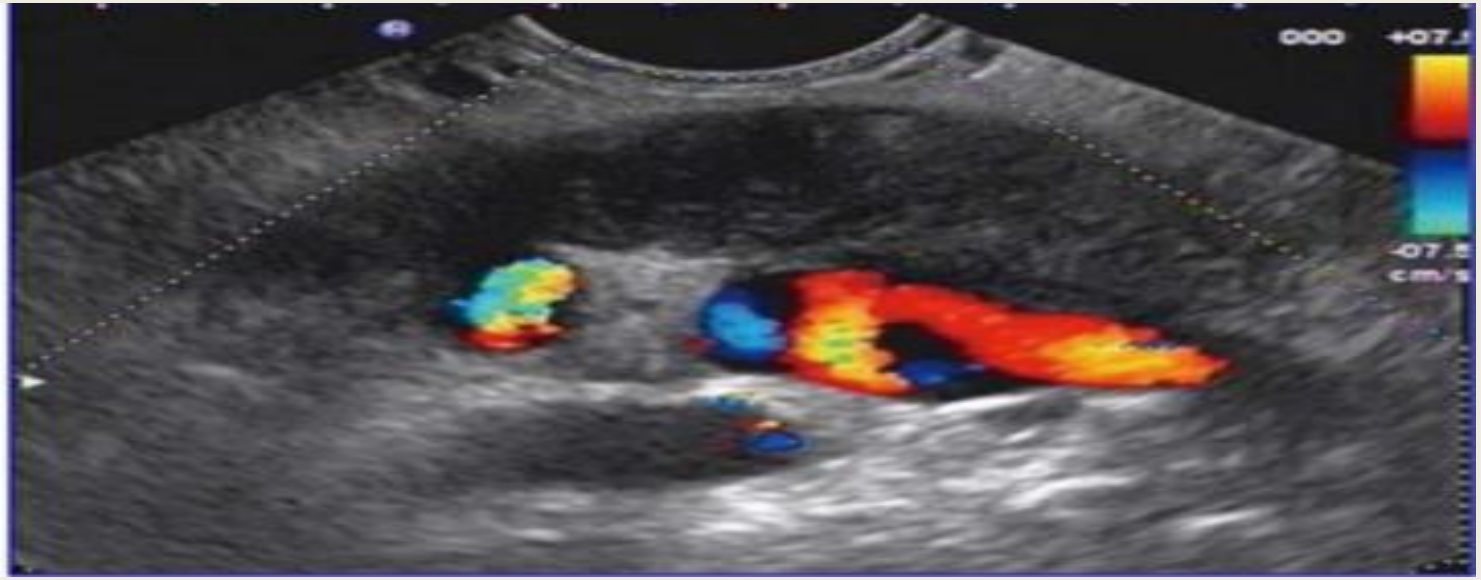
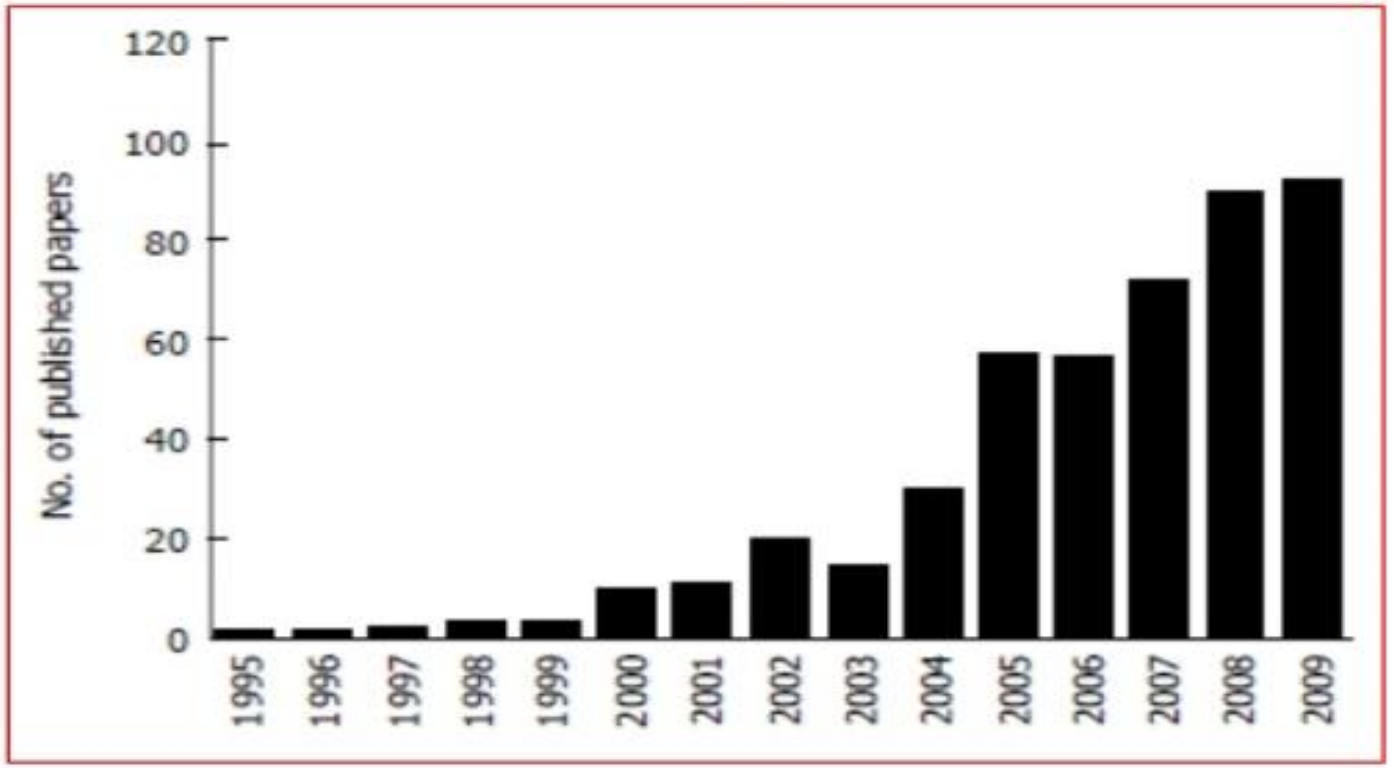
AUTOIMMUNE PANCREATITIS



Sarah Al-Amine M.D.
Al-Mouassat University Hospital
Damascus – Syria

Increased number of published papers on autoimmune pancreatitis



Searching in Pubmed up to 2009

Search terms: autoimmune pancreatitis – Limit: field title

Frulloni L et al. World J Gastroenterol 2011 ; 17 : 2076 – 2079.

History of autoimmune pancreatitis

Sarle	**1961**	Idiopathic chronic pancreatitis with elevated γG
Yoshida	**1995**	Propose concept of autoimmune pancreatitis
Hamano	**1995**	Increased serum levels of IgG4 in AIP
JPS	**2002**	Japan Pancreas Society: 1st guidelines of AIP
Kamisawa	**2003**	Novel entity: IgG4-related sclerosing disease
Chari	**2010**	Two distinct subtypes: type 1 & type 2 Honolulu consensus

Sarles H et al. Am J Dig Dis 1961 ; 6 : 688 – 698.
Yoshida K et al. Dig Dis Sci 1995 ; 40 : 1561 – 1568.
Hamano H et al. New Engl JMed 1995 ; 344 : 732 – 738.
Japan Pancreas Society. J Jpn Pancreas 2002 ; 17 : 585 – 7.
Kamisawa T et al. J Gastroenterol 2003 ; 203 ; 38 : 982 – 984.
Chari ST et al. Pancreas. 2010 ; 39 : 549 – 554.

- 0.82 /100,000 persons.
- 6% chronic pancreatitis

Definition of AIP

- 2 different chronic inflammatory and fibrosing diseases of the pancreas that are responsive to steroid treatment.

initial presentation

- Pancreatic mass → acute . Most common . **Painless obstructive jaundice** 70%

  → chronic **asyptomatic pancreatic mass**

- A less common initial presentation is **acute pancreatitis**, 15% especially with type 2 AIP.
- weight loss, vomiting, and glucose intolerance.
- **pain is not frequently** present but abdominal and referred back pain may occur
- **Burnt out stage** painless chronic pancreatitis steatorrhea and atrophic pancreas

Features of Type 1 and Type 2 Autoimmune Pancreatitis

Feature	Type 1	Type 2 20%
Histology	Lymphoplasmacytic infiltration Dense periductal infiltrate without damage to ductal epithelium Storiform fibrosis Obliterative phlebitis Abundant (>10 cells/HPF) IgG4-positive cells Fibroinflammatory process may extend to peripancreatic region	Periductal lymphoplasmacytic and neutrophilic infiltration Destruction of the duct epithelium by neutrophils (granulocytic epithelial lesion, or GEL) Obliterative phlebitis is rare No IgG4-positive cells
Average age at presentation	60-70 years	40-50, but may present in young adults and even children
Gender predominance	Male	Equal
Usual clinical presentations	Obstructive jaundice (75%) Acute pancreatitis (15%)	Obstructive jaundice (50%) Acute pancreatitis (33%)

Features of Type 1 and Type 2 Autoimmune Pancreatitis

Feature	Type 1	Type 2
Pancreatic imaging	Diffuse pancreatic enlargement (40%) Focal pancreatic enlargement (60%)	Diffuse pancreatic enlargement (15%) Focal pancreatic enlargement (85%)
IgG4	Level elevated in serum (=2/3 of patients) Positive in staining of involved tissues	Not associated
Other organ involvement	Biliary strictures Pseudotumors Kidney Lung Others Retroperitoneal fibrosis Sialoadenitis	Not associated
Associated diseases	See above (other organ involvement)	IBD 30%
Long-term outcome	Frequent relapses	Rare or no relapse

Diagnostic criteria (HISORT)

- proposed by several groups including
  - *the Japanese Pancreas Society,*
  - *an expert group from Korea,*
  - *Mayo Clinic in the United States*
- Sen 85 % sp 99%

Diagnosis of AIP

Combination of 1 or more of 5 cardinal features **HISORt**	
Histology TCB/resection	LPSP – IDCP
Imaging **P**arenchyma Pancreatic **D**uct	US – EUS – CT – PET – MRI ERCP – MRCP
Serology	IgG4
Other Organ Involvement	IgG4-related diseases – IBD
Response to **t**herapy	Steroid trial

LPSP: **L**ympho-**P**lasmacytic **S**clerosing **P**ancreatitis

IDCP: **I**diopathic **D**uct-**C**entric **P**ancreatitis

Shimosegawa T et al. Pancreas 2011 ; 40 : 352 – 358.

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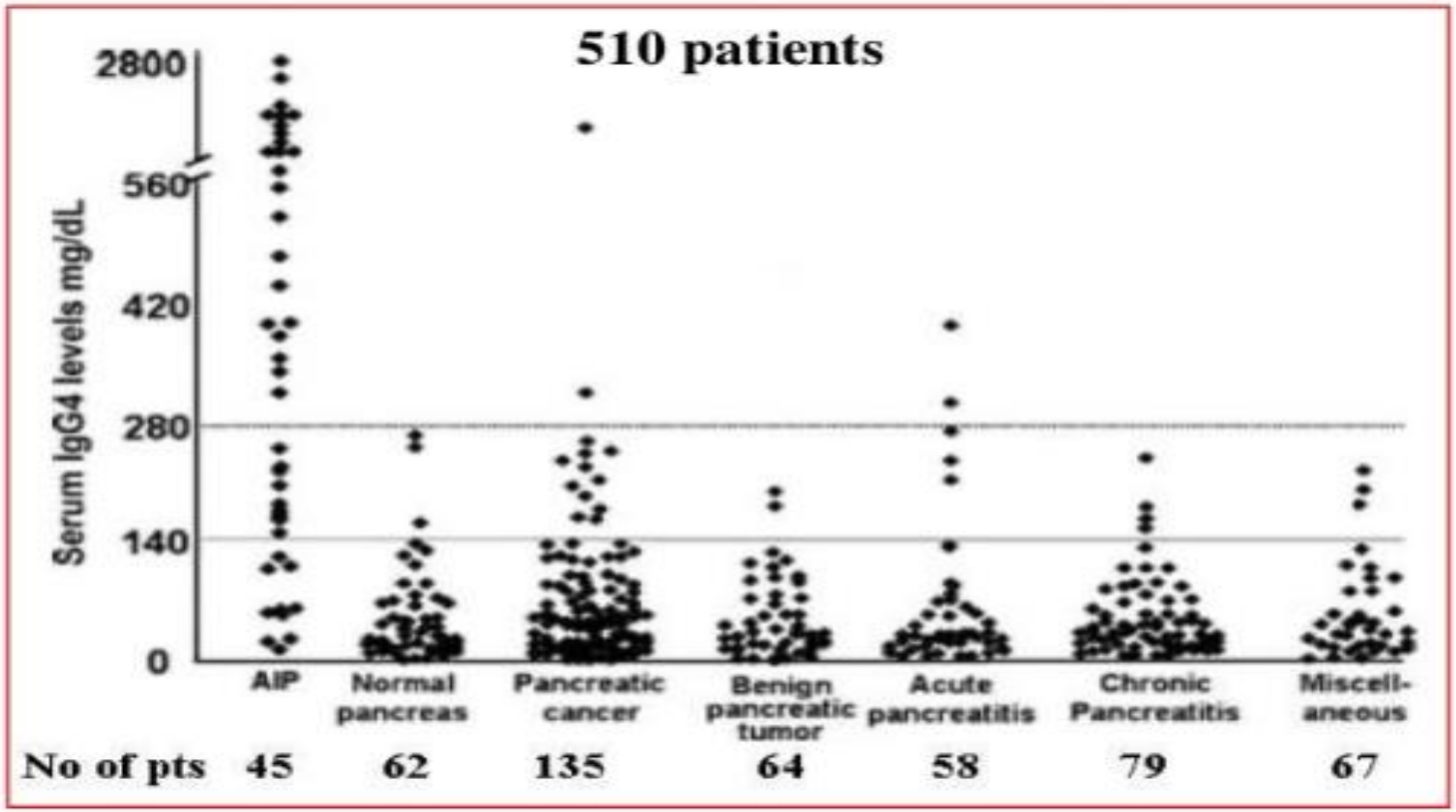
Shimosegawa T et al. Pancreas 2011 ; 40 : 352 – 358.

IgG-4

- Normal value : 8-140 mg/dl
- does not activate the classical complement cascade,
- **no specific target antigen**
- **not** involved in **pathogenesis** of disease
- Sen **70 %** sp 99%

Serum IgG4 in diagnosing AIP



Cutoff > 140 mg/dL: Sen 76% – Sp 93% – PPV 36%

Cutoff > 280 mg/dL: Sen 53% – Sp 99% – PPV 75%

Ghazale A et al. Am J Gastroenterol 2007 ; 102 : 1646 – 1653.

- , serum IgG4 values above normal but ≤280 mg/dL described in a number of disorders that do not involve the pancreas,:
- atopic dermatitis,
- asthma,
- parasitic diseases,
- pemphigus vulgaris,
- pemphigus foliaceus

elevation in serum IgE.

Anti-PBP peptide antibodies

- Anti-plasminogen-binding protein (PBP) peptide antibodies
  - *Sen 94% sp 95%*
  - *5% with pancreatic cancer*
  - *(cannot be used to distinguish between these two diseases)*
- CA 19-9 concentrations were much more common with pancreatic cancer (71 versus 9 percent)
- Other antibodies:
  - *carbonic anhydrase II antigens (positive in 30 to 59 percent)*
  - *RF- ANA – p-ANCA – AMA – ASMA -antithyroglobulin*

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Shimosegawa T et al. Pancreas 2011 ; 40 : 352 – 358.

What to biopsy?

Histopathology is diagnostic but not usually available

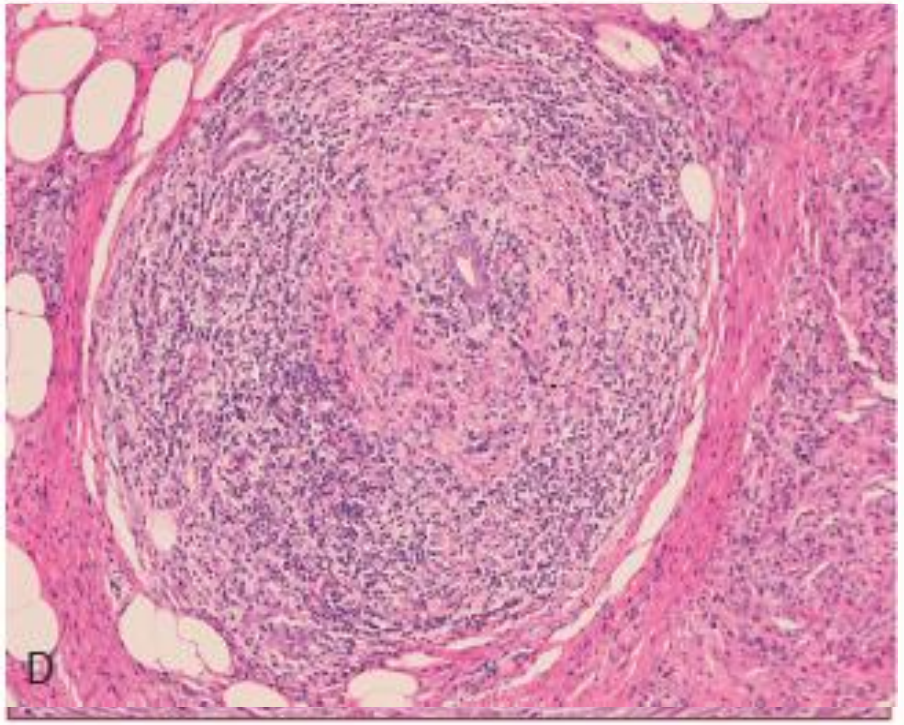
• **Pancreatic biopsy**	EUS-FNA: not reliable EUS-TCB: better sen & sp Surgery
• **Papillary biopsy**	Specific, not very sensitive
• **Intraductal BD biopsy**	Still under debate
• **Liver biopsy**	Not strictly necessary

lymphoplasmacytic sclerosing pancreatitis (LPSP),type 1

- A lymphoplasmacytic sclerosing pancreatitis or
- more than 10 IgG4-positive cells
  - ***with at least two of the following:***
    - periductal lymphoplasmacytic infiltrate,
    - obliterative phlebitis,
    - and acinar fibrosis

Histopathological findings of AIP / LPSP

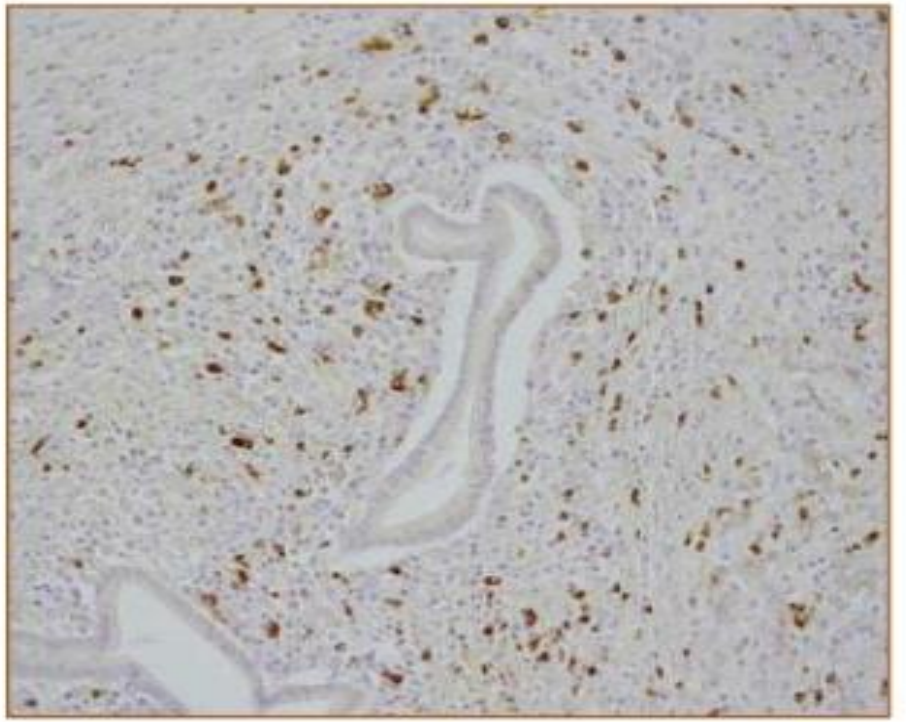
H&E staining



Infiltration of plasma cells & lymphocytes

‘**storiform fibrosis**”

IgG4 immuno-staining

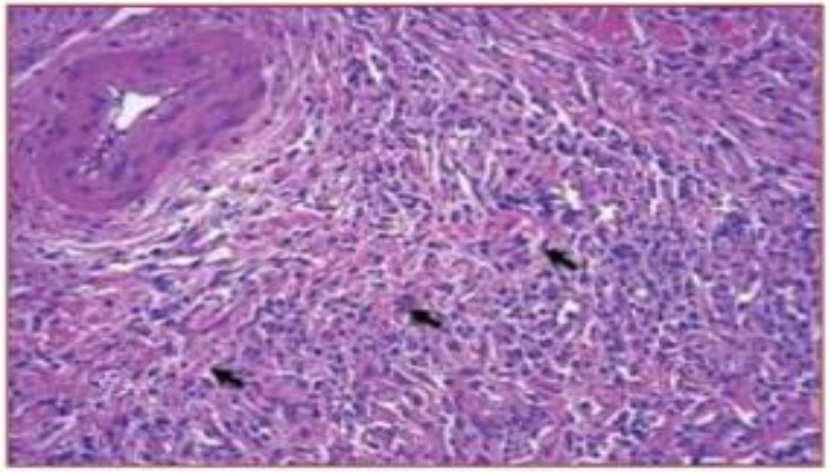


Abundant infiltration of IgG4-positive plasma cells

Shimosegawa T & Kanno A. J Gastroenterol. 2009 ; 44 : 503 – 17.

Obliterative venulitis

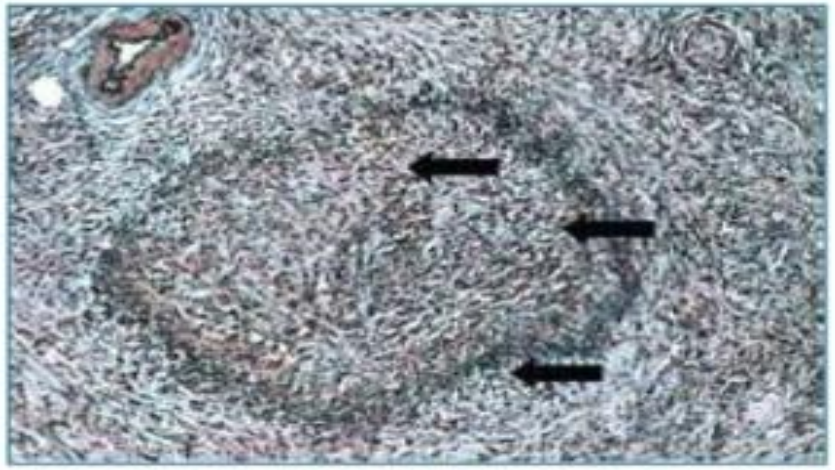
H&E stain



Artery easily found

Poorly visualizes obliterative venulitis

Movat pentachrome stain



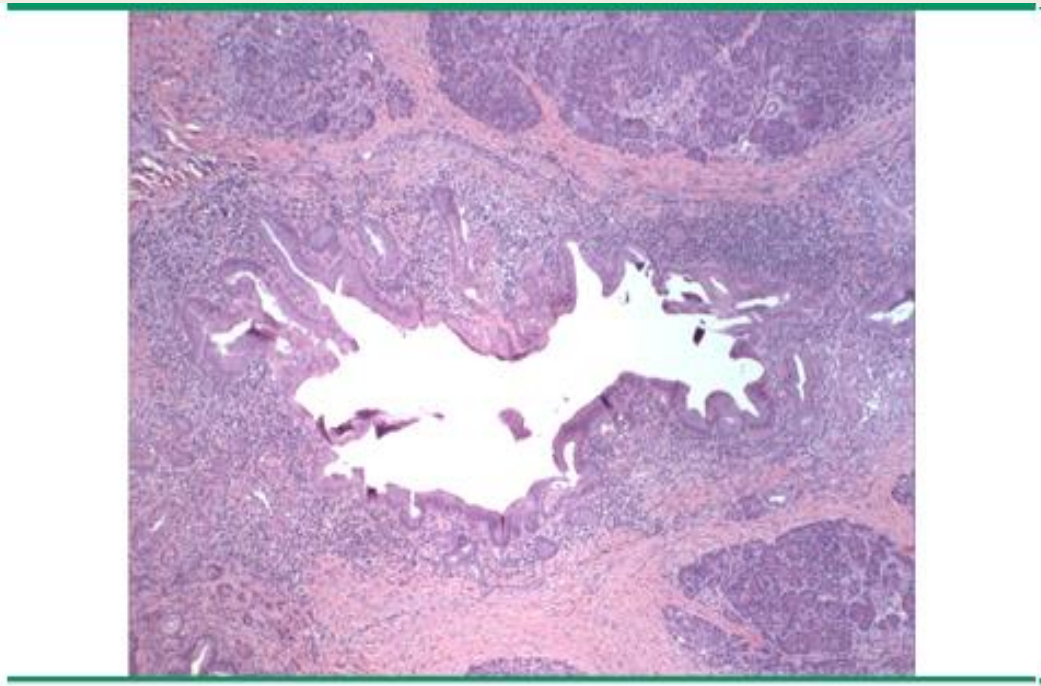
Lymphoplasmacytic infiltration

Fibrosis destroying vein wall

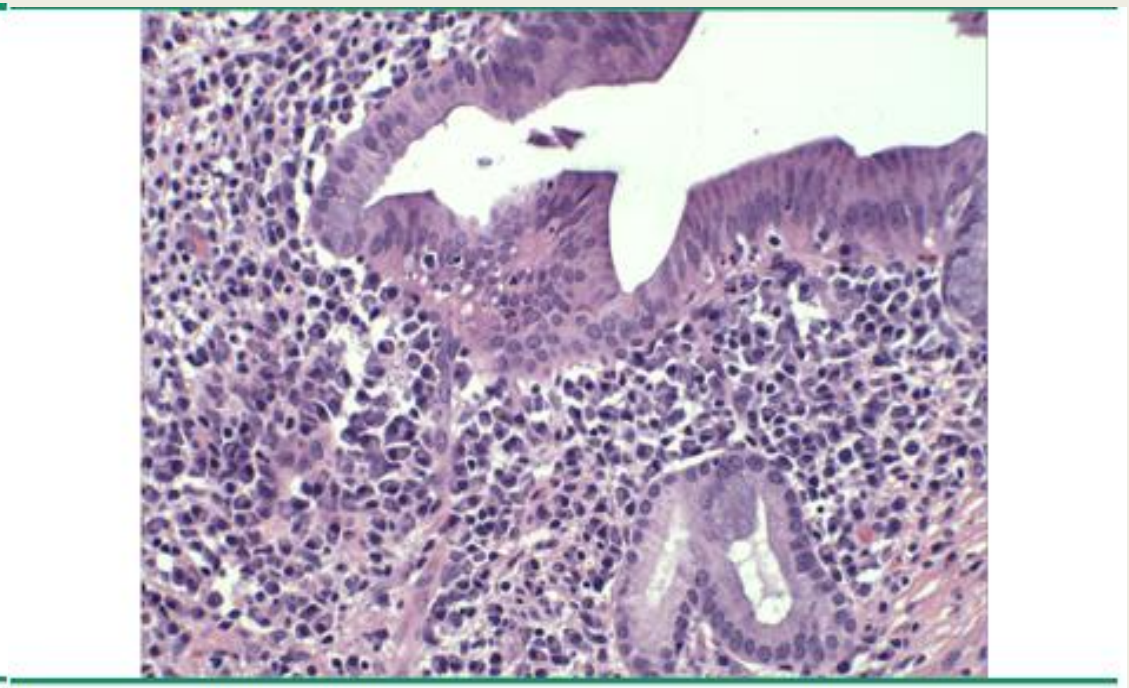
resulting in narrowing & occlusion

Law R et al. Clev Clin J Med 2009 ; 76 : 607 – 615.

periductal lymphoplasmacytic infiltrat



Low power (40X) view of a pancreas biopsy in a patient with autoimmune pancreatitis showing a large pancreatic duct surrounded by a dense lymphoplasmacytic infiltrate.



High power (200x) view of a pancreas biopsy in a patients with autoimmune pancreatitis showing an infiltrate composed primarily of plasma cells admixed with lymphocytes.

Idiopathic duct-centric pancreatitis (IDCP) (type 2)

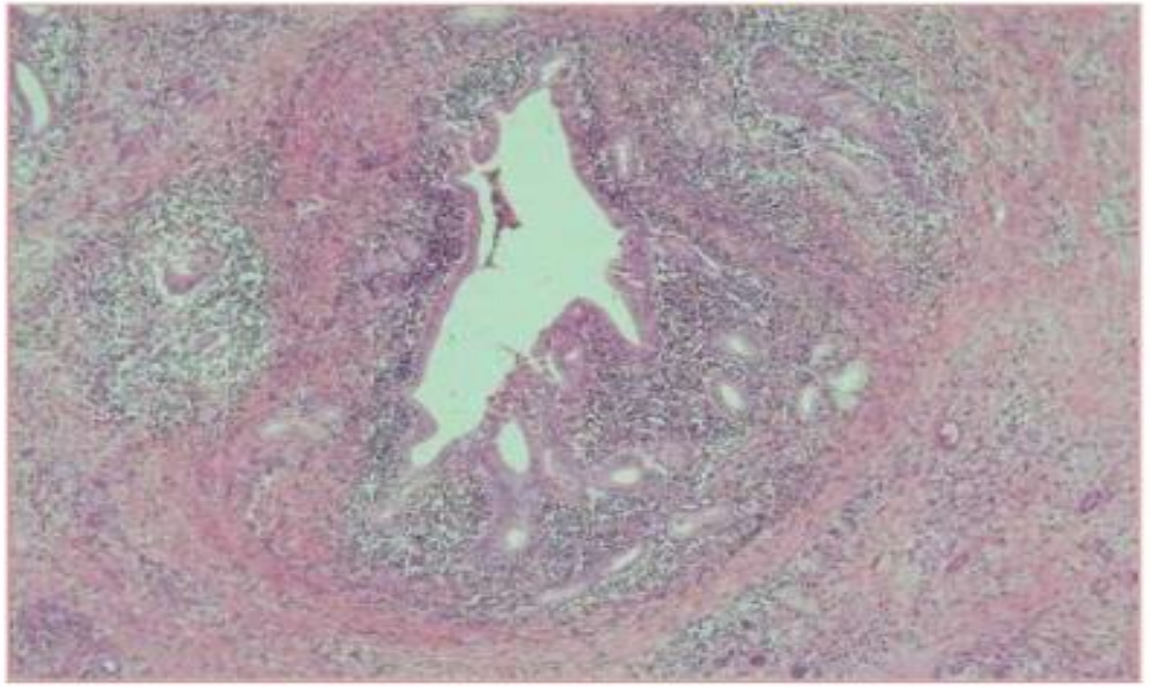
- Periductal lymphoplasmacytic and neutrophilic infiltration
- Destruction of the duct epithelium by neutrophils

(granulocytic epithelial lesion, or GEL) microabcseses

- Obliterative phlebitis is rare
- No IgG4-positive cells

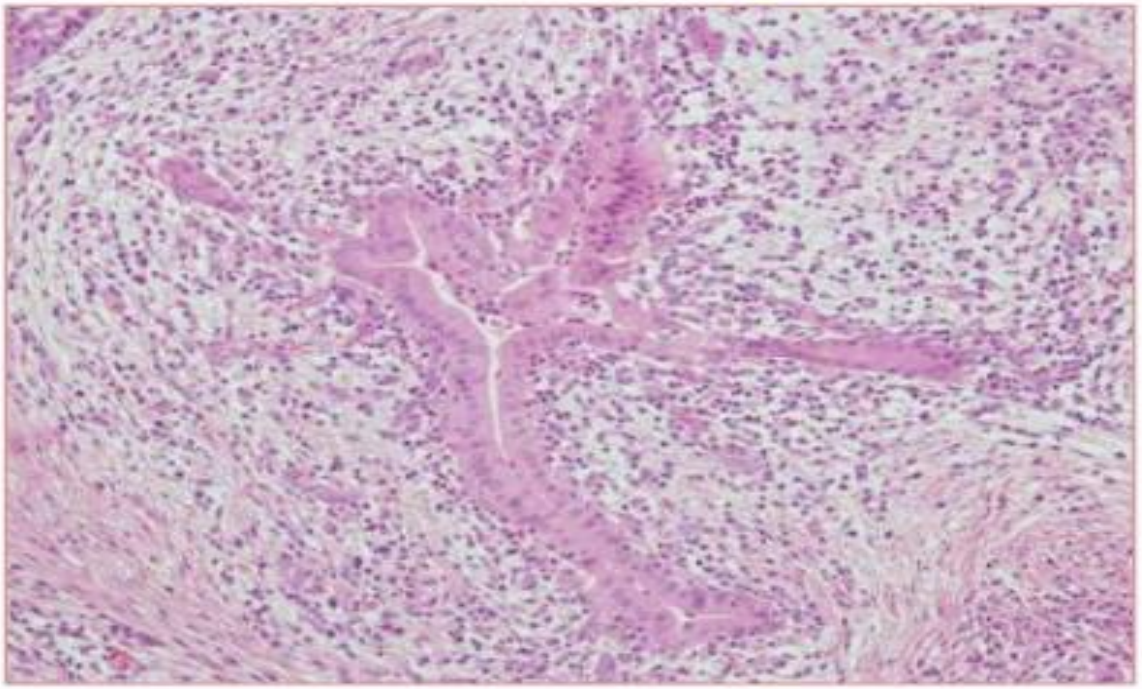
Idiopathic Duct-Centric Pancreatitis (IDCP)

H&E staining



Periductal inflammation
Destruction of pancreatic epithelia
Suggested GEL

H&E staining



Inflammatory cells few in fibrosis
Microabscess in intra-lobular duct

GEL: **G**ranulocyte **E**pithelial **L**esions

Kusuda T et al. Intern Med 2010 ; 49 : 2569 – 2575.

Diagnosis of AIP

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Serology	IgG4
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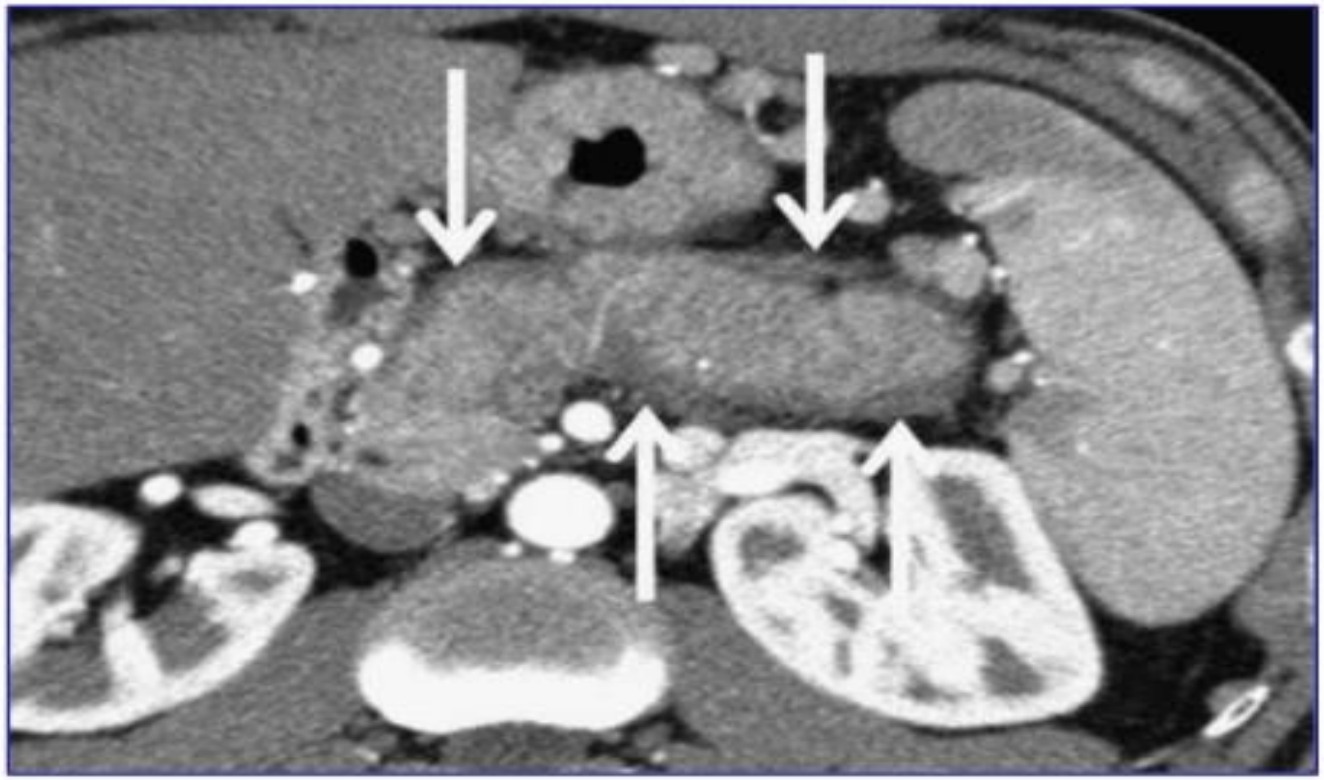
Shimosegawa T et al. Pancreas 2011 ; 40 : 352 – 358.

Parenchymal imaging CT- MRI

Criteria	Level 1 Evidence	Level 2 Evidence
P: Parenchymal imaging	Typical imaging: Diffuse enlargement of pancreas with delayed enhancement With or without rim-like enhancement of pancreas	Indeterminate imaging: Segmental or focal enlargement of the pancreas with delayed enhancement

Dynamic CT in auto-immune pancreatitis



Diffusely enlarged pancreas

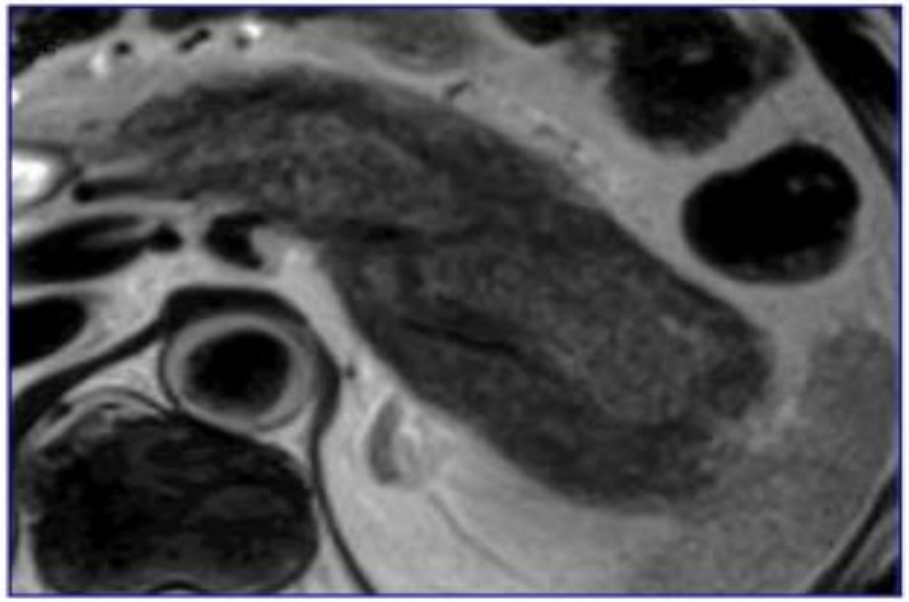
Slow and delayed enhancement

Capsule-like rim

Okazaki K et al. Pancreas 2009 ; 38 : 849 – 866.

MR imaging of AIP

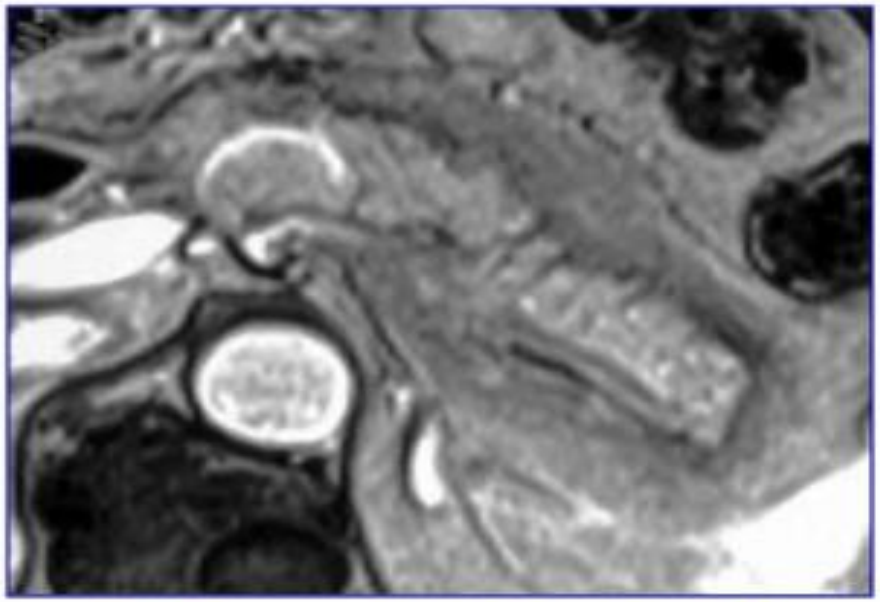
T2-weighted MRI



Swollen pancreas (low signal)

"Capsule-like rim" (low signal)

Gd-enhanced MRI



"Capsule-like rim"

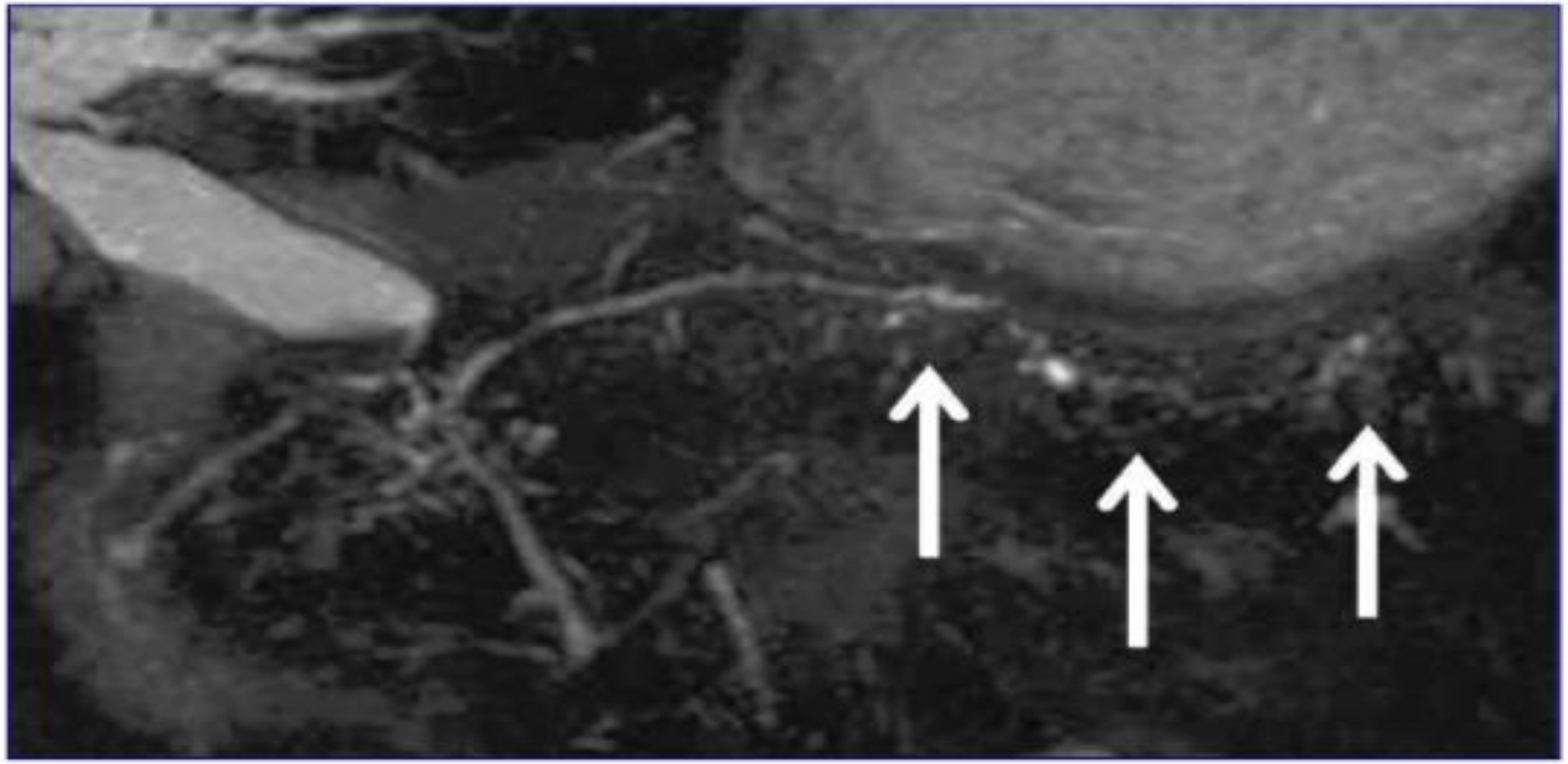
Depicted more clearly

Shimosegawa T & Kanno A. J Gastroenterol. 2009 ; 44 : 503 – 17.

Ductal imaging (ERCP or MRCP)

Criteria	Level 1 Evidence	Level 2 Evidence
D: Ductal imaging (ERCP or MRCP)	Long (>1/3 of the length of pancreatic duct) stricture *OR* Multiple strictures without upstream dilatation of the pancreatic duct	Segmental or focal narrowing of pancreatic duct Without marked (>5 mm) upstream dilatation of pancreatic duct

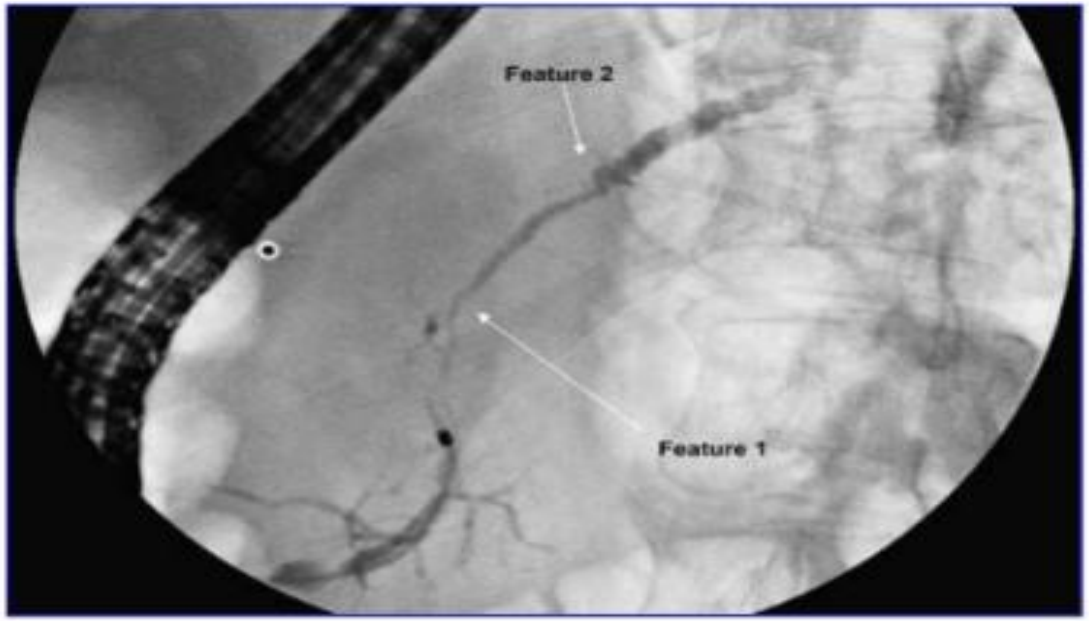
MRCP in auto-immune pancreatitis

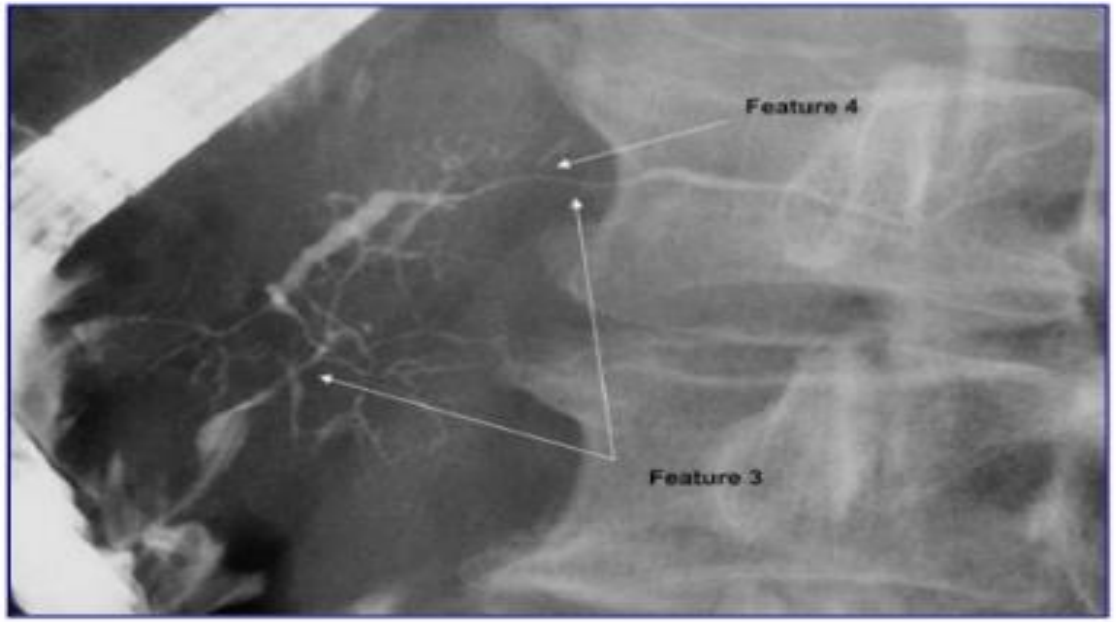


Narrowing of main pancreatic duct (tail)

Okazaki K et al. Pancreas 2009 ; 38 : 849 – 866.

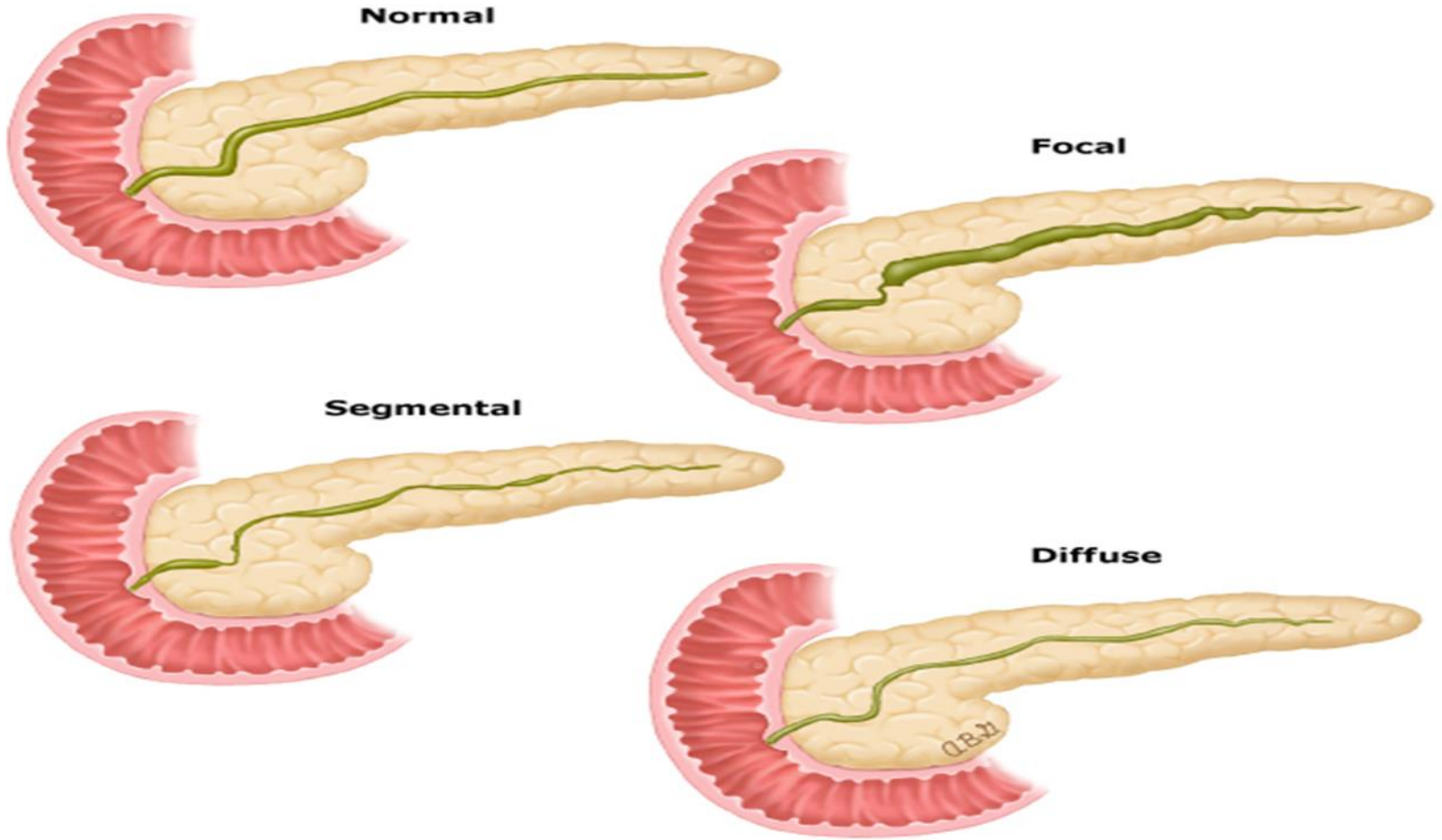
ERCP criteria to diagnose AIP





Sugumar A et al. Gut 2011 ; 60 : 666 – 670.

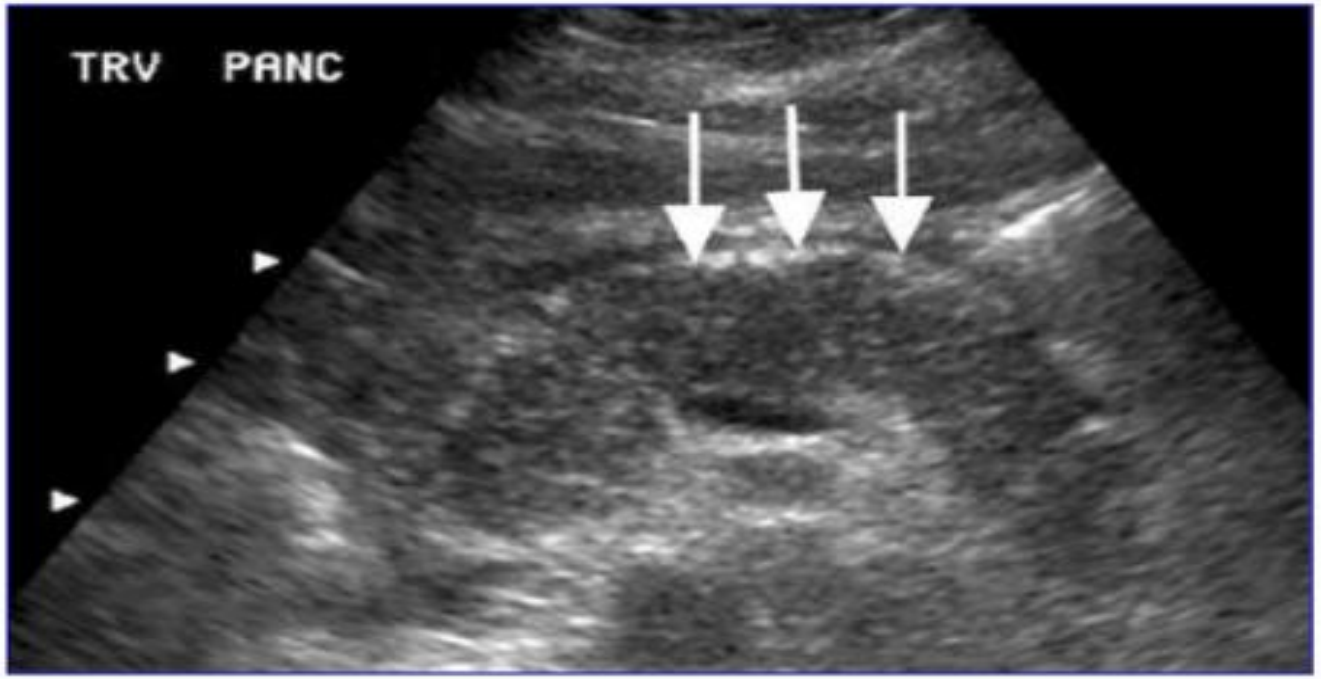
Pancreatograms either by MRCP or ERCP in autoimmune chronic pancreatitis



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

Ultrasonograpy in AIP

Trans-abdominal transverse US



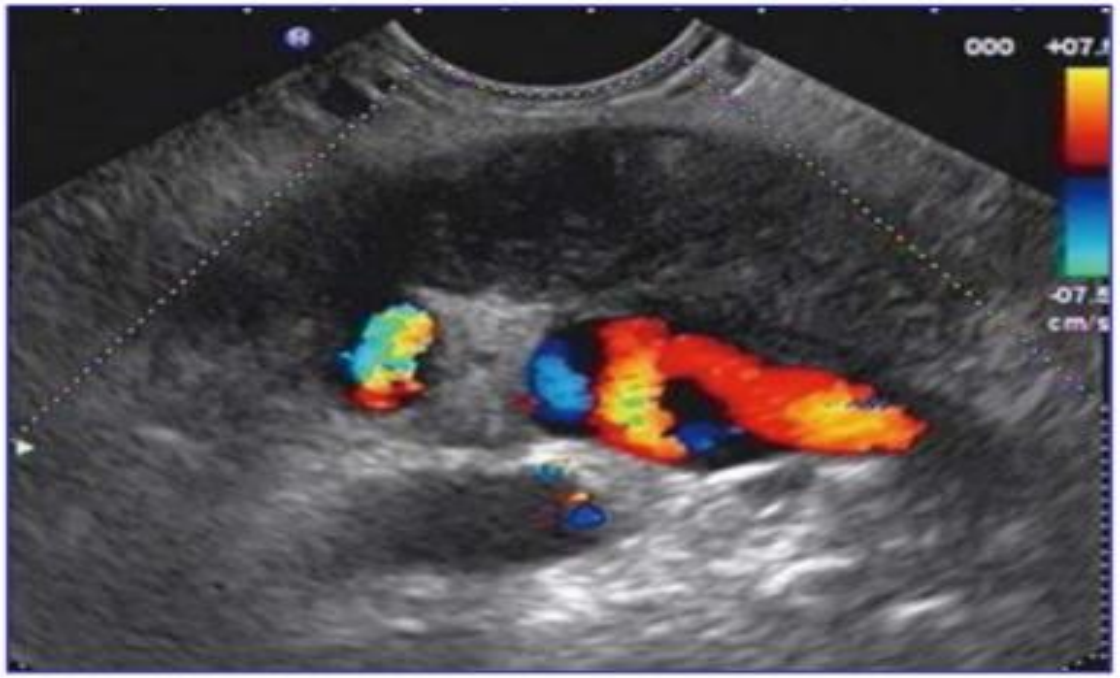
Diffuse enlargement of pancreas

Minimal decreased echotexture

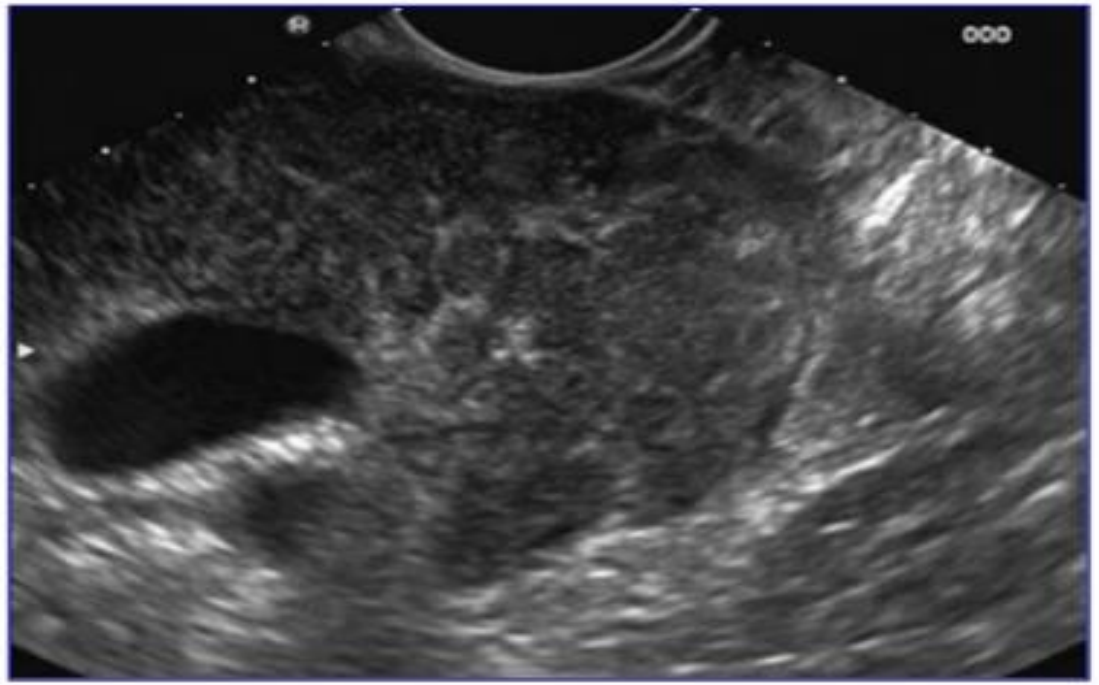
“sausage-like appearance”

Sahani DV et al. Radiology 2004 ; 233 : 345 – 352.

Diffuse form of autoimmune pancreatitis
EUS



Diffuse pancreatic enlargement
Echopoor echotexture
Loss of interface with splenic vein



Parenchymal lobularity
Hyperechoic strands

Buscarini E et al. World J Gastroenterol 2011 ; 17 : 2080 – 2085.

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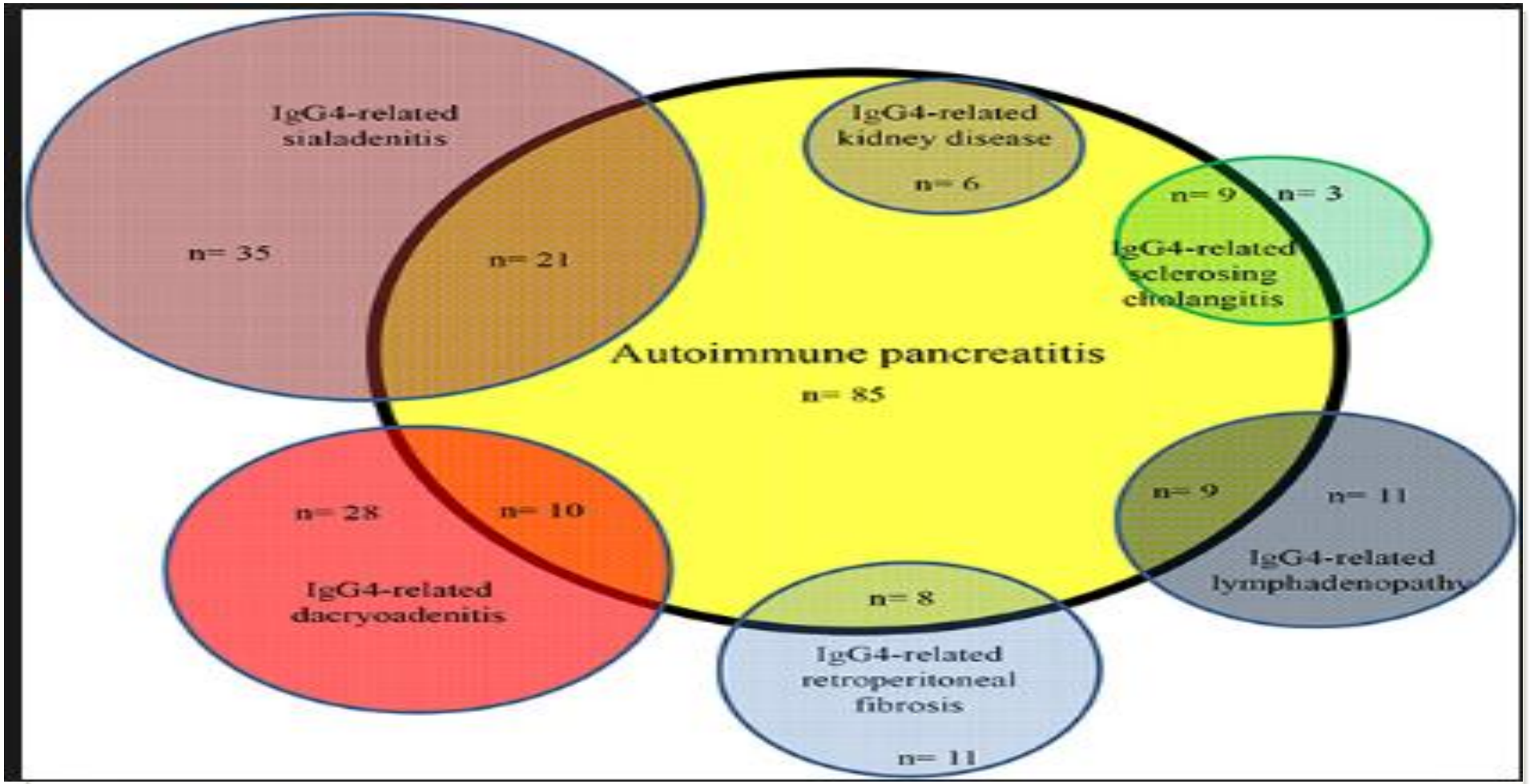
Shimosegawa T et al. Pancreas 2011 ; 40 : 352 – 358.

IgG-4 related diseases

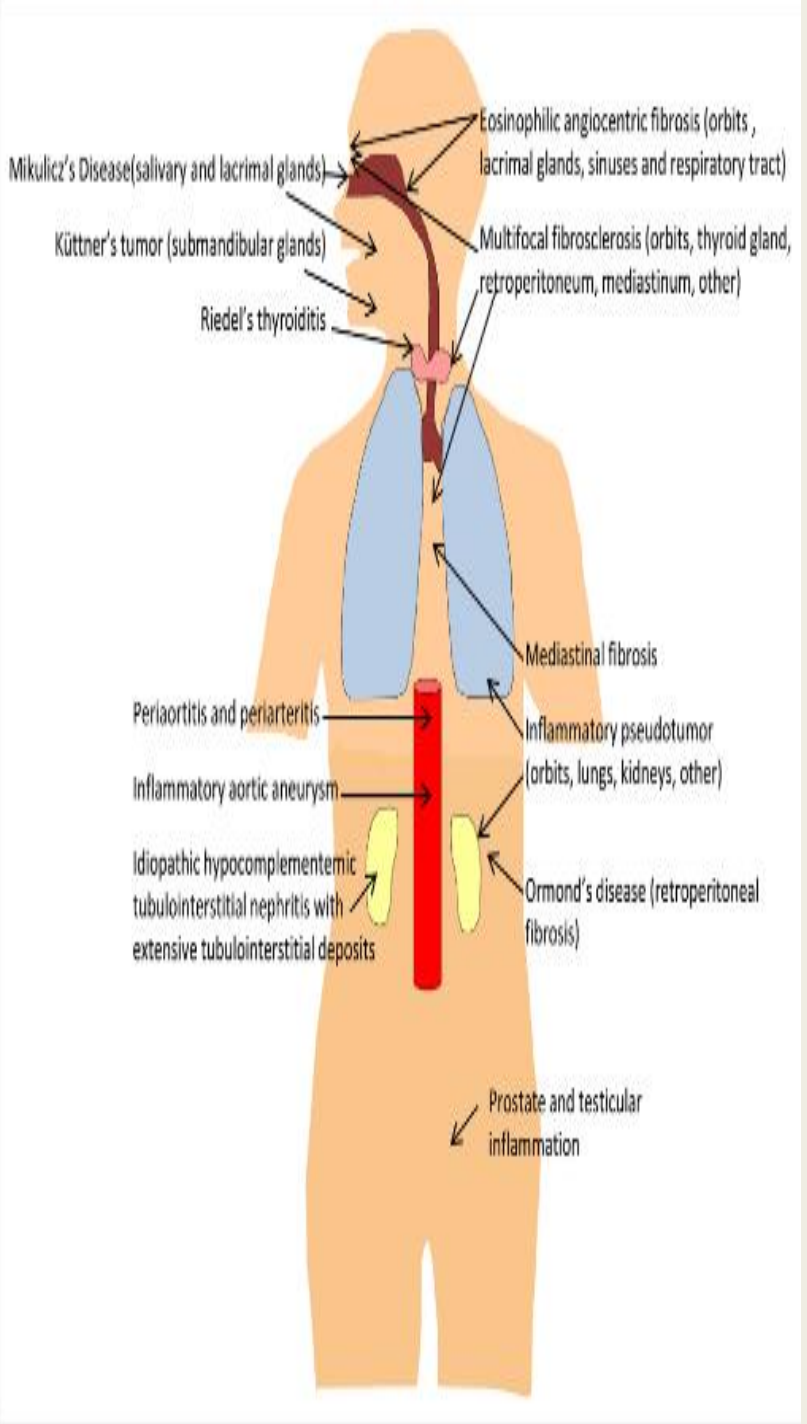
- **Type-1 AIP** may occur in an **isolated pancreatic** form or may be associated with **extrapancreatic** manifestations.
- occurs in around **60%** of patients,
- **Biopsies** :
  - *inflammatory dense* **lymphoplasmacytic** *infiltrations*
  - *accompanied by* **fibrosis** *and most of the time by* ***obliterative phlebitis***
  - *with a predominance of* ***IgG4-positive*** *plasma cells,*
- Serum IgG4 levels are elevated (>135 mg/dL) in about 70%
- may occur **before**, **after**, or at the **same time** as the pancreatic disease.
- **Type-2 AIP :** 15-30% IBD

IgG4-related sclerosing disease



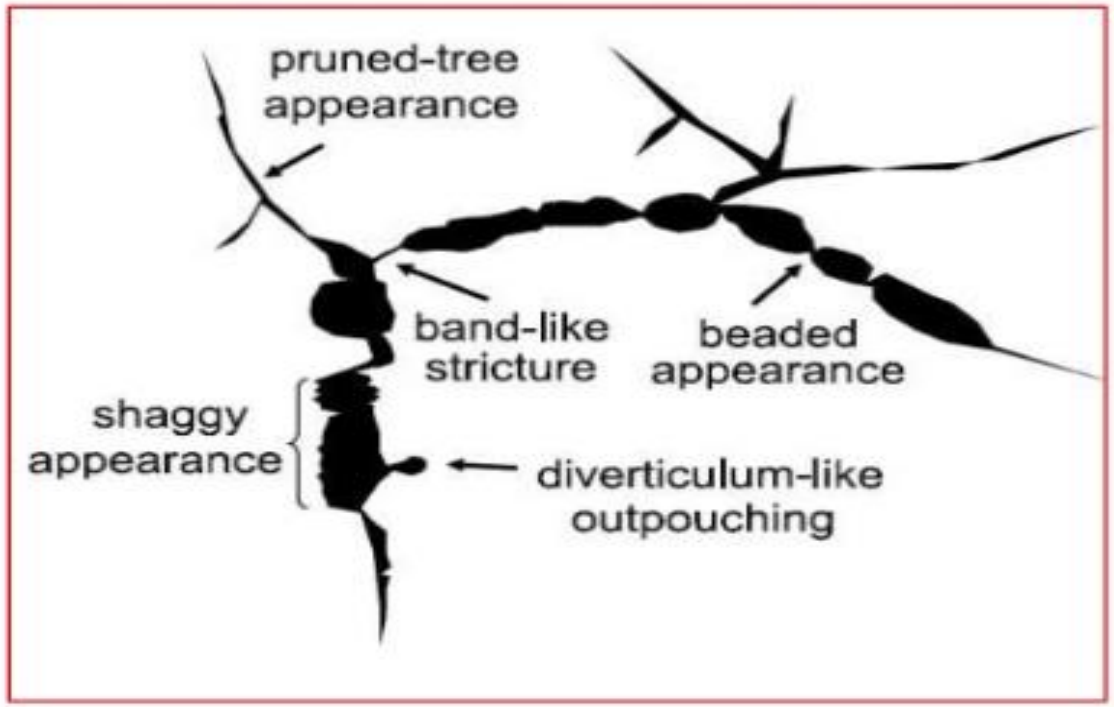
Kamisawa T et al. Expert Opin Pharmacother 2011 ; 12 : 2149 – 2159.

Pancreas
Autoimmune pancreatitis
Bile ducts
IgG4-associated cholangitis
Salivary gland
Chronic sclerosing sialadenitis (Küttner's tumor)
Mikulicz's disease (IgG4-related plasmacytic exocrinopathy)
Chest
Patchy ground glass, nodular, and consolidative lung opacities
Mediastinal fibrosis, adenopathy
Retroperitoneum
Chronic periaortitis
Idiopathic retroperitoneal fibrosis
Kidneys
Tubulointerstitial nephritis
Orbits
IgG4-associated pseudolymphoma
Inflammatory bowel disease
Ulcerative colitis

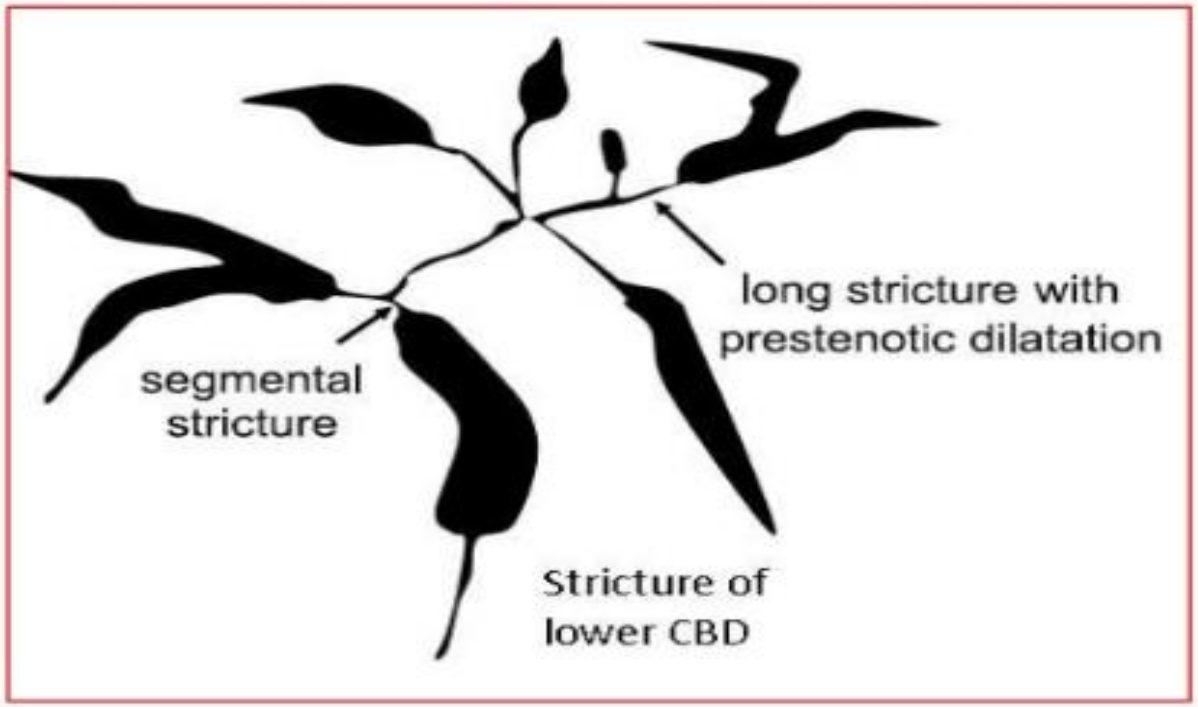


Cholangiography in PSC & AIP

PSC

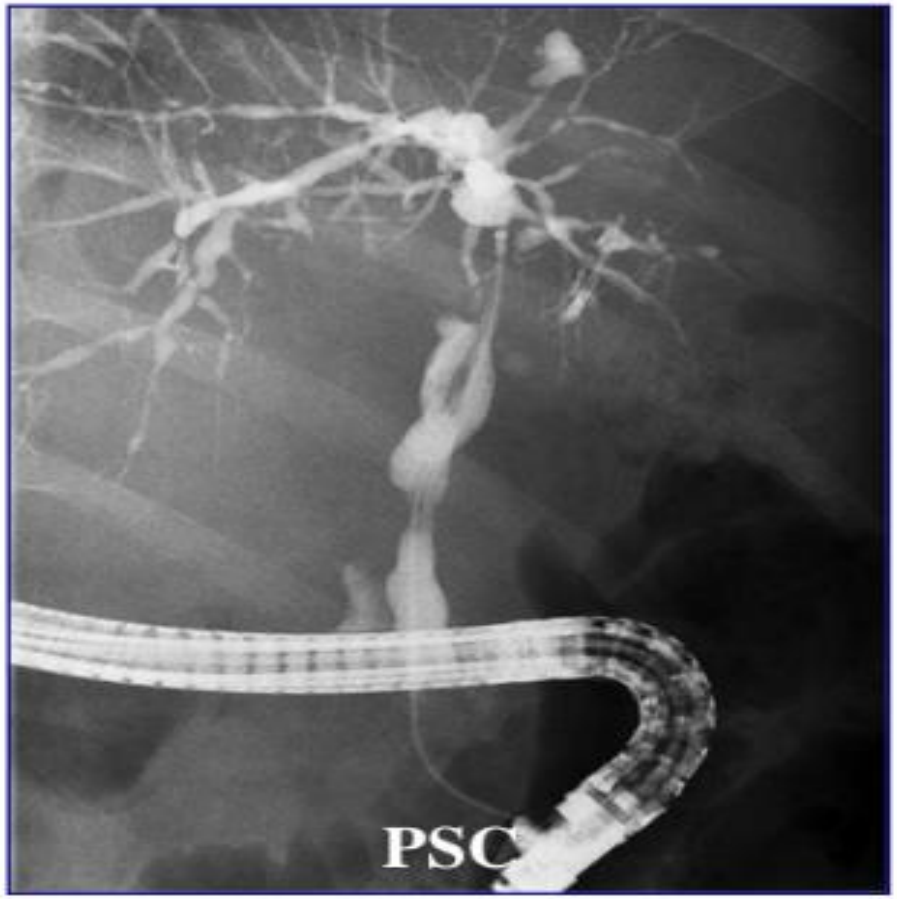


AIP



Kawa S et al. J Gastroenterol 2010 ; 45 : 355 – 369.

ERC in IgG4-associated cholangitis & PSC



Difficulty to distinguish IAC from PSC based on ERC

de Buy Wenniger LM et al. Endoscopy 2012 ; 44 : 66 – 73.

Does ERC distinguish IgG4-associated cholangitis from PSC or cholangiocarcinoma?

- 17 physicians from USA, Japan, & UK
- Unaware of clinical data
- 40 ERCs IgG4-associated cholangitis: 20 patients
  PSC: 10 patients
  Cholangiocarcinoma: 10 patients
- Results Sensitivity: 45%
  Specificity: 88%
  Inter-observer agreement: 0.18

IAC may be misdiagnosed with PSC or cholangiocarcinoma

Kalaitzakis E et al. Clinical Gastroenterol Hepatol 2011 ; 9 : 800 – 803.

In all patients with possible PSC,

we suggest measuring serum IgG4 levels

to exclude IgG4-associated sclerosing cholangitis

AASLD practice guidelines: Diagnosis & management of PSC.
Chapman R et al. Hepatology 2010 ; 51 : 660 – 678.

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Shimosegawa T et al. Pancreas 2011 ; 40 : 352 – 358.

Treatment

Induction for remmsion with high dose of steroid **40** mg/day (0.6-1mg/kg/day)

for **2 to 4** weeks

↓

Repeat pancreatic imaging (CT or MRI , whichever was obtained initially)

↓

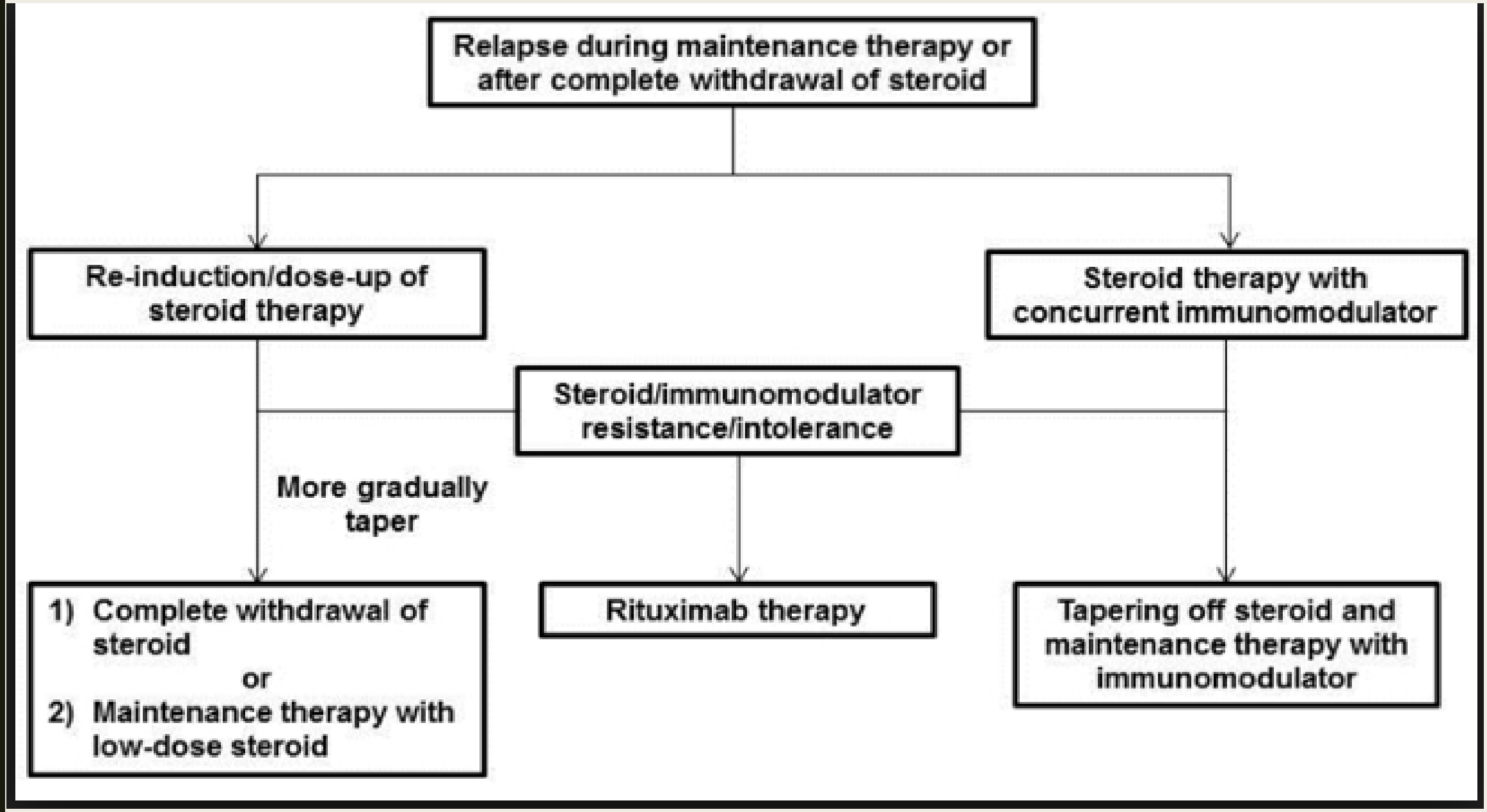
Response rate type 1 & type 2 : 97%

↓

taper of 5 mg/week for a total treatment duration of 10 to 12 weeks.

type 1 AIP a relapse 30% and 50%

type 2 AIP relapse rare


Relapse during maintenance therapy or after complete withdrawal of steroid
Re-induction/dose-up of steroid therapy
Steroid therapy with concurrent immunomodulator
Steroid/immunomodulator resistance/intolerance
More gradually taper
1) Complete withdrawal of steroid
or
2) Maintenance therapy with low-dose steroid
Rituximab therapy
Tapering off steroid and maintenance therapy with immunomodulator

Treatment

- AZA at dosage of 2 mg/kg/day sustained remission at 3 years (75%)
- Maintenance low-dosage steroids keep in remission at 3 years 76.7%

When to Offer Rituximab

Reserve RTX for patients who cannot tolerate steroids or are refractory to immunomodulators; we do not generally recommend it as a first-line agent.

1.000 mg every week for 1 month, followed for 1.000 mg every 2–3 months for 24 months
maintaining remission 83%

aga American Gastroenterological Association

Challenges to diagnosing AIP

- **Closely mimics other well known diseases**

  Pancreatic cancer & PSC: need high index of suspicion

- **Rare compared to diseases it mimics**

  2 – 3 % of patients suspected to have pancreatic cancer

- **No single test is diagnostic**

  Histology is diagnostic but rarely available

- **Heavy price of misdiagnosis**

  AIP mistaken for cancer results in major surgery

  Cancer mistaken for AIP results in delay in surgery

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REVIEW AND META-ANALYSIS

Distinguishing Autoimmune Pancreatitis From Pancreaticobiliary Cancers

Current Strategy

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Ann Surg 2012;255:248–258


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