4 levels to greater than twice normal can facilitate a preoperative diagnosis of AIP.[10] Histological distinction of AIP from adenocarcinoma is not a problem, if an adequate sample is examined.

Alcoholic pancreatitis

Chronic pancreatitis typically presents after 10 years of alcohol abuse and affects 10% of heavy drinkers. It is generally the result of recurrent attacks of acute pancreatitis. Histologically, the typical feature is inter- and intra-lobular scarring that can vary in degree, but affects most of the parenchyma in advanced stages.[30] The interlobular ducts are distorted and irregular and can show stenosis, hyperplasia/metaplasia and eosinophilic secretions.[31] Calculi are present in the majority (up to 90%) of cases.[32] Inflammation is generally modest and may be localized or diffuse. Calcification is common. Pseudocysts are present in 30–50% of cases.[33] Foci of resolving fat necrosis and a large number of vacuolated macrophages are frequently present.

The presence of duct dilatation with proteinaceous plugs, pseudocysts, fat necrosis, parenchymal necrosis, calcification and calculi strongly favour alcoholic chronic pancreatitis (Table 3). Intense and duct-centric lymphoplasmacytic inflammation, phlebitis, stenotic ducts and high numbers of IgG4-positive cells favour AIP. Rare cases of pseudocyst or calculi have been reported in AIP[34] and occasional cases of alcoholic pancreatitis can have increased IgG4-positive plasma cells. Hence, no single feature can be considered pathognomonic and the final diagnosis rests on a constellation of clinical and pathological features.

Autoimmune versus alcoholic pancreatitis: histological differential diagnosis

	Autoimmune pancreatitis	Alcoholic pancreatitis
Clinical		
Symptom duration	Typically short (3–4 weeks)	Typically 5–6 months
Jaundice	More common	Less common
Pain	Mild or absent	Commonly present
Alcohol abuse	Absent	Present
Response to steroids	Present	Absent
Imaging		
Pancreatic duct	Stenosis	Dilatation
Pseudocysts	Rare or absent	Often present
Calcification	Rare or absent	Often present
Calculi	Rare or absent	Often present
Immunology		
IgG levels	Increased	Typically normal
IgG4 levels	Increased	Typically normal
Autoantibodies	Often present	Typically absent
Pathology		
Duct-centric inflammation	Characteristic	Not present
Phlebitis	Characteristic	Typically absent
IgG4+ plasma cells (> 10/HPF)	Often present	Typically absent
Pseudocysts	Typically absent	Often present
Fat necrosis	Typically absent	Often present
Calculi and calcifications	Typically absent	Often present

Table 3

Paraduodenal pancreatitis

Paraduodenal pancreatitis (also known as groove pancreatitis, cystic dystrophy of heterotopic pancreas, paraduodenal wall cyst) typically occurs in young males (40–50 years) with a history of alcohol intake, and can be clinically mistaken for pancreatic cancer. The minor papilla in the duodenal wall and the adjacent pancreatic parenchyma are typically involved. There is marked fibrosis in the wall of the duodenum associated with dilated ducts and pseudocyst formation.[35] The dilated ducts contain mucoid material and are often surrounded by granulation tissue and foreign body giant cell reaction. Brunner gland hyperplasia is common. The fibrosis extends into the pancreas and peripancreatic tissue. The 'groove' area of the pancreas, which lies between the common bile duct and the duodenum, is principally involved. In addition to fibrosis, the stroma shows abundant spindle-shaped myoid cells admixed with pancreatic acini, leading to histological descriptions like myoadenomatosis and hamartoma.[36,37] The characteristic location and histological features of paraduodenal pancreatitis, along with sparse lymphocplasmacytic inflammation, lack of duct-centric features and no increase in IgG4-positive plasma cells, allow separation from AIP.

Pancreatitis: other causes

Obstructive pancreatitis can lead to duct dilatation, acinar atrophy and fibrosis. This may be due to neoplasm, papillary hyperplasia or viscous mucus plug.[31] Obstruction related to biliary stones is more likely to cause acute pancreatitis, and progression to chronic pancreatitis is not common. Hereditary pancreatitis is a rare disorder that usually starts in childhood or adolescence. Chronic pancreatitis can also occur with metabolic conditions like hypercalcaemia. The histological findings in both hereditary and metabolic pancreatitis resemble alcoholic pancreatitis.[31]

Diagnostic criteria

Although the clinical and pathological characteristics of AIP have been widely described, there is no consensus on the minimum criteria for diagnosis. Since AIP is a steroid responsive disease, it is imperative to establish a preoperative diagnosis. If the imaging shows typical features of diffuse enlargement and narrowing of the pancreatic duct, and is accompanied by elevated IgG4 and normal CA19-9 levels, some feel that the diagnosis can be made without histology.[38] A favourable response to steroid therapy can further bolster the diagnosis.

In the more recently proposed Mayo criteria, the importance of including histological findings as a criterion has been emphasized since typical radiological features are seen in a minority of cases.[39,40] However, the reliability of establishing a histological diagnosis based on limited material obtained by fine needle aspiration (FNA) or core biopsy is not fully established. Diagnostic lesions of AIP, such as periductal inflammation, phlebitis or high IgG4-positive plasma cells, were identified in only 55% of EUS-guided trucut biopsies.[41] EUS-guided FNA in AIP shows numerous background inflammatory cells and stromal fragments with embedded lymphocytes. Unfortunately, similar features were also seen in 12.5% of pancreatic adenocarcinoma.[42] IgG4-positive cells in biopsy of the major duodenal papilla have been shown to be useful for the diagnosis of AIP.[43] However, the series was small and more thorough studies are required before biopsy diagnosis of AIP can be advocated.

Extrapancreatic involvement

AIP can involve any part of the biliary tree including the gall bladder, cystic duct and common bile duct.[9,20] From 20% to 50% of patients with AIP will have biliary involvement, characterized by dense transmural lymphoplasmacytic inflammation, fibrosis, phlebitis and lymphoid follicles.[5,44] Bile ducts may develop strictures resembling primary sclerosing cholangitis (PSC). Salivary gland involvement resembling Sjögren disease is common in AIP.[20] In contrast to AIP, cholelithiasis and PSC show more superficial mucosal inflammation. AIP cases with sclerosing cholangitis and sialadenitis can be distinguished from PSC and Sjögren disease, respectively, by increased IgG4-positive plasma cells and response to steroids.[5,9]

AIP is also associated with other sclerosing disorders such as idiopathic retroperitoneal fibrosis and Riedel thyroiditis. Other immunological disorders (rheumatoid arthritis, Grave disease, Hashimoto thyroiditis and inflammatory bowel disease) have been documented with AIP.[5,9] Inflammatory involvement with numerous IgG4-positive plasma cells with or without pseudotumours has been reported in the stomach, colon, major duodenal papilla, liver, lung, kidney and breast.[2,5,45] The occurrence of multiple organ involvement in AIP has led to the proposal of the novel entity 'IgG4-related systemic fibrosclerosing disease'.[46]

It is likely that AIP represents the pancreatic manifestation of a systemic IgG4-related immunological disease.[5] ◆

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Practice points

- Autoimmune pancreatitis commonly presents with obstructive jaundice and elevated serum IgG4 levels.
- Imaging studies show diffuse pancreatic enlargement with diffuse or focal narrowing of the pancreatic duct, common bile duct stricture and/or mass-like lesion. The latter features can easily be mistaken for adenocarcinoma.
- Duct-centric inflammation, dense lymphoplasmacytic infiltrate, fibrosis and phlebitis are characteristic histological features. High numbers of IgG4-positive cells are typically present.
- Duct dilatation, pseudocysts, fat necrosis, parenchymal necrosis, calcification and calculi are typically absent, distinguishing autoimmune from alcoholic chronic pancreatitis.
- Extrapancreatic involvement (gall bladder, biliary tree, salivary gland) and association with other sclerosing (idiopathic retroperitoneal fibrosis) and immunological disorders (rheumatoid arthritis, inflammatory bowel disease) can occur.
- The outcome is favourable due to the excellent response to oral steroids.