Autoimmune pancreatitis: Clinical manifestations and diagnosis

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INTRODUCTION

Autoimmune pancreatitis (AIP) is an uncommon but well-established form of pancreatic inflammation. Unlike other pancreatic diseases, it typically has a dramatic response to glucocorticoid therapy. AIP can appear radiographically as a focal mass that is indistinguishable from pancreatic cancer or as a diffuse pancreatic process that can be pathognomonic for AIP. If untreated, AIP can lead to pancreatic insufficiency, fibrosis, and other complications. The discovery of elevated immunoglobulin G4 (IgG4) as a biomarker of AIP helped establish the disorder as distinct from other forms of chronic pancreatitis; although, later studies demonstrated that IgG4 levels are often normal in AIP and that other diseases such as pancreatic cancer may be associated with moderately elevated IgG4 levels.

EPIDEMIOLOGY AND CLASSIFICATION

Prevalence — Autoimmune pancreatitis (AIP) has been reported worldwide, but the overall prevalence is higher in Asia than in the Americas, Europe, or Africa. Type 1 AIP is the more common form and represents the vast majority of cases in Asia. Type 2 AIP is more common in Europe and the United States than in Asia but remains a minor subtype. (See "Pathogenesis and clinical manifestations of IgG4-related disease".)

Subtypes — AIP is a syndrome defined by clinical, laboratory, and pathologic criteria [1].

- **Type 1 AIP** – Type 1 AIP is defined histologically as lymphoplasmacytic sclerosing pancreatitis (LPSP). The International Consensus Diagnostic Criteria (ICDC) defined type 1 AIP as: dense infiltration of plasma cells and lymphocytes, particularly periductal; storiform (a swirling, "cartwheel" pattern) fibrosis; venulitis with lymphocytes and plasma cells, often leading to obliteration of the affected veins; and abundant (>10 cells per high-power field [HPF]) immunoglobulin G4 (IgG4)-positive plasma cells [1]. Type 1 AIP may present as an isolated disorder or as part of an IgG4-related disease (IgG4-RD) syndrome with other organ involvement (OOI). (See 'Clinical manifestations' below and 'Histology' below.)

- **Type 2 AIP** – Type 2 AIP is defined histologically as idiopathic duct-centric pancreatitis (IDCP) or AIP with granulocyte epithelial lesions (GELs). The GEL lesions are intraluminal and intraepithelial neutrophils in medium-sized and small ducts as well as in acini, often leading to the destruction and obliteration of the duct lumen [1]. IDCP usually has very few IgG4-positive plasma cells (<10 cells/HPF). Type 2 AIP appears to be limited to the pancreas and often co-occurs in patients with inflammatory bowel disease (IBD). (See 'Clinical manifestations' below and 'Histology' below.)

- **AIP NOS** – AIP NOS is a term to classify patients who do not meet criteria for type 1 or type 2 AIP. Tissue may not be available for histology, and they do not have markedly elevated serum IgG4 levels, OOI (as in type 1 AIP), or IBD (as in type 2 AIP) [1,2].

- **IgG4-RD** – IgG4-RD is an immune-mediated fibroinflammatory condition that is capable of affecting multiple organs. It is characterized by multi-organ involvement, serum IgG4 elevation, and infiltration of the affected organs with IgG4-positive plasma cells [3-5]. Type 1 AIP is one of the most common features of this systemic syndrome. IgG4-related sclerosing cholangitis (IgG4-SC) is cholangitis associated with elevated serum IgG4 levels, dense infiltration of IgG4-positive plasma cells with storiform fibrosis, and/or obliterative phlebitis in the bile duct wall and good response to glucocorticoids [6,7]. IgG4-SC and type 1 AIP often overlap as a pancreatobiliary syndrome within the IgG4-RD spectrum. (See "Pathogenesis and clinical manifestations of IgG4-related disease", section on 'Clinical manifestations'.)

CLINICAL MANIFESTATIONS

Clinical features

Type 1 AIP — Patients with autoimmune pancreatitis (AIP) most commonly present with painless obstructive jaundice. More than one-third of cases are discovered in asymptomatic patients undergoing evaluation for a pancreatic mass, pancreatic enlargement, or pancreatic duct strictures on abdominal imaging; a cholestatic pattern of liver test elevation; or diabetes mellitus [8]. Type 1 AIP is generally seen in males in the sixth to seventh decade of life, with elevation of serum IgG4 (>2 times upper limit of normal [ULN]). In a nationwide survey of Japan that included 4297 patients, the most common clinical symptoms were painless jaundice (49 percent), abdominal pain (26 percent), extrapancreatic lesions (12 percent), weight loss (3 percent), acute pancreatitis (1 percent), or others [8]. Males were more commonly affected than females in a ratio of 3:1, and the average age of onset was 68 years.

Type 1 AIP may present as an isolated disorder or as part of an IgG4-related disease (IgG4-RD) syndrome with other organ involvement (OOI). Organs typically involved in IgG4-RD include the pancreas (type 1 AIP); bile duct (sclerosing cholangitis); submandibular, parotid, and sublingual glands (sclerosing sialadenitis); orbital area with lacrimal gland involvement (sclerosing dacryoadenitis often associated with Mikulicz disease); lung; retroperitoneum (fibrosis); and kidney (tubulo-interstitial nephritis) [4,5,9,10]. (See "Pathogenesis and clinical manifestations of IgG4-related disease", section on 'Clinical manifestations'.)

Type 2 AIP — The clinical symptoms of type 2 AIP overlap those of type 1 AIP except that the disorder is confined to the pancreas. Patients may have a cholestatic pattern of elevation in liver tests similar to type 1 AIP. Approximately 25 percent of patients with type 2 AIP have a >2-fold elevation in IgG4 levels. IgG4 levels are generally normal or only mildly elevated [11,12]. Patients are typically younger than those with type 1 AIP, presenting in the third to fourth decade of life, and males and females are affected in a 1:1 ratio [12]. Type 2 AIP may present with acute pancreatitis (45 to 65 percent), jaundice (18 to 25 percent), or pain. Type 2 AIP appears to be limited to the pancreas and often co-occurs in patients with inflammatory bowel disease (IBD). In a multicenter study of 91 individuals with AIP and IBD, the majority (98 percent) had type 2 AIP [13]. Two-thirds had ulcerative colitis (UC; often with proctitis) and one-third had Crohn disease. In this series, the mean age at diagnosis of type 2 AIP was 35±12 years, younger than persons with type 1 AIP, and the sex distribution was equal. (See 'Serum IgG4' below.)

Imaging findings — AIP is usually first suggested by an imaging test such as dynamic contrast-enhanced (DCE) computed tomography (CT) or magnetic resonance imaging (MRI) (image 1), which demonstrates a diffusely enlarged pancreas with featureless borders and delayed enhancement with or without a capsule-like rim [14]. Magnetic resonance cholangiopancreatography (MRCP) can help delineate ductal abnormalities. (See 'Magnetic resonance cholangiopancreatography' below.)

Complications — Pancreatic atrophy can develop in 25 percent of patients with AIP and may manifest as exocrine pancreatic insufficiency or pancreatogenic diabetes mellitus (type 3c). Patients with AIP do not appear to be at an increased risk for pancreatic cancer.

DIAGNOSTIC APPROACH

When to suspect AIP — Autoimmune pancreatitis (AIP) should be considered in patients presenting with painless jaundice and abdominal pain or a diffusely enlarged pancreas or pancreatic mass on imaging. The suspicion for AIP should be further increased in those with other autoimmune conditions.

Initial evaluation — The evaluation of patients with suspected AIP includes selected laboratory testing, pancreatic imaging with magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound-guided biopsy. This evaluation serves to identify the characteristic features of AIP and to exclude other disorders, particularly pancreatobiliary cancer. Even when AIP is appropriately diagnosed, 1 to 2 percent of patients will also have pancreatic cancer [1]. Among patients with immunoglobulin G4-related sclerosing cholangitis (IgG4-SC), over 20 percent present with features resembling bile duct malignancies [15].

Magnetic resonance cholangiopancreatography — MRCP is recommended for evaluation of the pancreatic duct in patients with suspected AIP [16]. As compared with abdominal CT, MRI has a higher sensitivity but a similar specificity in distinguishing AIP from pancreatic ductal adenocarcinoma [17]. Imaging should include the head, neck, thorax, abdomen, and pelvis to evaluate for involvement of other organs associated with IgG4-related disease (IgG4-RD) [18]. (See 'Clinical features' above.)

- **Parenchymal imaging** – Diffuse enlargement of the pancreas with delayed enhancement is highly suggestive of AIP (image 2). There may also be a rim-like hypoenhancement surrounding the gland (image 2). Segmental or focal enlargement with delayed enhancement is considered indeterminate and requires additional evidence. An AIP lesion is a low signal intensity area on T1-weighted MR sequences (or occasionally speckled hyperintensity), and a hyperintense area on T2- and diffusion-weighted imaging (DWI) sequences. [18]. AIP is hypovascular on the pancreatic phase of dynamic contrast-enhanced (DCE)-CT and MRI and homogeneously enhanced on the delayed phase of DCE-CT and MRI [18].

- **Ductal imaging** – MRCP with or without secretin may reveal a normal duct but may also demonstrate a narrowed main and dorsal pancreatic duct; diffuse, irregular narrowing of

the pancreatic duct (beaded appearance) or a focal stricture of the pancreatic duct or of the proximal or distal common bile duct; or irregular narrowing of the intrahepatic ducts (figure 1 and image 2 and image 3) [19,20].

Narrowing or strictures of the main pancreatic duct seen on MRCP can be long (eg, greater than one-third of the pancreatic duct length) or multiple but without significant dilatation above the narrowed area upstream of the main duct. Segmental or focal narrowing without extended areas of involvement is considered indeterminate and requires additional evidence (image 3).

Cholangiographic findings of IgG4-SC can involve the hilar and/or intrahepatic bile ducts and can be similar to those of hilar cholangiocarcinoma or primary sclerosing cholangitis (PSC). Cholangiograms from patients with PSC are more likely to show band-like strictures, a beaded or pruned-tree appearance, or diverticulum-like formation [21]. By contrast, IgG4-SC strictures are more often segmental strictures, long strictures with prestenotic dilatation, and strictures of the distal common bile duct [21-23]. Ductal wall thickening and enhancement may also be seen and suggests IgG4-SC.

Endoscopic ultrasonography guided biopsy — We perform endoscopic ultrasonography (EUS)-guided biopsy to rule out pancreatic cancer and obtain tissue to diagnose AIP [8,16,24,25]. In cases where imaging identifies a mass in the head of the pancreas consistent with AIP, the International Consensus Diagnostic Criteria (ICDC) guidelines recommend EUS-guided core biopsy or resection. Endoscopic biopsy of the duodenal papilla may be a useful adjunctive method because ampulla often is involved pathologically in AIP [1].

Endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) of the pancreas can provide diagnostic histology in a significant fraction of patients with type 1 AIP. Diagnosis of type 2 AIP may also be possible, but additional studies are needed [26,27]. This was illustrated in a prospective study that included 56 patients, of which 55 were suspected to have type 1 AIP and one to have type 2 AIP. Lymphoplasmacytic infiltration, obliterative phlebitis, storiform fibrosis, and >10 IgG4-positive cells per high-power field (HPF) were detected in 100, 44, 73, and 66 percent, respectively. The detection rates of level 1 and level 1 or 2 histology for AIP were 58 and 93 percent, respectively (table 1).

Although fine-needle aspiration (FNA) may be useful for evaluating suspicious lesions for malignancy, it may be inadequate for diagnosing AIP, especially type 2 AIP [25,28,29]. A prospective multicenter feasibility study in Japan of the use of a 22-gauge needle for the diagnosis of (type 1) AIP demonstrated the utility of this approach [28]. IgG4-positive plasma cell counts of >10, 5 to 10, and 1 to 4 per HPF were obtained from 29 (37 percent), 18 (23 percent),

and 15 (19 percent) of 78 patients, respectively. Storiform fibrosis was detected in 49 of 78 patients (63 percent). Obliterative phlebitis was observed in 38 of 78 patients (49 percent). Based on ICDC criteria, histopathologic levels corresponded to level 1 and 2 in 32 (41 percent) and 13 (27 percent), respectively, allowing for a histopathologic diagnosis of AIP in 58 percent of individuals (table 2).

Histology — Characteristic histologic findings of AIP include the following (table 1) [14,24,30]:

- **Type 1 AIP** – A lymphoplasmacytic sclerosing pancreatitis **or** >10 IgG4-positive cells with at least two of the following: periductal lymphoplasmacytic infiltrate, obliterative phlebitis, and/or swirling collagen fibers (storiform fibrosis) (figure 2 and image 4) [24]. Similar histologic findings can be found in biopsy specimens of extrapancreatic organs involved in patients with IgG4-RD.

- **Type 2 AIP** – Idiopathic duct-centric pancreatitis (IDCP) is characterized by a granulocytic epithelial lesion in the pancreatic duct with minimal IgG4-positive cells in the pancreatic parenchyma (figure 3) [5,24].

Laboratory testing

Serum IgG4 — Serum IgG4 >2 times the upper limit of normal (ULN; >280 mg/dL) is highly suggestive of AIP [14,31]. Elevations in IgG4 >2 times ULN are seen in approximately two-thirds of patients with type 1 AIP and one-fourth of patients with type 2 AIP. (See 'Clinical features' above and 'Subtypes' above.)

Elevations in serum IgG4 are not specific for AIP, and up to 10 percent of individuals with pancreatic cancer also have elevated IgG4 levels. However, only 1 percent of patients with pancreatic cancer have serum IgG4 levels above 280 mg/dL [31-33]. Patients with PSC may also have elevations in IgG4. In one series of 127 patients with PSC, 9 percent of patients had elevated serum IgG4 levels [23]. Serum IgG4 values above normal but ≤280 mg/dL have been described in a number of disorders that do not involve the pancreas, including atopic dermatitis, asthma, some parasitic diseases, pemphigus vulgaris, and pemphigus foliaceus [34-36]. The elevation in serum IgG4 levels in these patients is usually accompanied by an elevation in serum immunoglobulin E (IgE). Among patients with AIP, serum IgG4 declines during treatment with glucocorticoids [31]. (See "Autoimmune pancreatitis: Management".)

Other — We do not routinely perform additional serologic tests to diagnose AIP or to exclude a pancreatic malignancy.

- **Cancer-associated antigen 19-9 (CA19-9)** – CA19-9 is a tumor marker commonly associated with pancreatic cancer. However, patients with specific inactivating genetic variants in fucosyltransferase 3 (*FUT3)* may have minimal or absent CA19-9 levels, while inactivating mutations in *FUT2* have higher than normal CA19-9 levels [37-39]. Thus, CA19-9 is not always elevated in pancreatic cancer or other conditions. (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Carbohydrate antigen 19-9'.)

  In a study of 123 type 1 AIP patients followed for a median of 55 months, two developed pancreatic cancer a year or more after AIP diagnosis and treatment. CA19-9 at initial diagnosis of AIP was normal in patients not progressing to pancreatic cancer (median, 21 U/mL [interquartile range, 8.25 to 36.25]). Levels were elevated in the two patients with pancreatic cancer (median 220.5 U/mL, [range 117 to 324]) [40]. The CA19-9 was the only feature that distinguished these patients. Of note, the two patients in whom cancer developed had IgG4 levels at initial diagnosis of AIP that were at the higher range of IgG4 levels in the cohort.

- **Non-IgG4 antibodies** – Antibodies that are variably elevated in patients with AIP include anti-plasminogen-binding protein (PBP) peptide antibodies (94 percent) [41], antibodies to carbonic anhydrase II antigens (30 to 59 percent) [42], and lactoferrin (50 to 76 percent) [43]. Other antibodies that have been associated with AIP, but that have not been consistently positive, include rheumatoid factor, perinuclear antineutrophil cytoplasmic antibodies, antinuclear antibodies, antimitochondrial antibodies, anti-smooth muscle antibodies, and antithyroglobulin [44-46]. IgG4/IgG RNA ratio does not accurately discriminate IgG4-RD from pancreatobiliary cancer [47].

Glucocorticoid trial — A glucocorticoid trial should be conducted only in patients with a negative work-up for pancreatic cancer. Cancer can mask as AIP and patients with AIP can have cancer concurrently. In patients with equivocal evidence of AIP and features concerning for pancreatic cancer (eg, age over 60 years, focal pancreatic involvement, moderately elevated IgG4, and no evidence of other organ involvement [OOI]), the probability of pancreatic cancer approaches 95 percent. In our practice, we use EUS-FNB in an attempt to make a diagnosis of pancreatic adenocarcinoma, since elevated serum and IgG4-postive cells on cytology can often be seen in patients with pancreatic cancer. In individuals with suspected AIP, we do not initiate a diagnostic trial of prednisone until there are **two** negative EUS-FNBs with adequate cytologic/pathologic specimens. (See 'Endoscopic ultrasonography guided biopsy' above.)

A response to a course of glucocorticoids (prednisone 40 mg daily), characterized by radiologic resolution or marked improvement in pancreatic/extrapancreatic manifestations, strongly

supports the diagnosis of AIP. The lack of response to a glucocorticoid trial within two to three weeks warrants referral for surgical exploration for pancreatic cancer [48]. (See "Autoimmune pancreatitis: Management", section on 'Assessment of response to therapy'.)

Diagnosis — The diagnosis of AIP is based on histology in the setting of supportive serologic studies (elevated IgG4) and imaging after the exclusion of alternative diagnoses. Diagnostic criteria for AIP, proposed by the International Association of Pancreatology in 2011 with subsequent modifications recommended by Japanese experts for simplicity, use findings on imaging of pancreatic parenchyma and the pancreatic duct, serology, OOI associated with IgG4-RD, pancreatic histology, and an optional criterion of response to glucocorticoid therapy to diagnose and classify AIP (table 1 and table 2 and table 3) [1,16]. The criteria are traditionally referred to as the HISORt (histology, imaging, serology, other organ involvement, and response to steroid therapy) criteria. The diagnosis of AIP and its subtypes are considered definitive or probable based on the specific findings. (See 'Subtypes' above and 'Clinical features' above.)

Diagnostic criteria for AIP have limitations in sensitivity (85 percent in one series) [49]. Clinicians should also consider the possibility of multiple conditions occurring in the same person (eg, AIP and cancer). The diagnosis, therefore, requires careful reassessment in the absence of response to treatment. (See 'Glucocorticoid trial' above.)

Differential diagnosis — The main differential diagnosis of concern for both AIP and IgG4-SC are pancreatobiliary cancers. Clinical and imaging features can often differentiate AIP from pancreatic cancer and chronic pancreatitis (table 4 and table 5). The differential diagnosis of IgG4-RD is discussed in detail separately. (See "Diagnosis and differential diagnosis of IgG4-related disease", section on 'Differential diagnosis'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Chronic pancreatitis and pancreatic exocrine insufficiency" and "Society guideline links: IgG4-related disease".)

SUMMARY AND RECOMMENDATIONS

- Autoimmune pancreatitis (AIP) is an uncommon but well-established form of pancreatic inflammation. Unlike other pancreatic diseases, it typically has a dramatic response to glucocorticoid therapy. (See 'Introduction' above.)

- Patients with AIP most commonly present with painless obstructive jaundice. More than one-third of cases are discovered in asymptomatic patients undergoing evaluation for a pancreatic mass, pancreatic enlargement, or pancreatic duct strictures on abdominal imaging; a cholestatic pattern of liver test elevation; or diabetes mellitus. (See 'Clinical manifestations' above.)

- Type 1 AIP is defined histologically as lymphoplasmacytic sclerosing pancreatitis (LPSP). Type 1 AIP may present as an isolated disorder or as part of an immunoglobulin G4-related disease (IgG4-RD) syndrome with other organ involvement (OOI). Organs typically involved in IgG4-RD include the pancreas (type 1 AIP); bile duct (sclerosing cholangitis); submandibular, parotid, and sublingual glands (sclerosing sialadenitis); orbital area with lacrimal gland involvement (sclerosing dacryoadenitis often associated with Mikulicz disease); lung; retroperitoneum (fibrosis); and kidney (tubulo-interstitial nephritis). Type 2 AIP is defined histologically as idiopathic duct-centric pancreatitis (IDCP) or AIP with granulocyte epithelial lesions (GELs). Type 2 AIP appears to be limited to the pancreas and often co-occurs in patients with inflammatory bowel disease (IBD). (See 'Histology' above.)

- The diagnosis of AIP should be considered in patients presenting with painless jaundice, abdominal pain, and in patients with a diffusely enlarged pancreas or pancreatic mass on imaging. The suspicion for AIP should be further increased in those with IBD. (See 'When to suspect AIP' above.)

- The evaluation of patients with suspected AIP includes selected laboratory testing, pancreatic imaging with multiphase CT or magnetic resonance imaging with cholangiopancreatography (MRCP), and endoscopic ultrasound-guided biopsy. This evaluation serves to identify the characteristic features of AIP and to exclude other disorders, particularly pancreatobiliary cancer. (See 'Diagnostic approach' above.)

- The diagnosis of AIP is based on histology in the setting of supportive serologic studies (elevated IgG4) and imaging after the exclusion of alternative diagnoses. Diagnostic criteria for AIP use findings on imaging of pancreatic parenchyma and duct, serology, OOI, pancreatic histology, and an optional criterion of response to glucocorticoid therapy to diagnose and classify AIP (table 1 and table 2 and table 3). The lack of response to a glucocorticoid trial warrants referral for surgical exploration for pancreatic cancer. (See 'Diagnostic approach' above and "Autoimmune pancreatitis: Management", section on 'Assessment of response to therapy'.)

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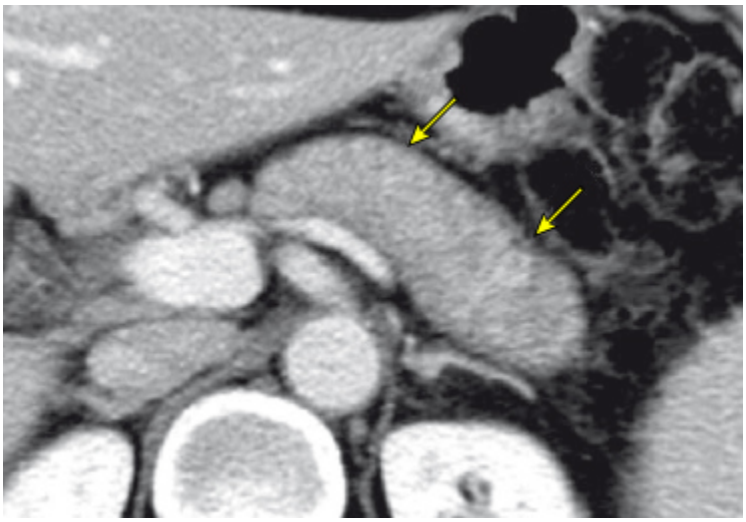
GRAPHICS

Autoimmune pancreatitis



Axial portal phase computed tomography (CT) image shows diffuse sausage-like swelling of pancreas with loss of pancreatic clefts and thin, symmetric capsule-like rim of low attenuation surrounding pancreas (arrows).

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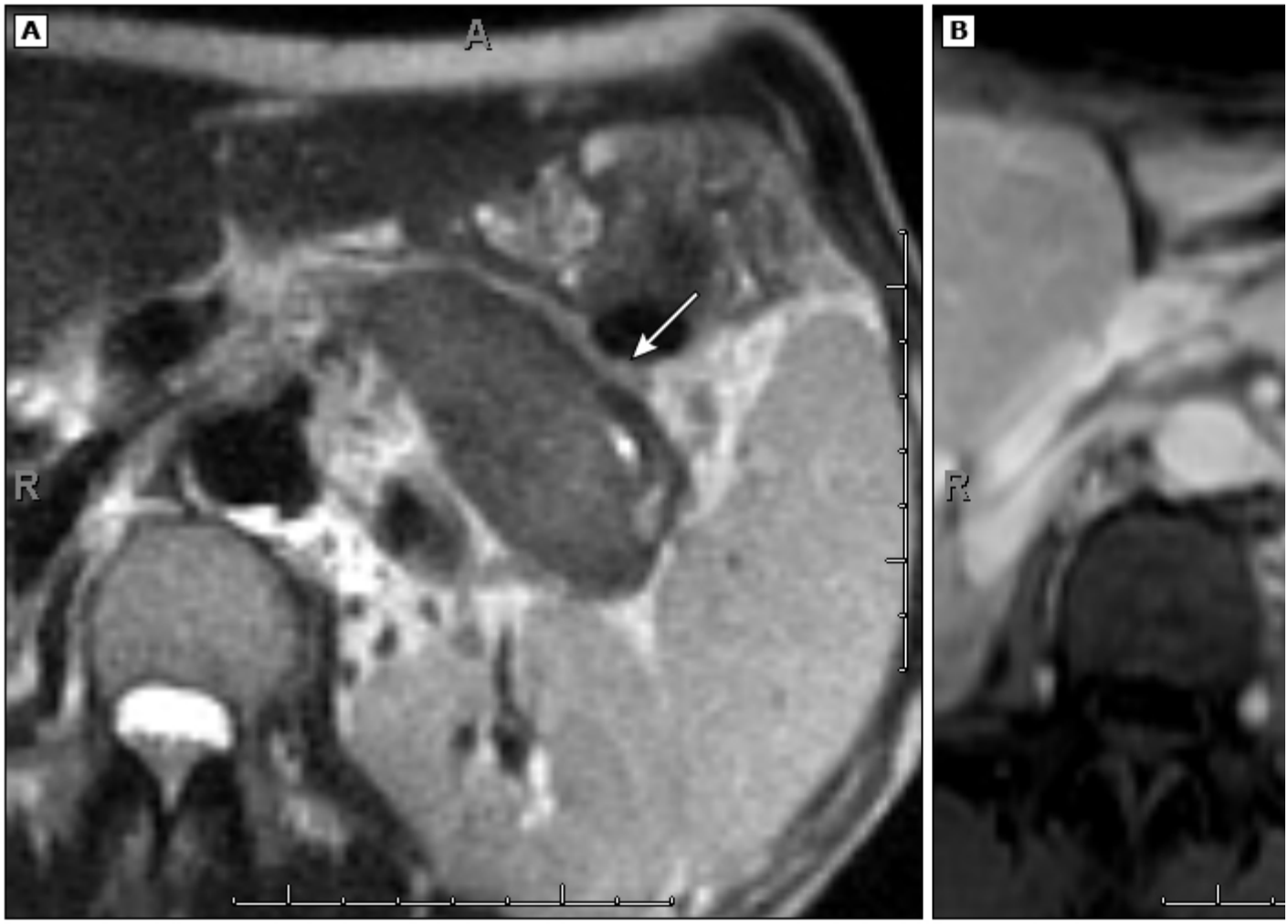
Graphic 87628 Version 1.0

Sausage-shaped pancreas in autoimmune pancreatitis



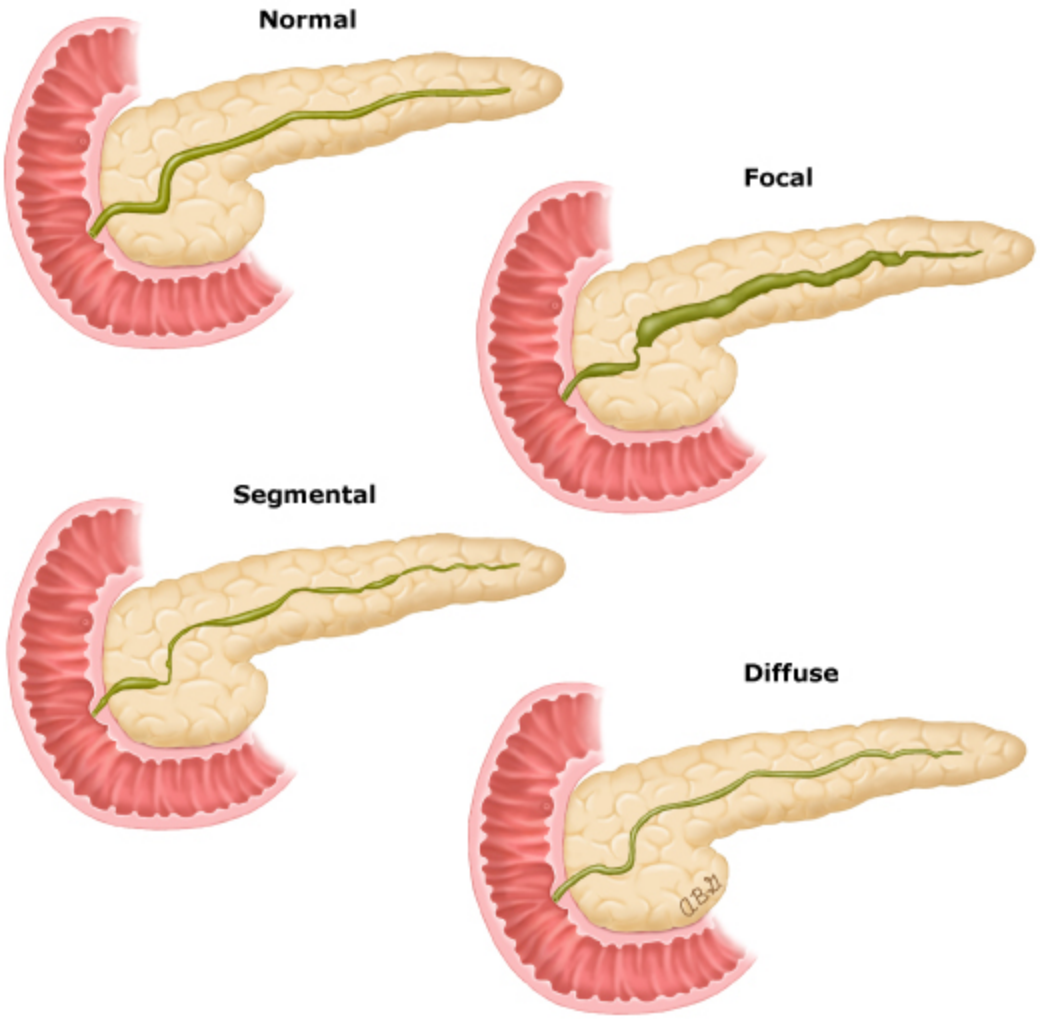
Sausage-shaped pancreas with T2 hypointense rim demonstrating delayed enhancement.

SSFSE: T2-weighted sequence single-shot fast spin echo; LAVA: T1-weighted sequence liver acquisition with v

Courtesy of Anil K Dasyam, MD.

Graphic 130732 Version 1.0

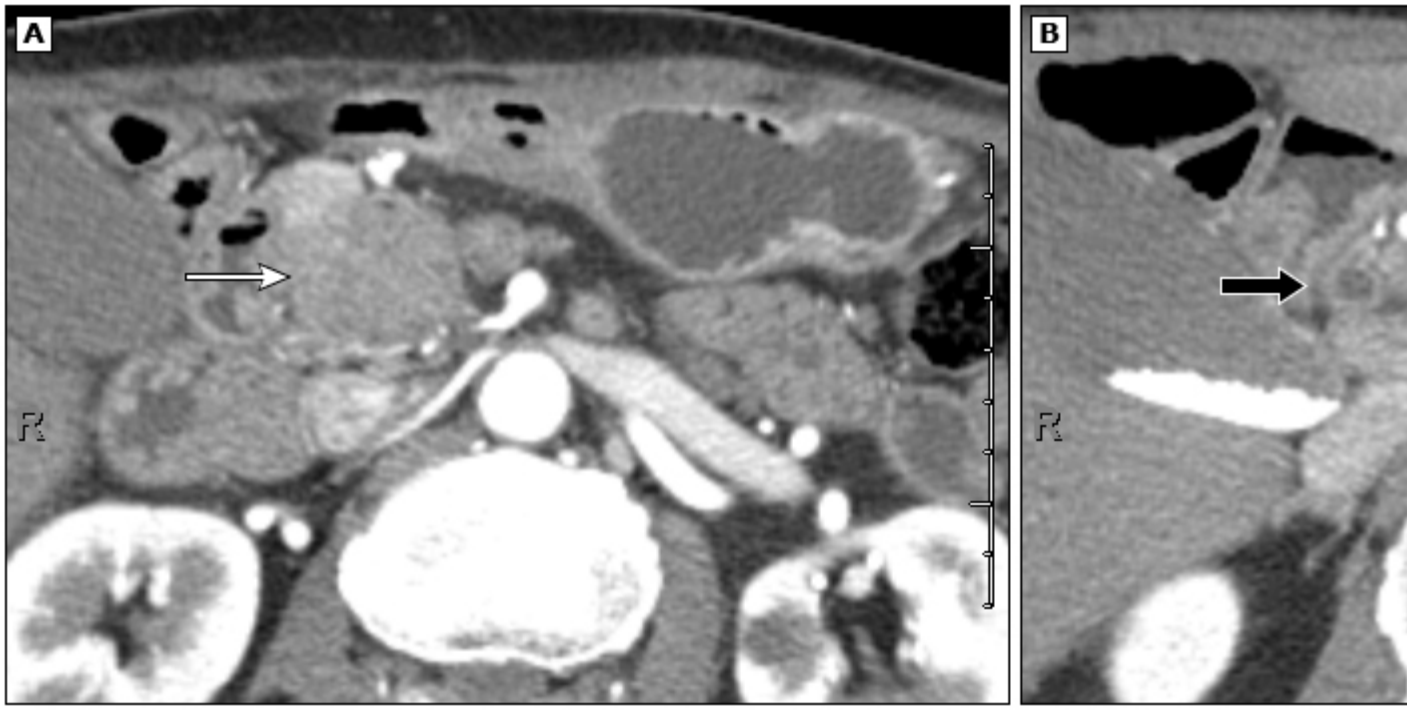
Pancreatograms either by MRCP or ERCP in autoimmune chronic pancreatitis



MRCP: magnetic resonance cholangiopancreatography. ERCP: endoscopic retrograde cholangiopancreatography.

Graphic 53448 Version 4.0

Focal autoimmune pancreatitis



Axial contrast-enhanced CT scan images (A, B) demonstrating focal AIP with hypoenhancing mass-like area i
enhancement of CBD wall (image B, thick black arrow), and central intrahepatic bile duct strictures with moc

AIP: autoimmune pancreatitis; CBD: common bile duct; CT: computed tomography; MRCP: magnetic resonar

Courtesy of Anil K Dasyam, MD.

Graphic 130734 Version 1.0

Diagnostic criteria for autoimmune pancreatitis

Criterion		Level 1	Level 2
P	Parenchymal imaging	Typical: ▪ Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical*): ▪ Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (greater than one-third length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
S	Serology	IgG4, >2× upper limit of normal value	IgG4, 1 to 2× upper limit of normal value
OOI	Other organ involvement	a or b	a or b
		a. Histology of extrapancreatic organs Any three of the following: 1. Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration 2. Storiform fibrosis 3. Obliterative phlebitis 4. Abundant (>10 cells/HPF) IgG4-positive cells b. Typical radiologic evidence At least one of the following: 1. Segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture 2. Retroperitoneal fibrosis	a. Histology of extrapancreatic organs including endoscopic biopsies of bile duct¶ Both of the following: 1. Marked lymphoplasmacytic infiltration without granulocytic infiltration 2. Abundant (>10 cells/HPF) IgG4-positive cells b. Physical or radiologic evidence At least one of the following: 1. Symmetrically enlarged salivary/lachrymal glands 2. Radiologic evidence of renal involvement described in association with AIP
H	Histology of the pancreas	LPSP (core biopsy/resection)	LPSP (core biopsy)
		At least 3 of the following: 1. Periductal lymphoplasmacytic infiltrate without granulocytic	Any 2 of the following: 1. Periductal lymphoplasmacytic infiltrate without granulocytic

		infiltration 2. Obliterative phlebitis 3. Storiform fibrosis 4. Abundant (>10 cells/HPF) IgG4-positive cells	infiltration 2. Obliterative phlebitis 3. Storiform fibrosis 4. Abundant (>10 cells/HPF) IgG4-positive cells
Response to steroid (Rt)[Δ]		Diagnostic steroid trial	
		Rapid (≤2 weeks) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations	

AIP: autoimmune pancreatitis; ERP: endoscopic retrograde pancreatogram; IgG4: immunoglobulin G4; HPF: high-power field; LPSP: lymphoplasmacytic sclerosing pancreatitis.

* Atypical: Some AIP cases may show low-density mass, pancreatic ductal dilatation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP, and a thorough workup for cancer is negative (refer to UpToDate topic on autoimmune pancreatitis).

¶ Endoscopic biopsy of duodenal papilla is a useful adjunctive method because ampulla often is involved pathologically in AIP.

Δ Diagnostic steroid trial should be conducted carefully by pancreatologists only after negative workup for cancer. Refer to UpToDate content on autoimmune pancreatitis for additional details.

From: Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011; 40:352. DOI: 10.1097/MPA.0b013e3182142fd2.

Graphic 130443 Version 1.0

Diagnostic criteria for type 1 autoimmune pancreatitis

Diagnosis	Primary basis for diagnosis	Imaging evidence	Collateral evidence
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (level 1 H)
	Imaging	Typical	Any non-D level 1/level 2
		Indeterminate	Two or more from level 1 (+level 2 D*)
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or level 1 D + level 2 S/OOI/H + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI/H + Rt

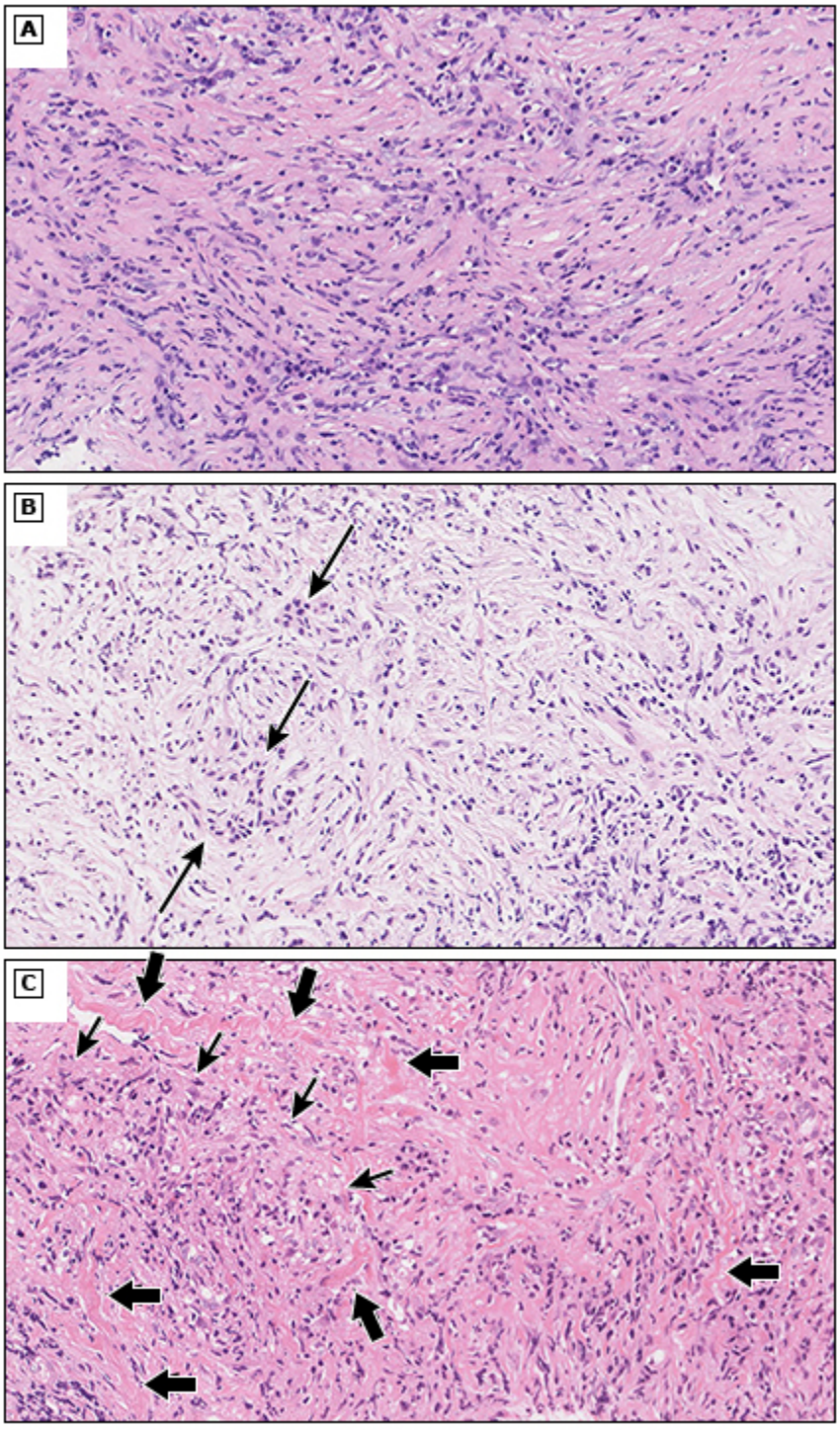
AIP: autoimmune pancreatitis; LPSP: lymphoplasmacytic sclerosing pancreatitis; H: histology; S: serology; OOI: other organ involvement; Rt: response to therapy.

* Level 2 D is counted as level 1 in this setting.

From: Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011; 40:352. DOI: 10.1097/MPA.0b013e3182142fd2.

Graphic 130440 Version 2.0

Storiform fibrosis in autoimmune pancreatitis

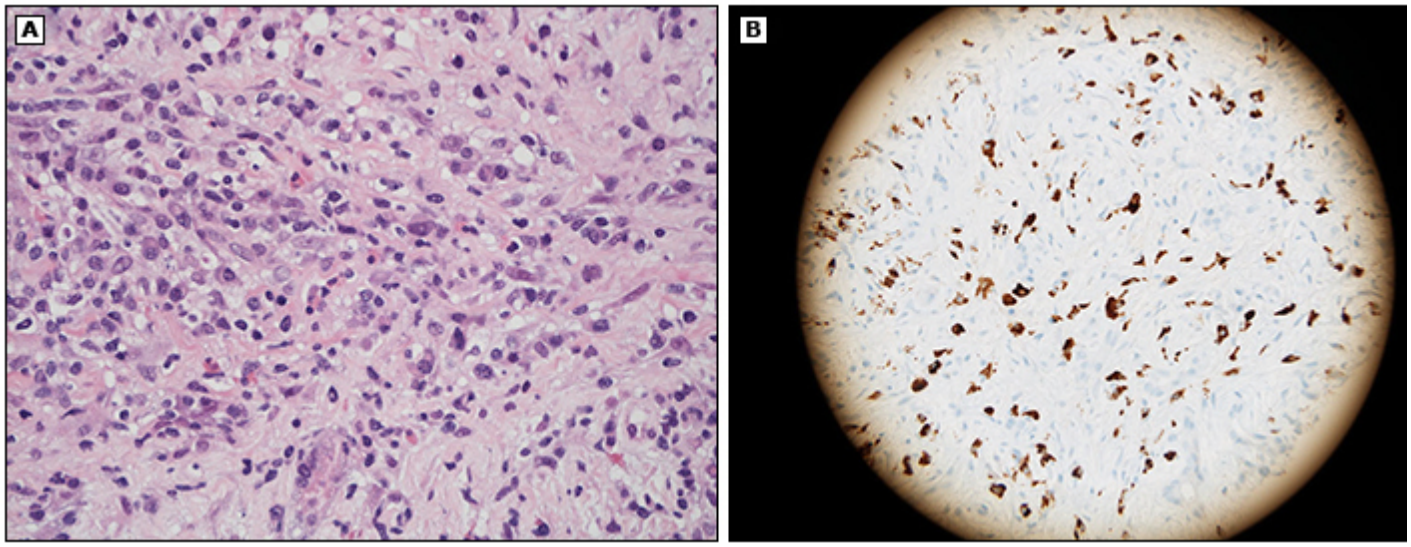


Storiform fibrosis (hematoxylin and eosin stain) in autoimmune pancreatitis. (A,B,C) Storiform fibrosis is characterized by a flowing arrangement of spindle-shaped cells, inflammatory cells and delicate collagen as a unit (A,B). Ductal structures may be involved and acinar-ductal metaplasia may be seen (arrows) (B). Although thick collagen strands (thick arrows) are atypical, a portion with the

typical features (short arrows) allows for the diagnosis of storiform fibrosis (C).

Graphic 130690 Version 1.0

Marked lymphoplasmacytic infiltration in autoimmune pancreatitis

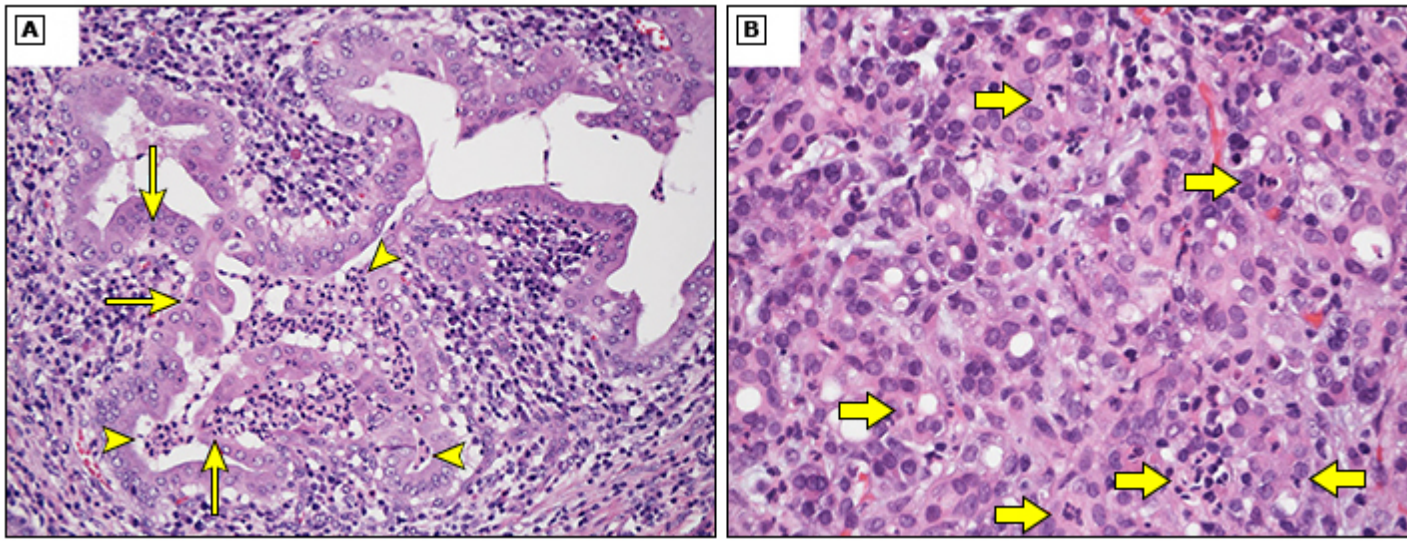


Marked lymphoplasmacytic infiltration with fibrosis (A) and numerous IgG4-positive plasma cells (B) in autoimmune pancreatitis. (A) The infiltration of plasma cells is easy to recognize. Eosinophils are also intermingled (hematoxylin and eosin stain). (B) More than ten positive cells in a high-power field are identified (immunostaining for IgG4).

IgG4: immunoglobulin G4.

Graphic 130688 Version 1.0

Histologic features of type 2 autoimmune pancreatitis



Histologic features of type 2 autoimmune pancreatitis (hematoxylin and eosin stain). (A) Granulocytic epithelial lesion with neutrophils infiltrating in the lumina (arrowheads) and epithelium (arrows) in a resecte specimen. (B) Acinar-ductal metaplasia with neutrophilic infiltration (thick arrows) in a lobule seen in a biops specimen.

Graphic 130691 Version 1.0

Diagnostic criteria for type 2 autoimmune pancreatitis

Diagnosis	Imaging evidence	Collateral evidence
Definitive type 2 AIP	Typical/indeterminate	Histologically confirmed IDCP (level 1 H) or clinical inflammatory bowel disease + level 2 H + Rt
Probable type 2 AIP	Typical/indeterminate	Level 2 H/clinical inflammatory bowel disease + Rt

AIP: autoimmune pancreatitis; H: histology; IDCP: idiopathic duct-centric pancreatitis; Rt: response to steroid trial.

From: Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011; 40:352. DOI: 10.1097/MPA.0b013e3182142fd2.

Graphic 130444 Version 1.0

Differential diagnosis of autoimmune pancreatitis[1]

Favors type 1 AIP	Favors type 2 AIP	Favors CP	Favors PDAC	Nonspecific
Older age (>60 years)	Younger (<60 years)	Younger (<60 years)	Older (>60 years)	NA
Male sex	Either	Either	Either	NA
OOI*	IBD (CD or UC)	RAP, alcohol/smoking (with RAP), CFTR-RD, (TIGAR-O¶)	Past history of cancer, family cancer history, smoking	Diabetes mellitus, alcohol without AP, smoking (without AP)
Markedly elevated IgG4	IgG4 mildly elevated/normal	CP genetic risk factors	Somatic genetic factors	Moderately elevated IgG4
Diffuse CT/MRI morphology with enhancing rim	Diffuse CT/MRI morphology with enhancing rim	Diffuse distorted morphology with atrophy and calcifications	Mass lesion, invasion of adjacent structures	Atrophy, fibrosis, cystic lesions
Small duct	Small duct	Large erratic duct with stones	Double duct sign, dilated ducts (IPMN)	NA
Good response to steroids	Good response to steroids	No effect of steroids	No effect of steroids	NA
Recurrence after steroids		Characteristic pain	Unexplained weight loss	

AIP: autoimmune pancreatitis; CP: chronic pancreatitis; PDAC: pancreatic ductal adenocarcinoma; NA: not applicable; OOI: other organ involvement; IBD: irritable bowel disease; CD: coeliac disease; UC: ulcerative colitis; RAP: recurrent acute pancreatitis; CFTR-RD: cystic fibrosis transmembrane conductance regulator gene-related disorder; AP: acute pancreatitis; IgG4: immunoglobulin G4; CT: computed tomography; MRI: magnetic resonance imaging; IPMN: intraductal papillary mucinous neoplasms.

* Refer to UpToDate topics on autoimmune pancreatitis.

¶ TIGAR-O: Etiologic list within general classifiers of Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent, -Obstructive.

Reference:

1. *Whitcomb DC, North American Pancreatitis Study Group. Pancreatitis: TIGAR-O Version 2 Risk/Etiology Checklist With Topic Reviews, Updates, and Use Primers. Clin Transl Gastroenterol 2019; 10:e00027.*

Graphic 130447 Version 2.0

Differential diagnosis of IgG4-SC[1-3]

Favors IgG4-SC	Favors PSC	Favors secondary cholangitis	Favors malignancy
Extrahepatic stenosis	Intrahepatic stenosis	Diffuse or focal	Focal with cut off, liver invasion
Male sex	Male sex		No difference by sex, old age
Pancreatic involvement (89%), OOI (80%)*	IBD (80%, typically ulcerative colitis)	Bile duct stones, gallbladder stones, previous surgeries (eg, Roux-En-Y)	Chronic inflammation, viral hepatitis, liver flukes, choledochal cysts
Elevated IgG4			Somatic genetic factors
Jaundice common	Jaundice uncommon	Variable	Jaundice common
Abdominal pain	Pain uncommon	Fever, pain, WBC	Pruritus, weight loss, pale stools, dark urine
Responses to steroids, immunosuppression			

IgG4-SC: immunoglobulin G4-related sclerosing cholangitis; PSC: primary sclerosing cholangitis; OOI: other organ involvement; IBD: inflammatory bowel disease; WBC: white blood cells.

* Refer to UpToDate topic on autoimmune pancreatitis.

References:

1. *Banales JM, Cardinale V, Carpino G, et al. Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol 2016; 13:261.*
2. *Okazaki K, Uchida K, Koyabu M, et al. IgG4 cholangiopathy: current concept, diagnosis, and pathogenesis. J Hepatol 2014; 61: 690.*
3. *Ali AH, Bi Y, Machicado JD, et al. The long-term outcomes of patients with immunoglobulin G4-related sclerosing cholangitis: the Mayo Clinic experience. J Gastroenterol 2020; 55:1087.*

Graphic 130453 Version 1.0

Contributor Disclosures

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