Clinico-radiological appraisal of uncommon types and causes of Pancreatitis

Pattern recognition approach on CT

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EE-162

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Compliance with ethical standards

Funding: No funding was received for this study.

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from individual participant included in the study.

Learning Objectives

1. To identify different types of pancreatitis.

2. To discuss the clinical and radiological features of various common and uncommon types of pancreatitis.

3. To tabulate and list different types of pancreatitis.

4. To identify key signs and radiological features in different types of pancreatitis.

Background

- Over one-half of cases of acute pancreatitis in adults are related to cholelithiasis or alcohol consumption.
- Trauma, viral infections, and systemic disease account for the majority of cases in children.
- Idiopathic pancreatitis is considered to be the most common cause of chronic pancreatitis in children.
- Hereditary and tropical pancreatitis is responsible for the majority of cases of chronic childhood pancreatitis, many of which are mislabelled as “idiopathic” category.
- Other causes are autoimmune pancreatitis, groove pancreatitis, pancreatitis in ectopic or heterotopic pancreatic tissue, *Ascaris*-induced pancreatitis, pancreatitis in cystic fibrosis, congenital anomalies, etc.
- Specific clinical and imaging features may be helpful in identifying the cause.

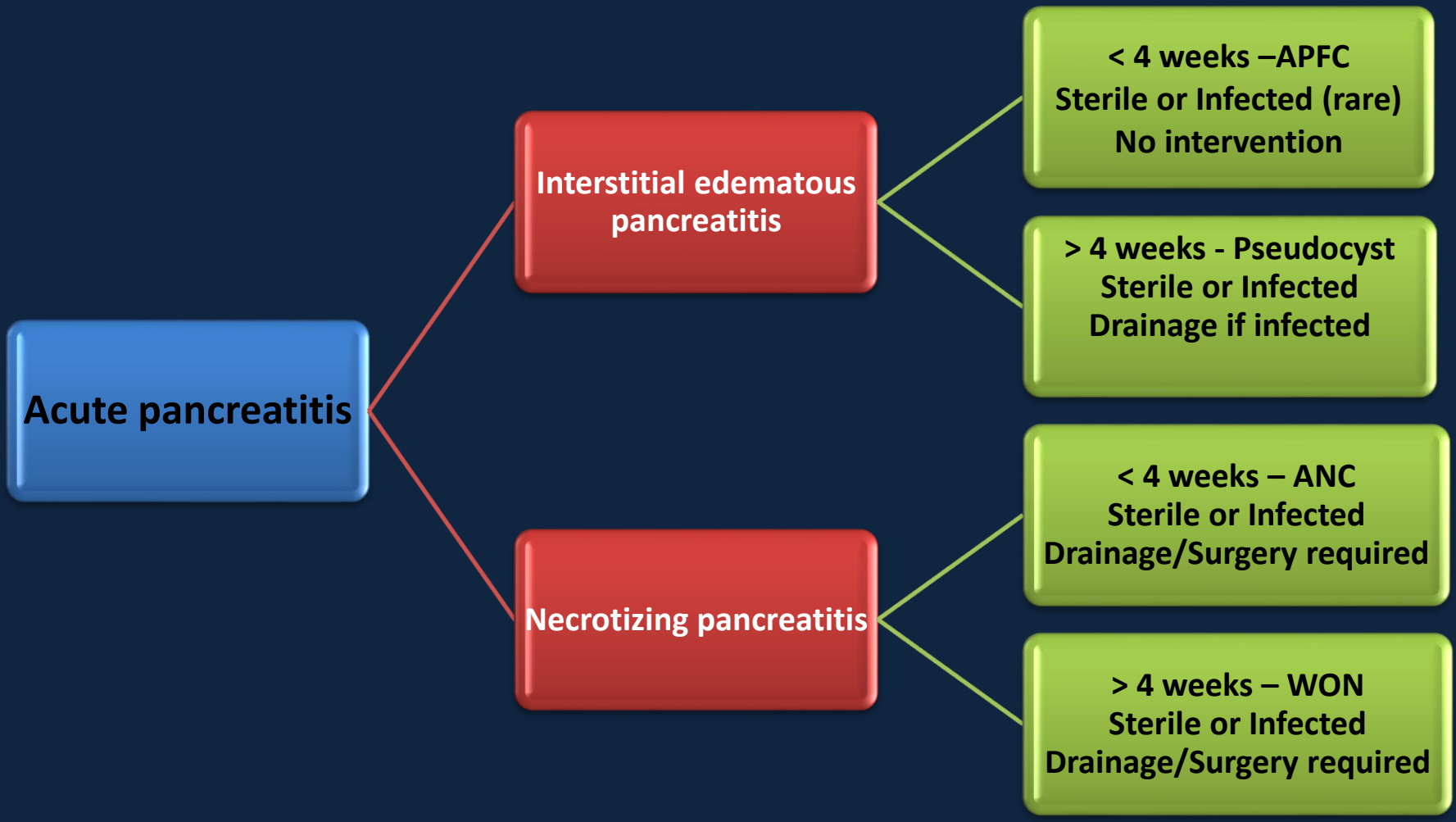
Introduction

- Pancreatitis is the most common pancreatic disease in children and adults and one of the most common causes of morbidity and mortality worldwide.
- Over one-half of cases of acute pancreatitis in adults are due to cholelithiasis or alcohol consumption, whereas trauma, viral infections, systemic disease account for cases in children.
- Incidence of chronic pancreatitis - 3-9 cases/100,000 persons/year.
- *Alcohol consumption accounts for the majority (80%) of cases of chronic pancreatitis in adults in developed countries, whereas malnutrition is the most common cause worldwide.*
- Chronic pancreatitis is a disabling illness in children that carries a high morbidity rate due to exocrine and endocrine pancreatic insufficiency, resulting in stunted growth.

Introduction

- Idiopathic pancreatitis is the most common cause of chronic pancreatitis in children (30%).
- However, hereditary and tropical pancreatitis are responsible for the majority of cases of chronic childhood pancreatitis, many of which may fall under the “idiopathic” category if unrecognized.
- Biliary tract abnormalities account for 47% of cases of childhood pancreatitis in Japan.
- Traditionally, CT has been used to help confirm the diagnosis, assess disease severity, detect complications, and provide a “road map” for interventional procedures.
- A handful of causes do have specific clinical and imaging features that may be helpful in identifying the cause and thus may have a significant impact on management.
- In cases with no underlying metabolic or systemic predisposing factors for acute or recurrent pancreatitis, special attention to these ancillary findings and critical reevaluation of these uncommon but potential causes are required.

Revised Atlanta Imaging Lexicon of Acute Pancreatitis



Clinical and Radiologic features of various uncommon types and unusual causes of Pancreatitis

Types of pancreatitis	Clinical Features	Imaging Features
Autoimmune pancreatitis	Absence of the classic acute attacks of pancreatitis, elevated immune markers, dramatic response to steroid therapy	“Sausage" shape pancreas, peripheral “rind” of hypoattenuation
Groove pancreatitis	Duodenal and biliary obstruction; symptoms overlap with those of pancreatic cancer, frequently leading to misdiagnosis	Soft tissue within the pancreaticoduodenal groove , small cysts along medial duodenal wall
Tropical pancreatitis	Young age, associated with malnutrition, regional predisposition in tropical countries, increased risk of adenocarcinoma	Multiple large discrete calculi up to 5 cm within a dilated pancreatic duct (>80% of cases)
Hereditary pancreatitis	Young age, at least 2 attacks of pancreatitis with no underlying cause, family history of pancreatitis in a first- or second-degree relative	Acute: nonspecific; chronic: significant pancreatic atrophy, pancreatic calcifications, and calculi
Pancreatitis in ectopic/ Heterotopic pancreas	Pancreatitis rarely diagnosed clinically and radiologically; may manifest as abdominal pain (77%), abdominal fullness (30%), or malena (24%)	CT: oval or round masses in the gastric wall that follow the enhancement pattern of pancreatic tissue

Clinical and Radiologic features of various uncommon types and unusual causes of Pancreatitis

Types of pancreatitis	Clinical Features	Imaging Features
Pancreatitis in cystic fibrosis	Exocrine pancreatic insufficiency, full-blown acute pancreatitis rare, pancreatitis may be the 1st manifestation of cystic fibrosis	Fatty replacement of pancreas, calcification (7%), and cyst formation (pancreatic cystosis)
Pancreas divisum with pancreatitis	Seen in young or middle-aged adults with recurrent acute pancreatitis or chronic relapsing pancreatitis with no other underlying cause	MRCP- lack of communication between the dorsal and ventral ducts, independent drainage sites, and a dominant dorsal duct
Uncommon obstructive causes of Pancreatitis	Pancreatic (carcinoma, lymphoma, metastases) or duodenal (adenoma, lipoma); high level of suspicion in elderly patients (weight loss, pain)	Abrupt change in MPD caliber with focal pancreatitis beyond the site of obstruction, Pancreatic atrophy, regional lymphadenopathy, vascular invasion
Ascaris induced pancreatitis	Most common parasitic infection worldwide	Linear filling defect within a dilated biliary radical, pancreatitis, worms rarely seen in MPD

Autoimmune Pancreatitis

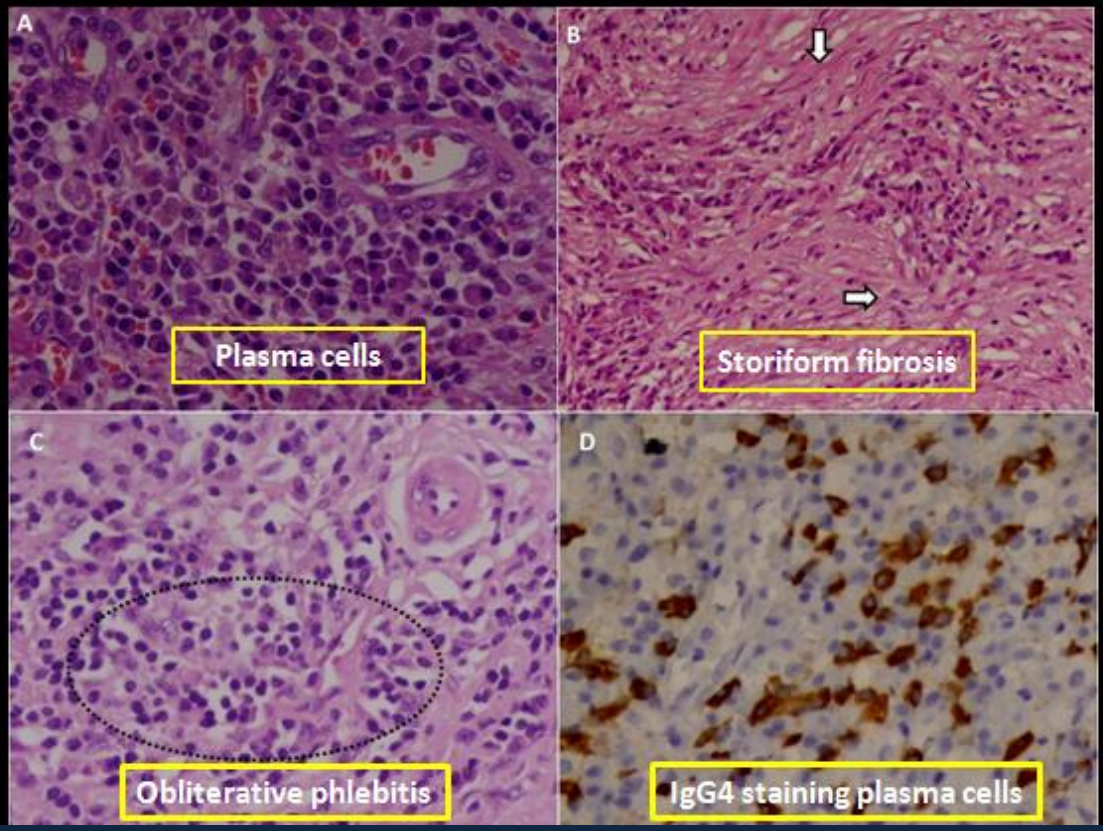
1961 - **Dr Henry Sarles coined the term idiopathic chronic pancreatitis**

1995 - **Yoshida et al concocted the term "Autoimmune Pancreatitis"**

Recently - **notified as *IgG4-related disease***

Various names - sclerosing pancreatitis, tumefactive pancreatitis and non-alcoholic destructive pancreatitis

Autoimmune pancreatitis is a distinct form of pancreatitis characterized clinically by frequent presentation with obstructive jaundice with or without a pancreatic mass, histologically by a lymphoplasmacytic infiltrate and fibrosis and therapeutically by a dramatic response to steroids



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Autoimmune Pancreatitis

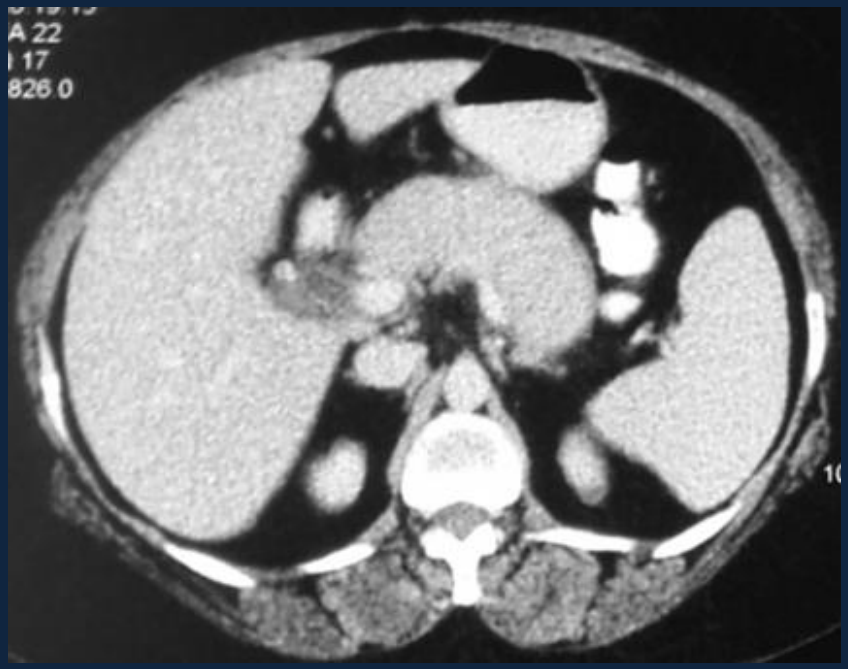
Parenchymal changes

- ✓ Pancreatic enlargement (Diffuse or Focal)
- ✓ Sausage shaped pancreas
- ✓ Halo/capsule/envelope
- ✓ Delayed enhancement
- ✓ Dotted enhancement
- ✓ No stranding, vascular invasion
- ✓ Duct penetrating sign (focal variant)/ Duct enhancement sign
- ✓ MR – Diffusion and ADC

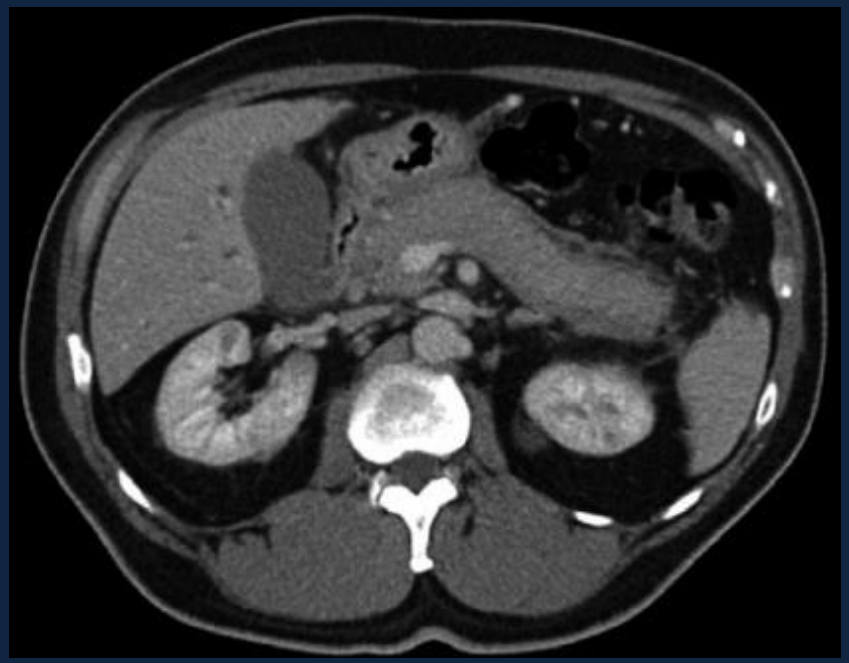
- ✓ *However, there may be scenarios in which **dual pathology** - AIP and ductal adenocarcinoma coexist in a single patient*

Autoimmune Pancreatitis

Parenchymal changes



Sausage shaped pancreas

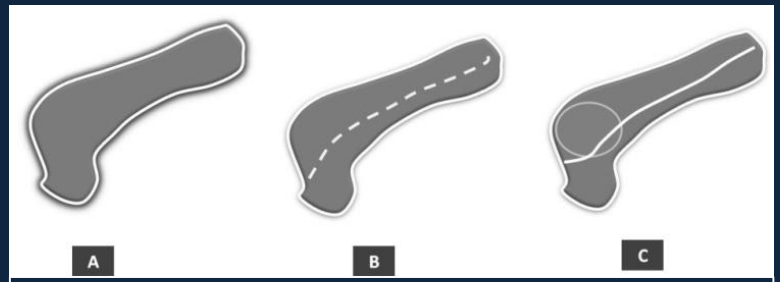


Peripancreatic halo

Autoimmune Pancreatitis

Ductal changes

- ✓ Long (> 1/3 duct length) segment involvement
- ✓ Multifocal strictures/ substenoses in the affected segment without upstream dilatation (< 5mm)
- ✓ Side branches arising from the strictured segment
- ✓ Intrapancreatic CBD narrowing
- ✓ Duct penetrating sign
- ✓ Duct enhancement sign



Pictorial diagram showing various types of autoimmune pancreatitis (**A**) sausage-shaped pancreas with loss of lobulation and peripancreatic halo (**B**) multifocal strictures without upstream dilatation (**C**) mass-forming AIP with a positive duct penetrating sign.

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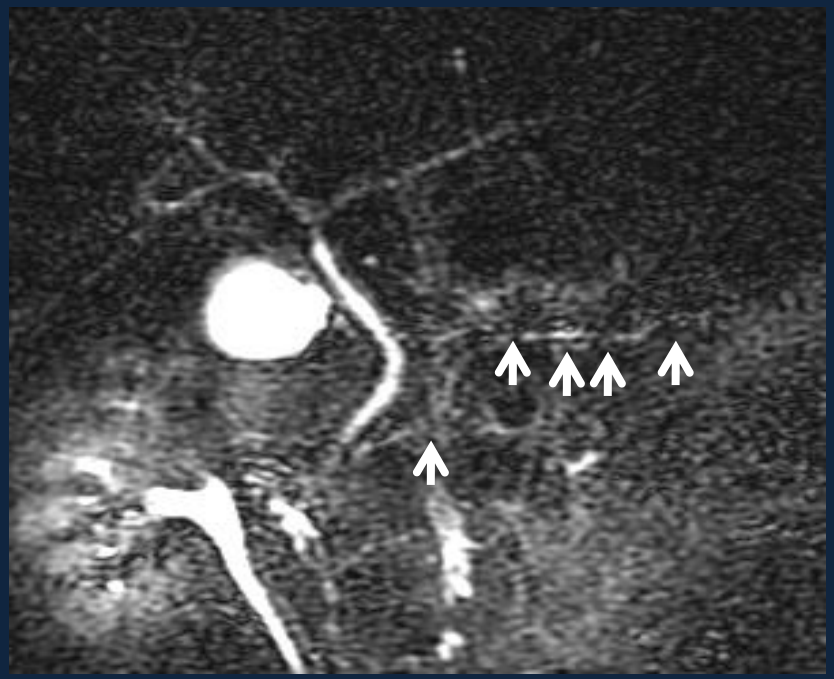
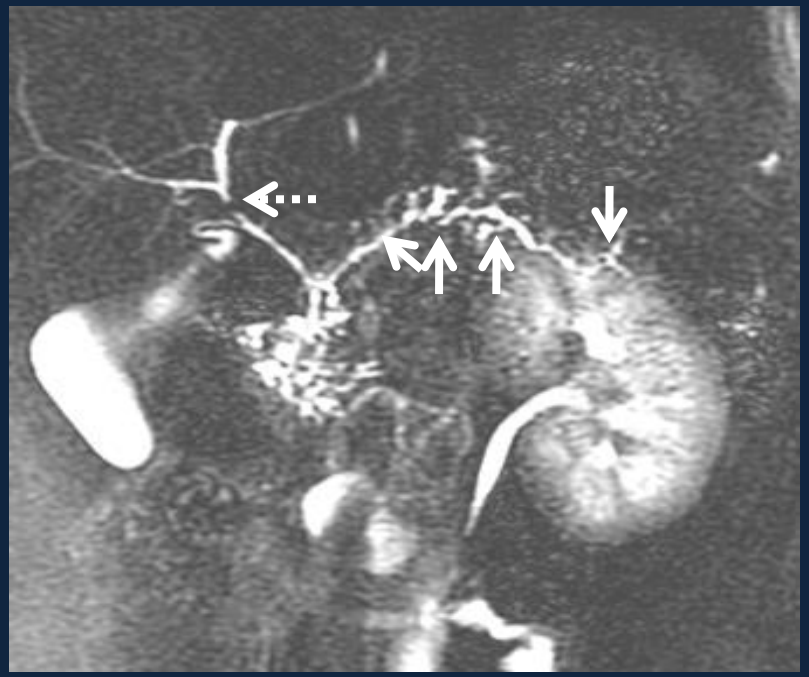
Autoimmune Pancreatitis

Ductal changes



AIP with multifocal strictures: Coronal 2D-MRCP image showing multiple areas of strictures and substenoses (arrows) without upstream dilatation of the main pancreatic duct.



Ductal involvement in AIP: Coronal 2D-MRCP image showing multiple areas of stricture (arrows) and side duct ectasia involving the main pancreatic duct without significant upstream dilatation. Vascular impression seen in the biliary tree at the hilum (dashed arrow).

Focal AIP vs Pancreatic Adenocarcinoma

Imaging Features	Autoimmune Pancreatitis (AIP)	Pancreatic Adenocarcinoma
Proximal gland atrophy	No	Yes
Abrupt MPD Occlusion	No	Yes
Lymphadenopathy	Rare	Common
Occlusion	Rare	Common
Duct penetrating sign	Yes	No
Duct enhancement sign	Yes	Rare
OOI	Common	Rare
MR-Diffusion weighted imaging	ADC values less than 1.075×10^{-3} mm^2/s Uniformity	Usually ADC values more than 1.075×10^{-3} mm^2/s Non-uniformity

Autoimmune Pancreatitis

Type 1 AIP	Type 2 AIP
AIP with IgG4-related LPSP	AIP with GEL; IgG4-unrelated IDCP
Asia > USA, EU	EU > USA > Asia
Old age	Younger age group
Male > Female	Male = Female
High serum IgG, IgG4, Auto Abs (+)	Normal serum IgG, IgG4, Auto Abs (-)
Other organ involvement +	Unrelated with OOI
Ulcerative colitis rare	Associated with ulcerative colitis
Steroid Responsive	Steroid Responsive
High rate of relapse	**Rarely relapses**

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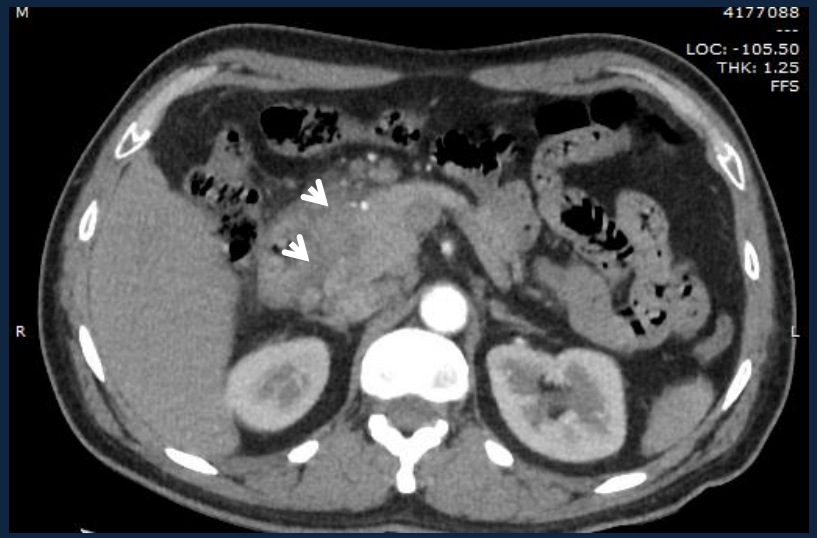
Groove Pancreatitis

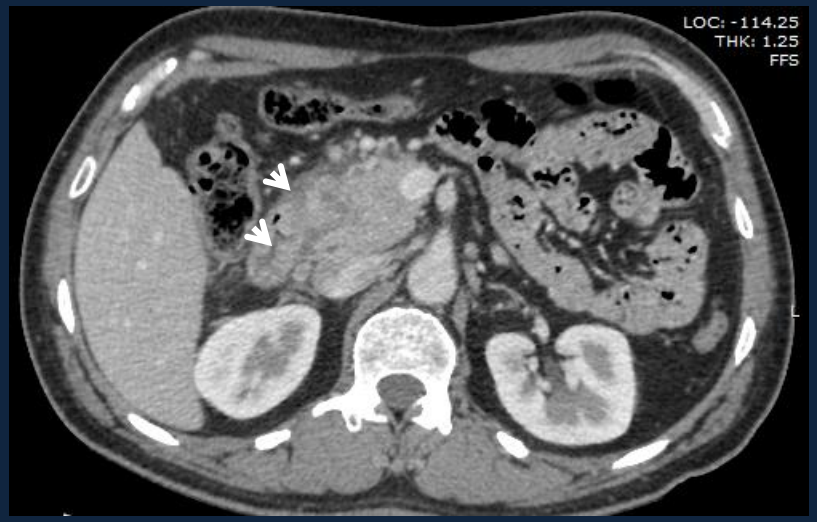
- Sheet-like mass between the head of the pancreas and the duodenal ‘‘C’’ loop. This mass is hypointense on T1-weighted images and hypo- to slightly hyperintense on T2-WI.
- Medial duodenal wall thickening is noted in both the pure and segmental form of PDP.
- T2-weighted hyperintense cysts can develop in the duodenal wall, as well as in the pancreaticoduodenal groove.
- In the segmental form, mass-like enlargement of the pancreatic head obscures the groove and demonstrates T1 hypointensity, mimicking pancreatic adenocarcinoma.
- In both forms, the CBD can appear attenuated or narrowed, although smoothly tapered to the ampulla without shouldering or irregular/abrupt margins; this is best appreciated on the coronal plane or on MRCP images.

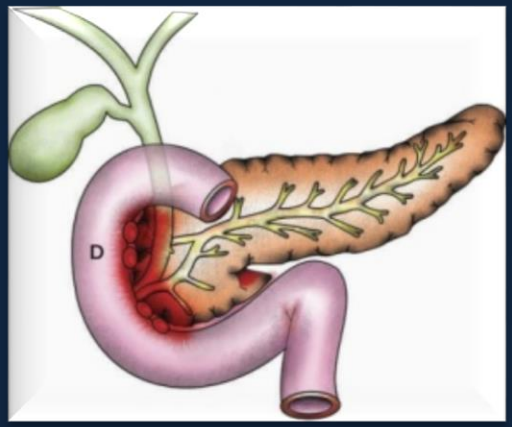
Groove Pancreatitis

- The pancreatic duct can also be narrowed in a smooth and gradual fashion toward the pancreatic head.
- The distance between the ampulla and duodenal lumen is typically widened in cases of PDP and associated with a dilated ***banana-shape gallbladder*** due to narrowing at the ampulla and stricturing of the distal CBD, seen as an ancillary finding in PDP.
- Diffuse retroperitoneal inflammatory changes and fluid surrounding the pancreas, which may extend into the pararenal spaces, commonly seen in acute edematous pancreatitis is rarely seen with PDP
- ***No vascular encasement***
- ***Heterogeneous patchy and delayed enhancement***

Groove Pancreatitis







Groove pancreatitis with cystic dystrophy of the duodenal wall

44-yr-old male, chronic alcoholic: Axial CECT images in pancreatic and hepatic venous phase showing sheet like soft tissue (arrowheads) in the pancreaticoduodenal groove in a case of pure form of paraduodenal pancreatitis.

Tropical Pancreatitis

- Young age at onset, association with malnutrition, regional predisposition in tropical countries
- First described in 1959 in Indonesia. Relatively large number of cases occur in the southern state of Kerala in India
- Etiopathogenesis of tropical pancreatitis - PEM, pancreatic ductal anomalies, food toxicities such as chronic cyanide toxicity from cassava, and possible genetic predisposition (SPINK 1 N34S mutation and CFTR mutation)
- Nearly two-thirds of affected patients develop fibrocalculous pancreatic diabetes within a decade of onset

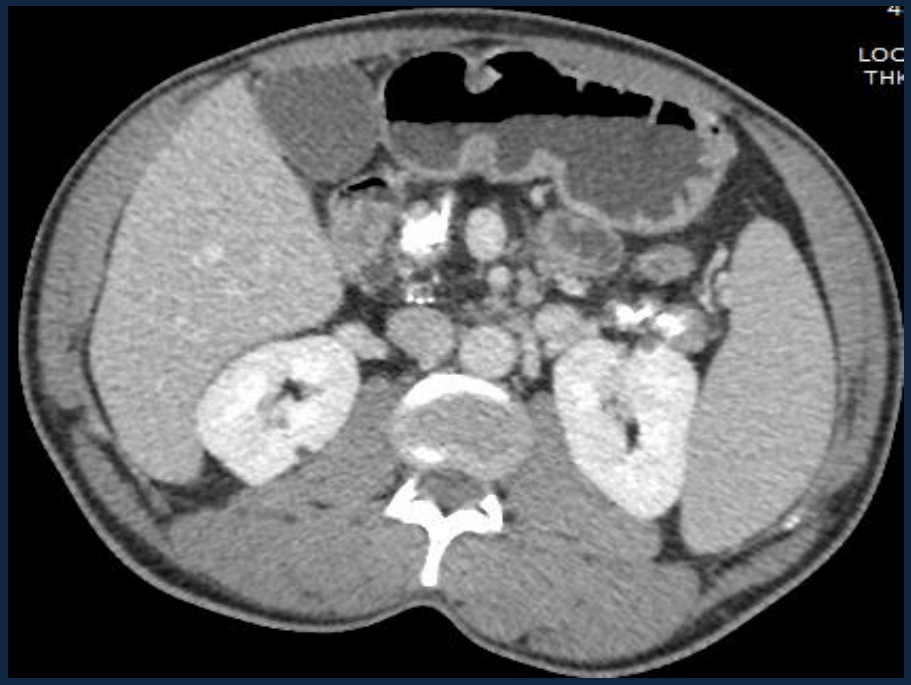
Tropical Pancreatitis

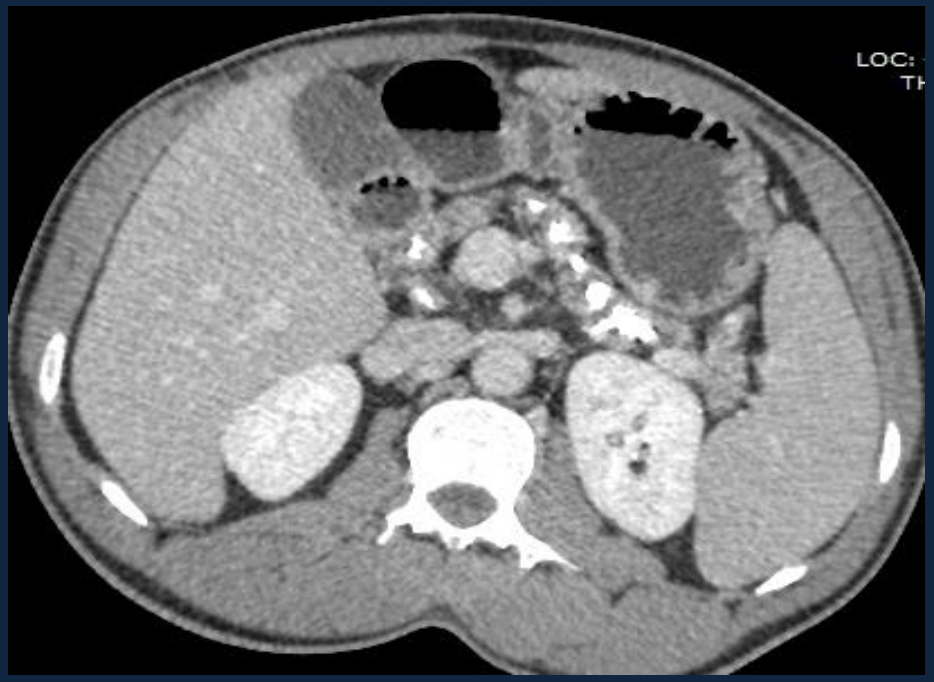
- The characteristic features are absence of association with alcohol consumption, biliary tract disease, and absence of other biochemical or structural predisposing factors for pancreatitis.

- On imaging, multiple large pancreatic calculi within a dilated pancreatic duct is seen. Ductal dilatation and calculi are known to occur in more than 80% of patients, with parenchymal atrophy occurring in nearly 50%. The intraductal calculi in tropical pancreatitis are discrete, dense, and up to 5 cm in size. In contrast, the intraductal calculi in alcohol-related chronic pancreatitis are usually small and speckled.

- Management consists largely of supportive treatment for associated pain, diabetes, and steatorrhea.

Tropical Pancreatitis





36-yr-old male, non - alcoholic: Axial CECT images showing shows a markedly dilated and tortuous MPD with large intraductal stones in a case of *tropical pancreatitis*.

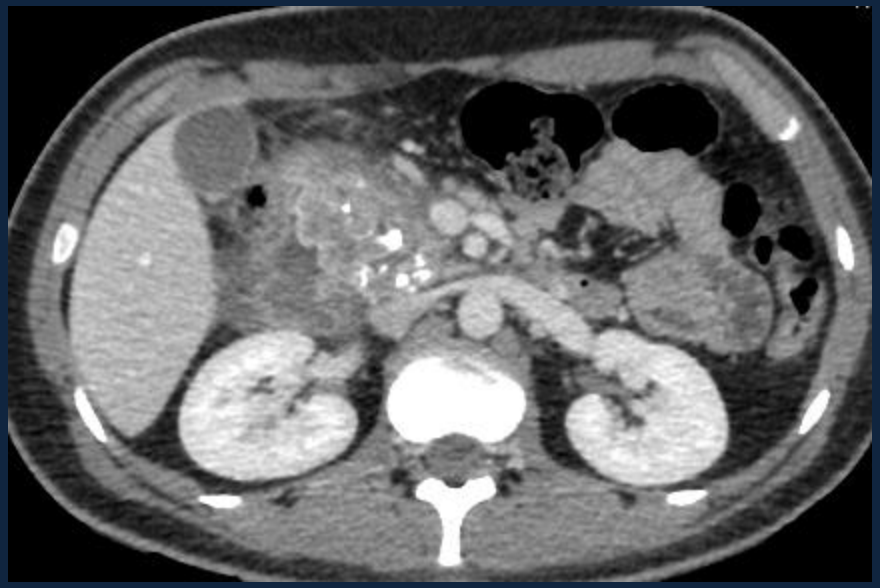
Hereditary Pancreatitis

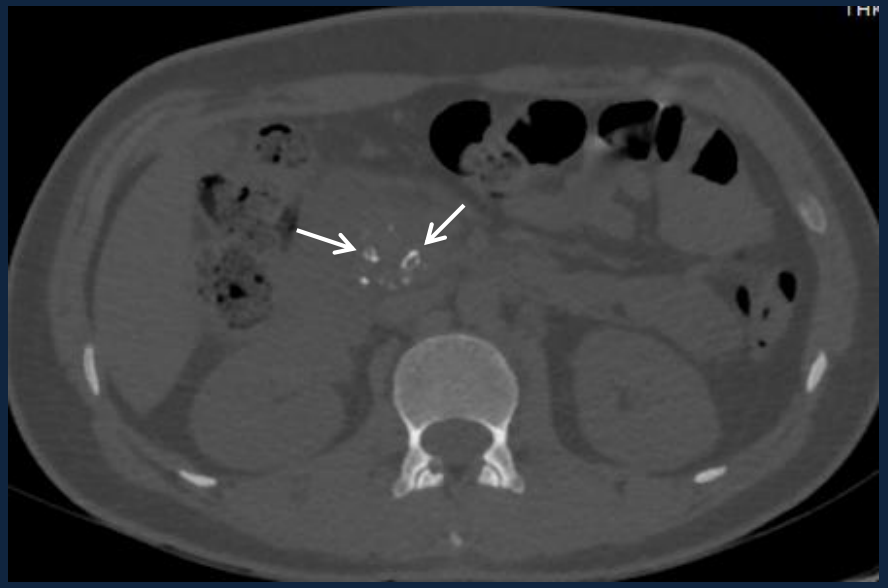
- Autosomal dominant disease involving mutation of the cationic trypsinogen gene
- Less than 1% of cases of recurrent and chronic pancreatitis
- As in tropical pancreatitis, acute attacks usually begin in childhood (5–10 years of age)
- The imaging manifestations of hereditary pancreatitis often resemble those of tropical pancreatitis. Chronic variety is characterized by significant pancreatic atrophy, pancreatic calcifications, and calculi
- Hereditary pancreatitis should be suspected in any patient who has suffered at least two attacks of acute pancreatitis for which there is no explanation (absence of anatomic anomalies, ampullary or MPD strictures, trauma, viral infection, gallstones, alcohol consumption, drug use, or hyperlipidemia).

Hereditary Pancreatitis

- The diagnosis may also be considered in patients with unexplained (idiopathic) chronic pancreatitis, patients with a family history of pancreatitis in a first- or second-degree relative, and children with an unexplained episode of pancreatitis that required hospitalization.
- Typically shows *" bull's-eye calcification"* with non-calcified central core better appreciated in bone window settings
- Mutations of various genes like PRSS1 and CFTR have been demonstrated.
- Hereditary pancreatitis carries a 50- to 70-fold increased risk of pancreatic cancer.

Hereditary Pancreatitis





19-yr-old male case of cystic fibrosis: Axial CECT images showing calcifications in pancreatic parenchyma with non-calcified central core giving *bull's eye configuration* (arrows)

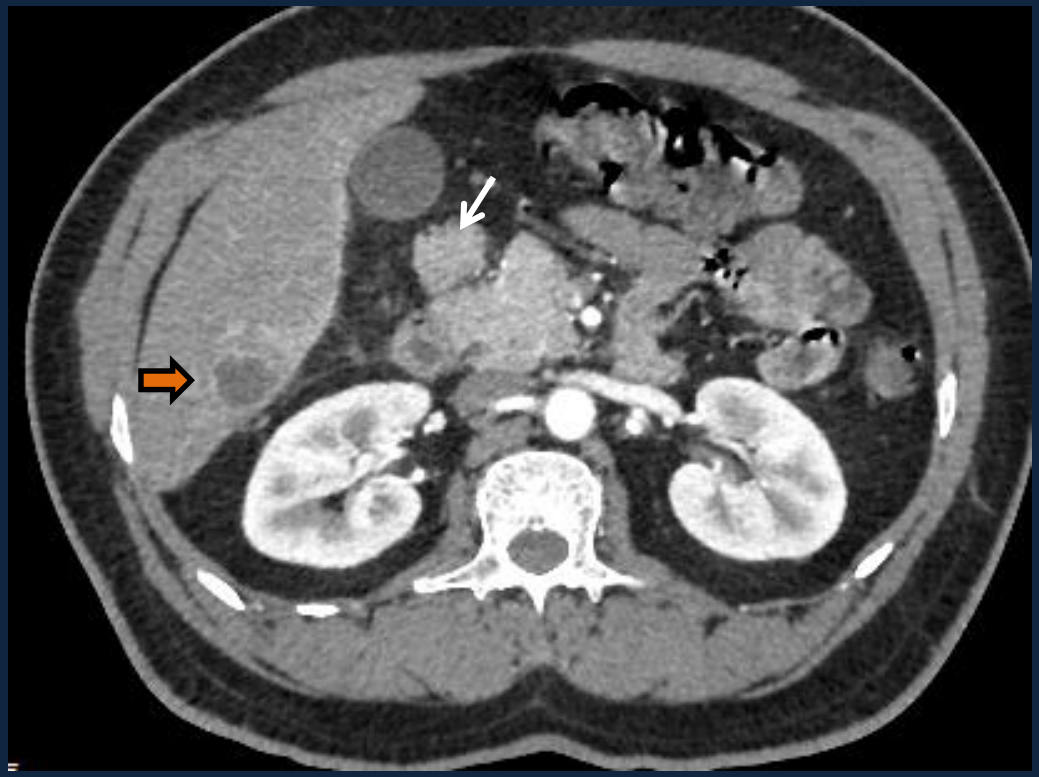
Pancreatitis in ectopic/heterotopic pancreatic tissue

- Heterotopic pancreas is defined as the presence of abnormally located pancreatic tissue with its own ductal system, with no vascular, neural, or anatomic contact with the normal pancreas.
- The most common locations for heterotopic pancreatic tissue include the duodenum (28% of cases), stomach (26%), and jejunum (16%).
- The majority of patients are asymptomatic at clinical examination, with the lesions being incidentally detected at surgery or autopsy.
- Common clinical manifestations include abdominal pain similar to that from peptic ulcer disease (77%), abdominal fullness (30%), and malena (24%).

Pancreatitis in ectopic/heterotopic pancreatic tissue

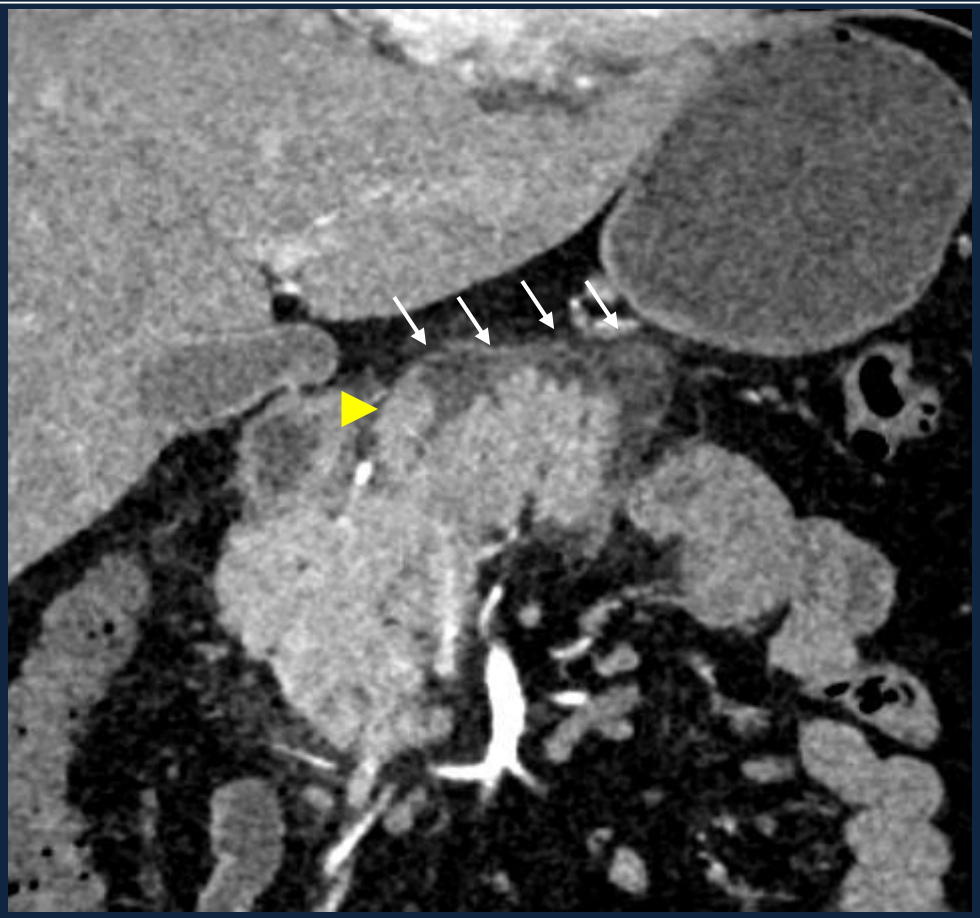
- Barium swallow upper gastrointestinal study demonstrates nonspecific fold thickening with the characteristic appearance of a centrally umbilicated nodule.
- CT may reveal nonspecific extrapancreatic inflammatory changes in relation to the gastric or intestinal wall with mural thickening. CT may also demonstrate oval or round masses in the gastric wall with an enhancement pattern similar to that of pancreatic tissue
- Cystic dystrophy of the duodenal wall is also associated with heterotopic pancreatic tissue in the duodenum
- MRCP may depict the presence of ducts within this tissue, a finding that is pathognomonic for heterotopic pancreas

Pancreatitis in ectopic/heterotopic pancreatic tissue



45-yr-old-male: Axial CECT image showing *ectopic pancreatic tissue* (arrow) with enhancement similar to main pancreatic parenchyma. Incidental note is made of small abscess (yellow arrow) in the liver.

Pancreatitis in ectopic/heterotopic pancreatic tissue



21-yr-old-male presented to emergency with pain abdomen: Coronal CECT image showing changes of acute pancreatitis with peripancreatic fluid and stranding (arrows). The cause of pancreatitis in this case is *ectopic pancreatic tissue* (arrowhead).

Pancreatitis in Cystic Fibrosis

- Autosomal recessive inherited disease secondary to mutation of a gene-encoding chloride channel, resulting in impaired chloride transport through the epithelial cells of exocrine glands.

- Gastrointestinal manifestations often precede the pulmonary manifestations. C/F: failure to thrive, steatorrhea, fat intolerance, abdominal pain, bloating, and flatulence

- Obstruction of the ducts caused by inspissated secretions is the primary event, resulting in an initial mild inflammatory reaction followed by progressive fibrosis, fatty change, calcification, and cyst formation.

- In 90% of cases, Fatty replacement with or without pancreatic glandular atrophy is the most common finding at CT

Pancreatitis in Cystic Fibrosis

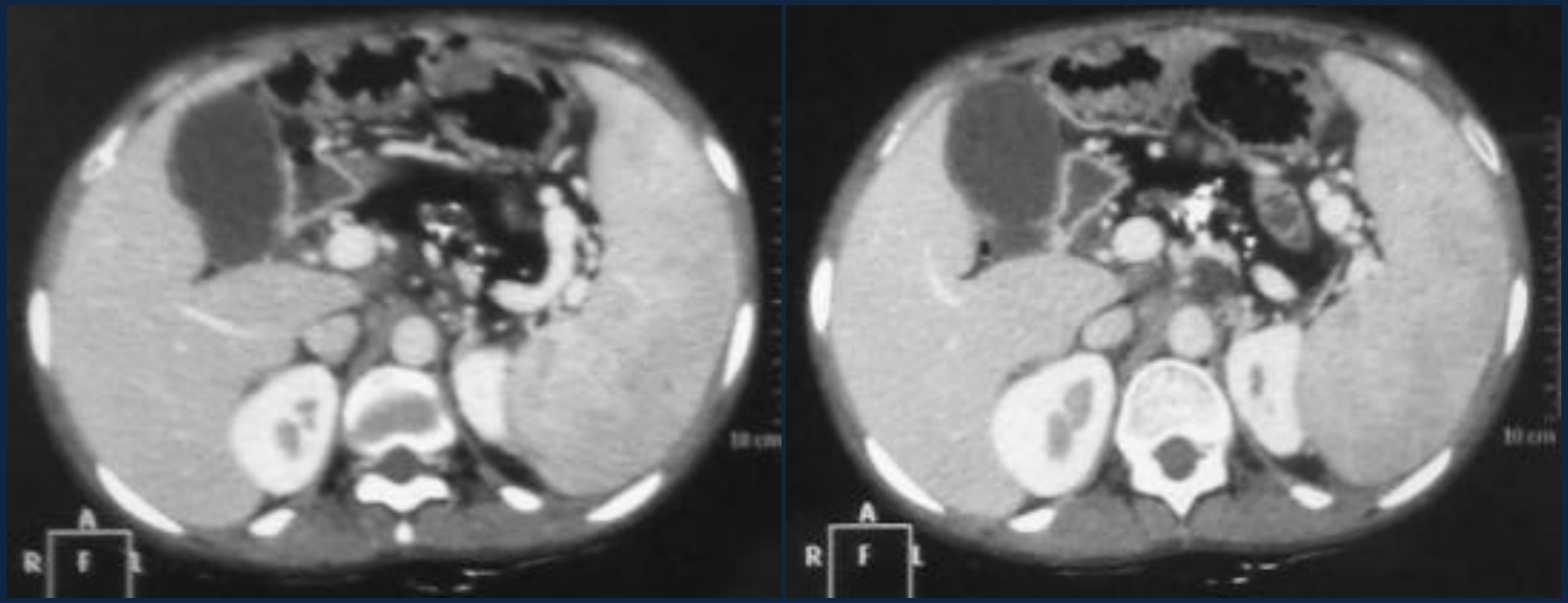
- Other CT findings include calcification (7%); cyst formation; strictures, beading, dilatation, and obstruction of MPD

- The peripancreatic inflammation and fluid collections seen in typical acute pancreatitis are rare. Pancreatic cystosis is a rare manifestation of cystic fibrosis.

- The differential diagnosis for fatty replacement with atrophy of the pancreas is obesity, severe malnutrition, aging, Cushing syndrome, steroid therapy, Shwachman-Diamond syndrome, hemochromatosis, and viral infections.

- Constellation of clinical and radiologic manifestations with foci of fat, calcification, and inflammatory changes around the pancreas helps establish the diagnosis of acute pancreatitis in cystic fibrosis.

Pancreatitis in Cystic Fibrosis



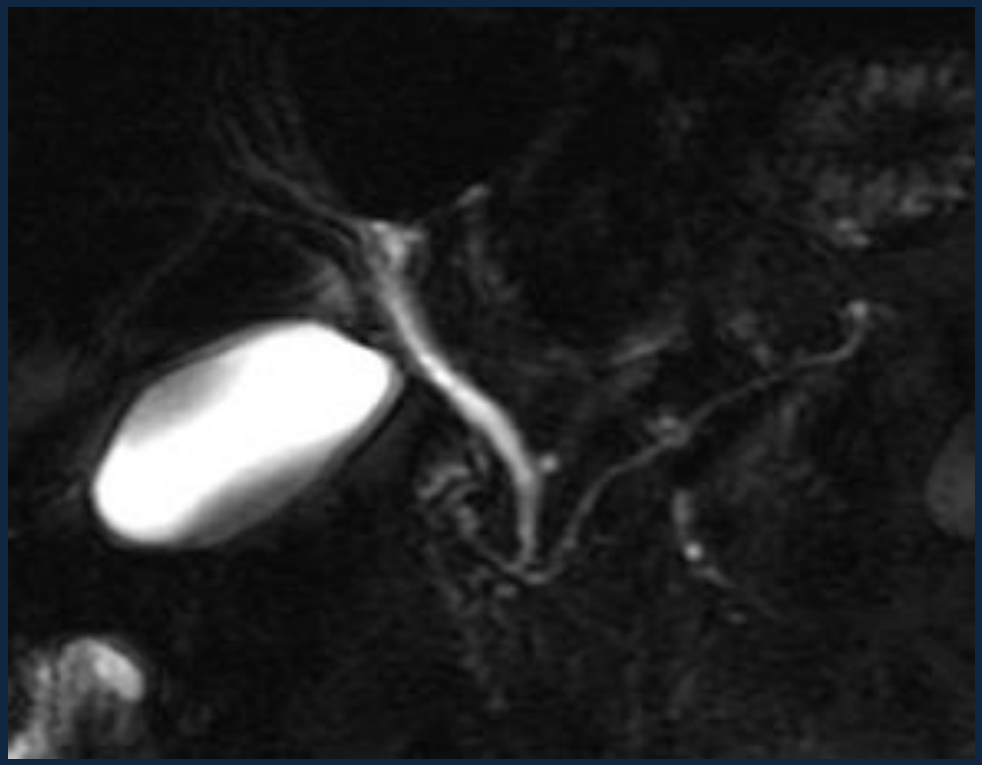
20-yr-old female: Axial CECT images showing *fatty replacement of pancreas* with intraductal calculi in a known case of cystic fibrosis

Congenital pancreatic anomalies associated with Pancreatitis

Pancreas Divisum:

- This condition results from the failure of fusion of the ventral and dorsal pancreatic anlagen. Pancreas divisum occurs in 4%–10% of the population and has been reported in 12%–50% of cases of so-called idiopathic acute pancreatitis in children.
- Pancreas divisum should be suspected in young or middle-aged adults who present with recurrent acute pancreatitis or chronic relapsing pancreatitis with no other obvious cause such as gallstones or alcohol consumption.
- Pathophysiologically, a relative obstruction to the flow of pancreatic juice is generated because the majority of the gland empties through the dorsal duct (duct of Santorini) into the minor papilla, which is small.
- MRCP has a very high sensitivity and specificity in demonstrating normal ductal anatomy and anomalies.
- Visualization of the MPD (dorsal duct) coursing anterior to the CBD before draining into the duodenum is also a valuable sign in pancreas divisum.

Congenital pancreatic anomalies associated with Pancreatitis



68-yr-old-male: 2D-MRCP image depicting dorsal pancreatic duct crossing anterior to CBD s/o *pancreas divisum* and secondary changes of chronic pancreatitis in the form of dilated side-duct branches

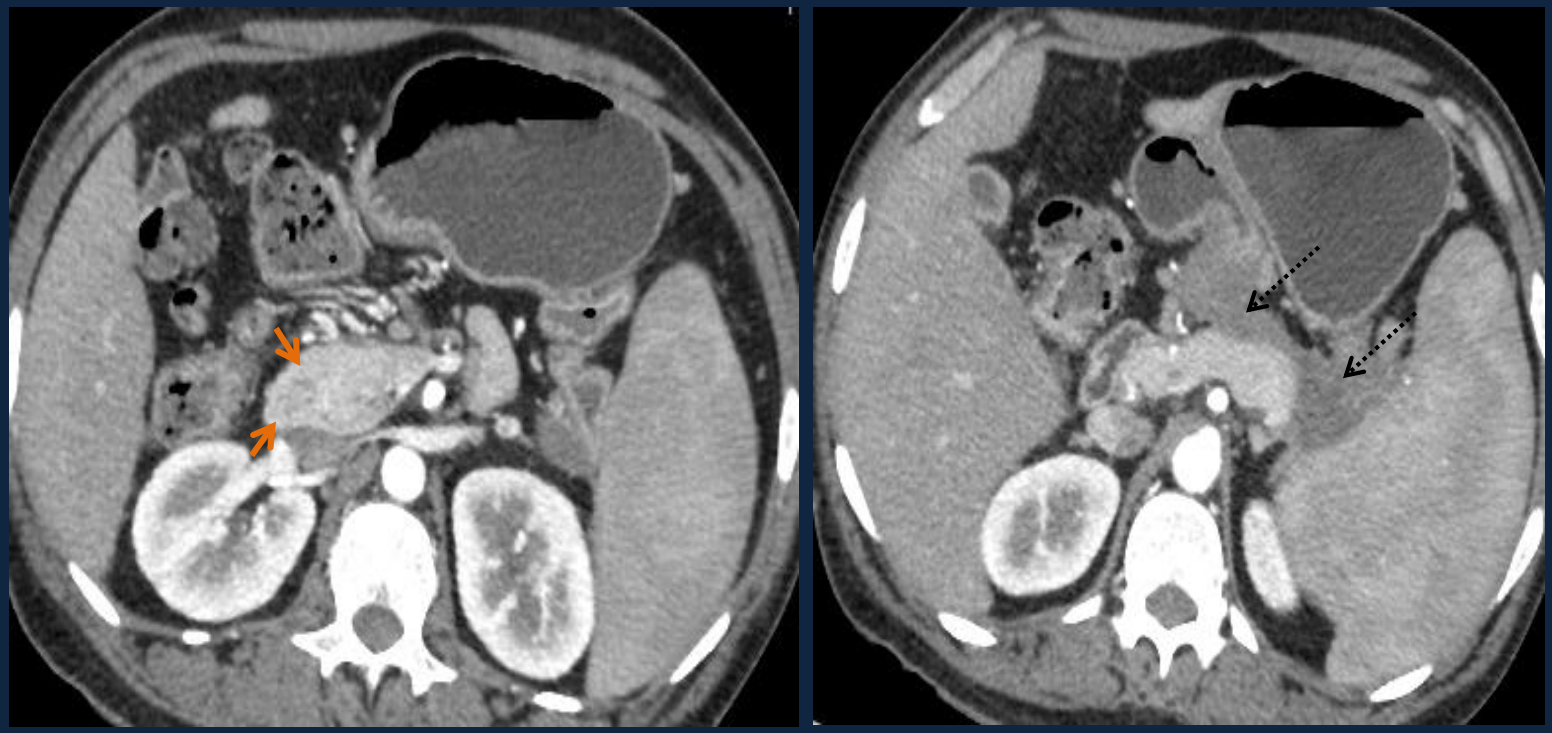
Congenital pancreatic anomalies associated with Pancreatitis

Annular pancreas:

- Ring of pancreatic tissue surrounds the second part of duodenum.
- On imaging, the diagnosis is established with visualization of the annular pancreatic parenchymal tissue and the duct encircling the second part of the duodenum. MR imaging, especially with T1 weighting, is useful in depicting the anatomy.

- MRCP of an aberrant pancreatic duct encircling the duodenum are corroboratory.

Congenital pancreatic anomalies associated with Pancreatitis



25-yr-old-male: Axial CECT images showing pancreatic tissue encircling the second part of duodenum (arrowheads) in keeping with *annular pancreas* with peripancreatic fluid in tail region (dashed arrows) s/o pancreatitis

Uncommon obstructive causes of Pancreatitis

Both primary pancreatic tumors and duodenal lesions obstructing the ampulla can rarely manifest as either acute or recurrent acute pancreatitis.

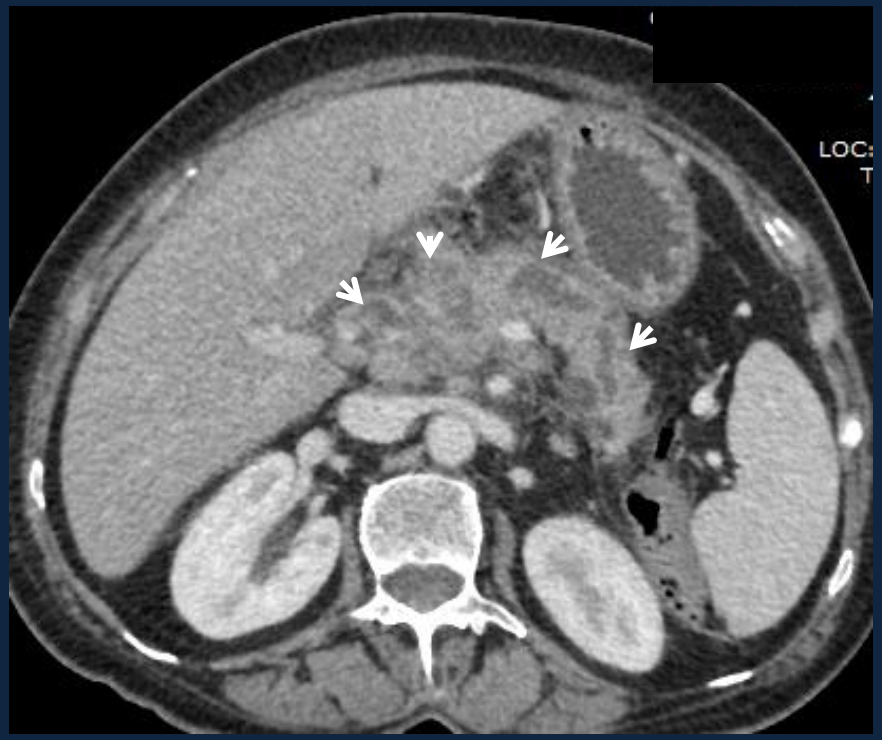
Pancreatic cancer:

- Pancreatitis due to pancreatic tumors such as adenocarcinoma, lymphoma, and metastases has been reported but is rare.
- On imaging, the findings that are useful in accurately identifying an underlying malignancy include significant dilatation of the pancreatic duct with acute pancreatitis, disproportion between the size of the pancreatic head and that of the pancreatic body (the head being substantially bulkier than the body and tail), peripancreatic and upper abdominal lymphadenopathy, distant metastases, and vascular invasion.

Duodenal Adenoma:

- Duodenal villous adenoma, the most common of these lesions, is a rare, benign epithelial lesion representing 1% of all duodenal tumors.
- Villous adenomas commonly occur around the ampulla of Vater, although they may be located anywhere within the duodenum.
- Endoscopic US is very sensitive in detecting small tumors in the ampullary-
- periampullary region. MRCP may demonstrate a mass in the ampullary region with the characteristic “double duct sign” that is common to all periampullary lesions, a finding that is helpful in making the diagnosis.

Uncommon obstructive causes of Pancreatitis



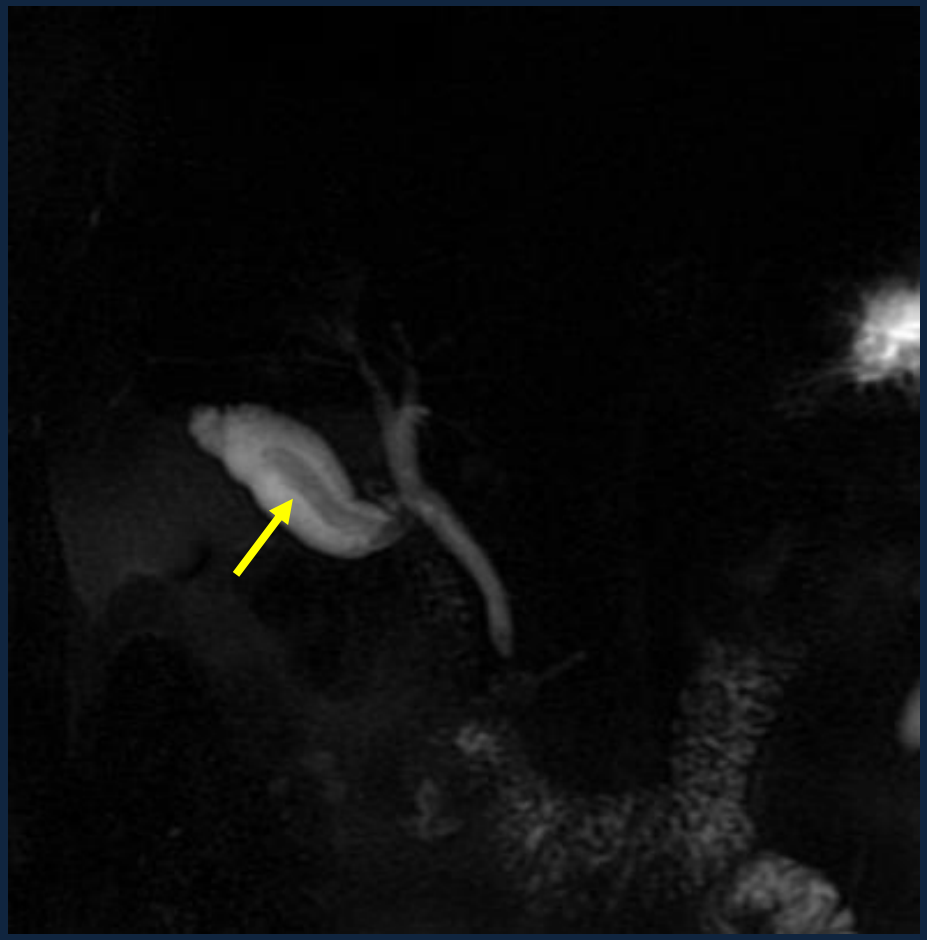
68-yr-old-female presenting with acute abdominal pain and raised serum lipase , CA 19.9 levels: Axial CECT image showing bulky pancreas with non-enhancing areas within suggestive of necrosis, mild prominence of MPD with significant peripancreatic stranding in a case of acute necrotizing pancreatitis.

On follow up scans, the findings did not show significant resolution so the patient underwent EUS-FNAC. Histology findings revealed *pancreatic adenocarcinoma in the background of pancreatitis.*

Ascaris - induced Pancreatitis

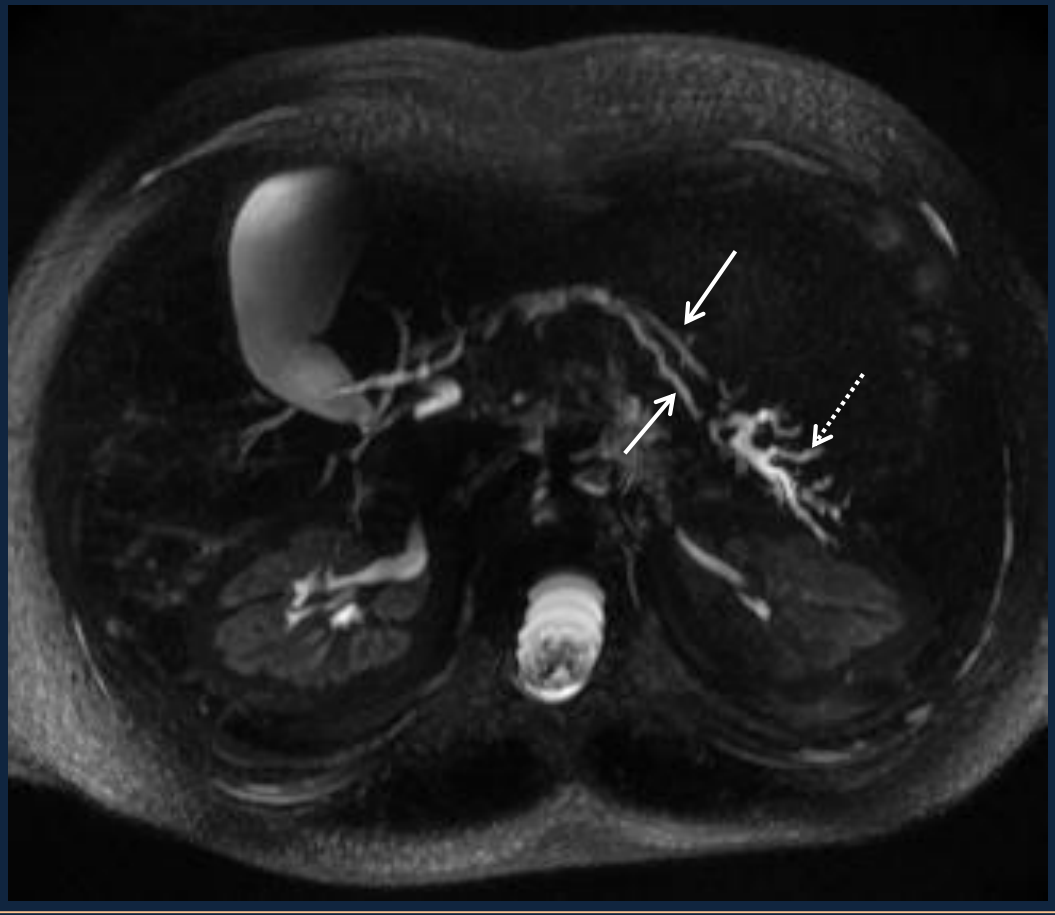
- Ascariasis is the most common parasitic infection worldwide, affecting an estimated 1 billion people.
- Biliary-pancreatic ascariasis most commonly affects adult women (male-to-female ratio, 1:3), with a mean age at presentation of 35–42 years.
- On rare occasions, the worm may enter the MPD, resulting in severe pancreatitis. *Ascaris*-induced pancreatitis is usually mild but can be fatal in rare instances.
- MRCP reveals a linear hypointense filling defect within the gallbladder or dilated biliary radical, a finding that, when associated with acute pancreatitis, is diagnostic for *Ascaris*-induced pancreatitis.

Ascaris - induced Pancreatitis



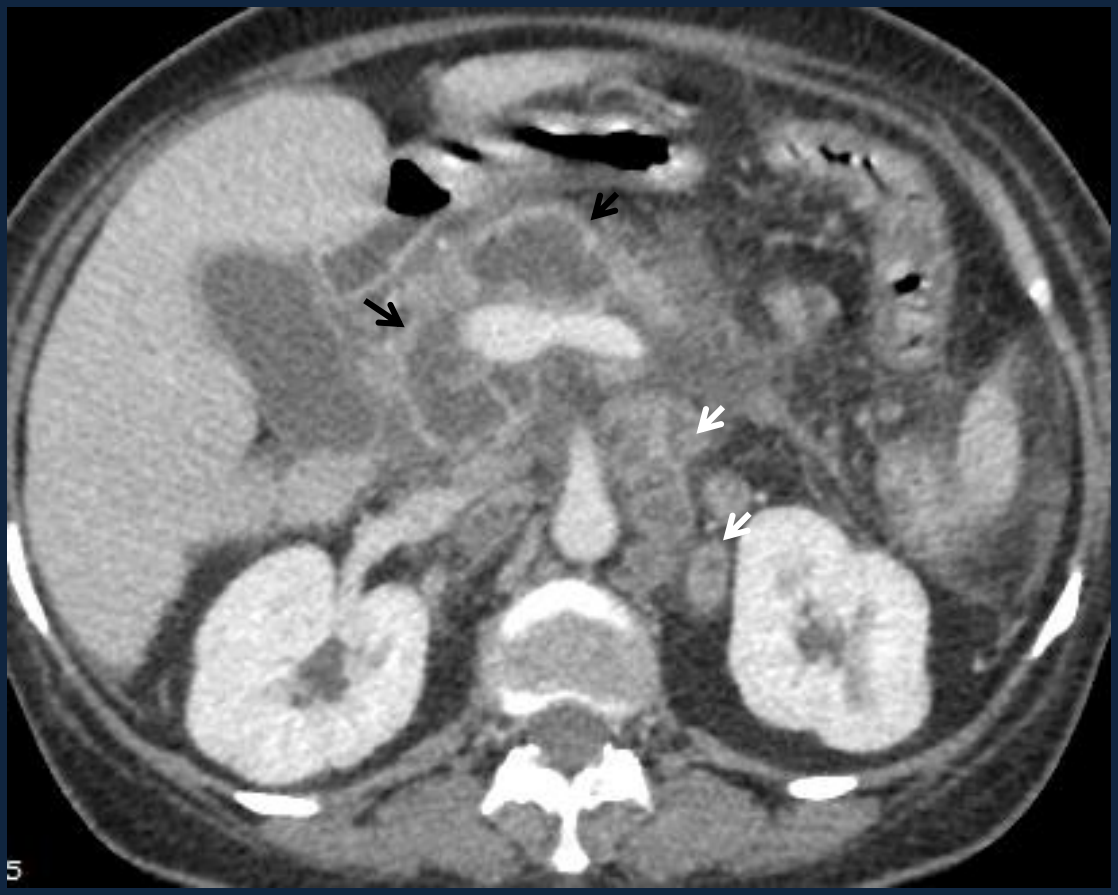
40-yr-old-male: 2D-MRCP image depicting linear hypointense filling defect in the *gallbladder lumen s/o ascariasis (arrow)* within the gallbladder with changes of mild pancreatitis in the form of prominent side-duct branches in uncinate region of pancreas

Few more unusual causes of Pancreatitis



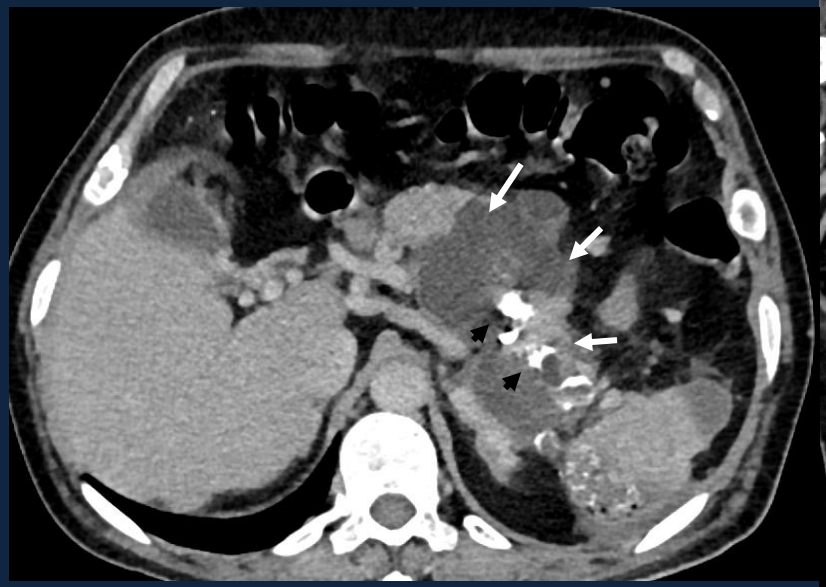
15-yr-old-female: Axial 3D-MRCP image depicting *bifid pancreatic duct* in body region of pancreas (arrows) with changes of moderate to severe pancreatitis in the tail region (dashed arrow) in the form of dilated side-duct branches

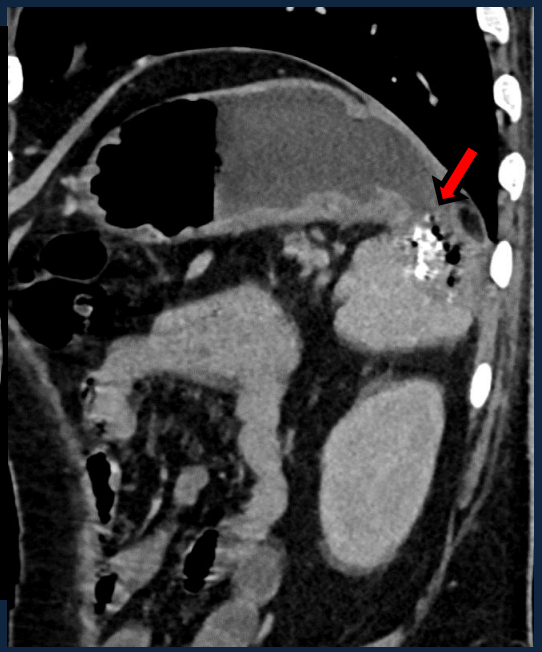
Few more unusual causes of Pancreatitis

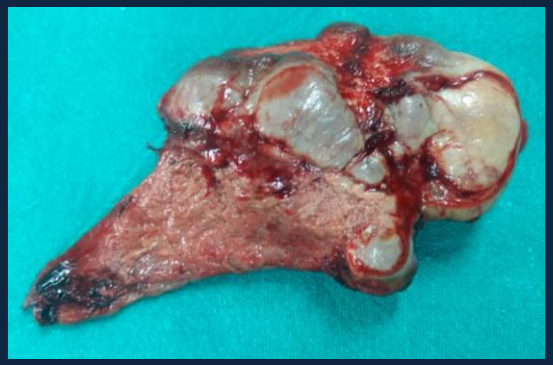


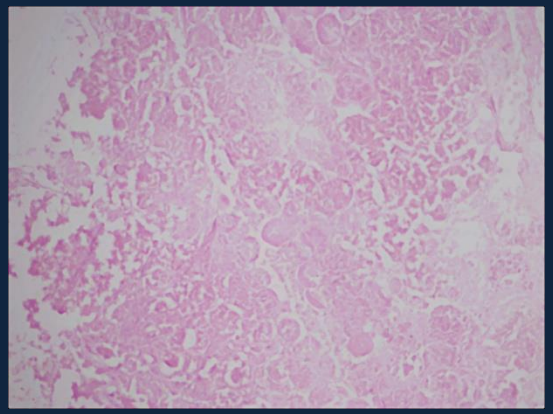
55-yr-old-female: Axial CECT image showing changes of necrotizing pancreatitis with intrapancreatic abscesses (black arrows) with necrotic retroperitoneal lymph nodes (white arrows) in a case of *pancreatic tuberculosis*

Gastro-splenic fistula resulting into Pancreatitis









47-year-old-male with past history of glue embolization of splenic artery aneurysms presenting with fever, vomiting and pain abdomen: Axial CECT image showing changes of necrotizing pancreatitis (white arrows) with hyperdense glue material (arrowheads) in pancreatic bed. Sagittal reformatted image showing gastro-splenic fistula (red arrow) and hypoattenuating collection with glue particles in the splenic parenchyma. Post-operative specimen of the patient. HPE slide showing necrotic pancreatic tissue.

Conclusion

- A variety of uncommon types and causes of pancreatitis have characteristic imaging features.
- For some of these entities, imaging findings may serve as the only clue to diagnosis.
- Therefore, despite the rarity of these entities, familiarity with their clinical and radiologic manifestations helps the radiologist in formulating an accurate differential diagnosis and allows him or her to exclude ominous pancreatic malignancy, thereby facilitating appropriate management in a timely fashion.

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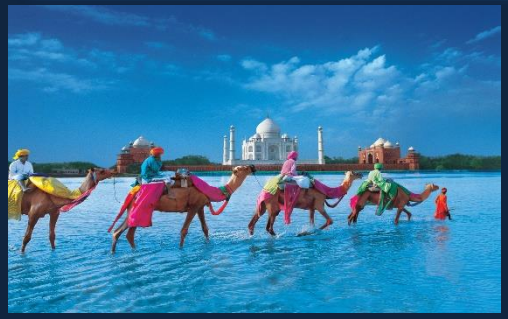

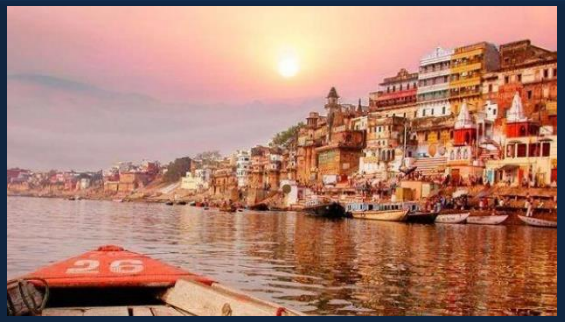

References:

1. Shanbhogue et al. Radiographics 2009
2. Sharma et al. Pancreapedia 2015 (online)
3. Sureka et al. PJR 2016
4. Graziani et al. JOP. 2005