How to stop syndromes slipping through your net?

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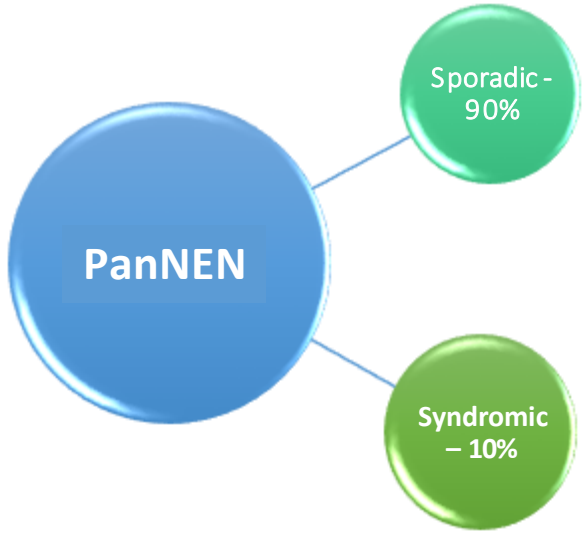
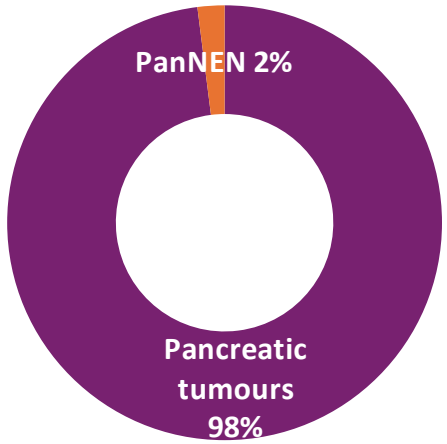
PANCREATIC NEUROENDOCRINE NEOPLASMS (PanNEN)



Learning objectives:

1. Know which genetic syndromes predispose to developing pancreatic neuroendocrine neoplasms (PanNEN).
2. Understand the key differences between the syndromic and sporadic PanNEN.
3. Understand the natural history and behaviour of PanNENs in these syndromes.

PanNEN comprise of **2%** of all clinically detected pancreatic tumours (10% in autopsy studies).



PanNEN predisposition syndromes:

- Multiple Endocrine Neoplasia –type 1
- Von-Hippel-Lindau Disease
- Neurofibromatosis Type 1
- Tuberous sclerosis
- Mahvash Disease
- Multiple Endocrine Neoplasia- 4
- Insulinomatosis

When to suspect PanNEN on imaging?

- ❖ Clinical history / biochemical features concerning for hormone excess.
- ❖ Arterially hyperenhancing pancreatic lesion/s on contrast enhanced CT / MRI / US.
- ❖ Cystic PanNEN – cyst with enhancing rim.
- ❖ Relative lack of pancreatic ductal dilatation.
- ❖ Hypervascular peripancreatic lymph nodes or liver lesions (metastatic PanNEN).

- ❑ Like most pancreatic lesions, PanNEN are typically hypoechoic on US, hypodense on unenhanced CT , hypointense on T1 and iso-hyper intense on T2. Calcifications may be present.
- ❑ Smaller lesions are homogeneous and well defined.
- ❑ Larger lesions can show heterogeneity with cystic changes.
- ❑ Malignant lesions show local invasion (but less vascular invasion and duct dilatation compared to PDAC) and metastases.

When to suspect syndromic PanNEN?

Clinical features:

- History of known PanNEN predisposing syndrome!!!☺
- Family history of PanNEN predisposing syndromes.
- Younger age at presentation (<50)
- Past history of other PanNEN.

Pancreatic findings:

- Multiplicity of lesions in the pancreas.
- Associated pancreatic cysts and serous cystic neoplasms.

Extra-pancreatic abdominal manifestations of associated syndromes:

- Gut neuroendocrine tumours.
- Adrenals: phaeochromocytoma, paraganglioma, adrenal cortical tumours
- GIST anywhere along the GI tract
- Kidneys: cysts, RCC, AML, nephrolithiasis / medullary calcifications
- Liver: cysts, AML, metastases
- Cutaneous neurofibroma, plexiform neurofibroma.

Clinical presentation

TYPE OF PanNEN	CAUSE	CLINICAL FEATURES
Nonfunctioning PanNEN (70%)	Local mass effect. Advanced / metastic neuroendocrine neoplasm	*Usually, asymptomatic*. In cases of advanced disease, they can cause unspecific tumor-associated symptoms such as abdominal or back pain, jaundice, or weight loss.
Functioning PanNEN (30%)	Hormone overproduction	
• Insulinoma	Insulin	Hypoglycemia (headache, diplopia, confusion, dizziness, abnormal behavior, amnesia, rarely seizures and coma) and symptoms resulting from the counter-regulation of the autonomic nervous system (sweating, weakness, hunger, tremor, anxiety, and palpitations). Weight gain. *Whipple triad* - hypoglycemia, plasma glucose level <40mg/dL, and relief of symptoms with administration of glucose.
• Gastrinoma	Gastrin	Abdominal pain, severe peptic disease (peptic ulcerations +/- bleeding), gastroesophageal reflux disease, and diarrhea (*Zollinger-Ellison syndrome (ZES)*.
• Glucagonoma	Glucagon	Dermatitis / necrotising migratory erythema, diabetes mellitus, deep vein thrombosis, depression *(4D syndrome)*
• VIPoma	Vasoactive Intestinal Polypeptide	*Verner–Morrison syndrome,* also called pancreatic cholera or WDHA syndrome (watery diarrhea, hypokalemia, and achlorhydria)
• Somatostatinoma	Somatostatin	*Inhibitory syndrome*, a triad of mild diabetes mellitus, cholelithiasis, and diarrhoea/steatorrhoea.

PanNEN in Multiple Endocrine Neoplasia - 1

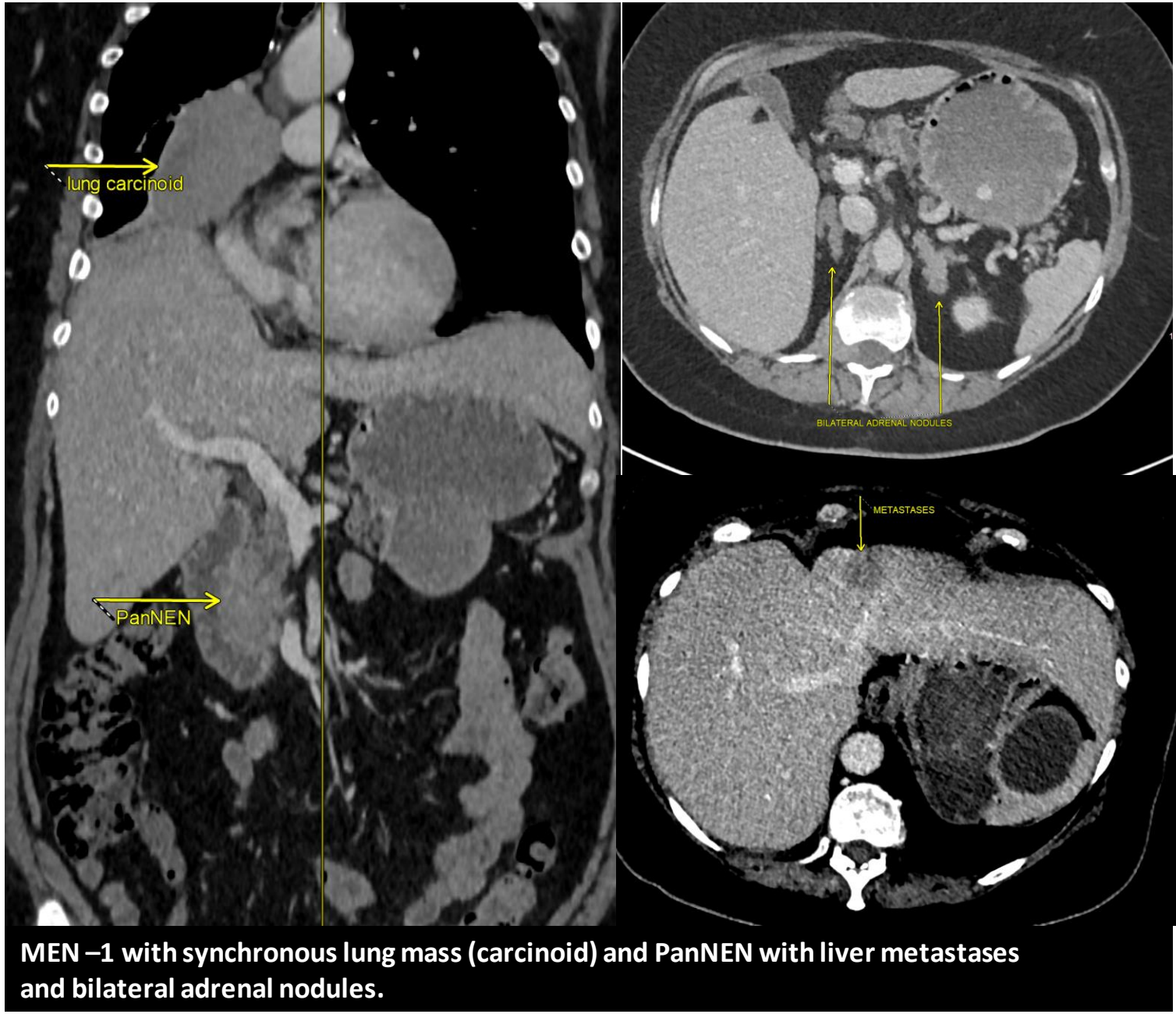
- **40–80%** of patients with MEN 1 will have a PanNEN. Nonfunctioning tumours are the most common subtype, followed by gastrinoma (40%) and insulinoma (10-30%).
- **Gastrinoma and MEN-1:** Present with Zollinger-Ellison Syndrome. 60% of patients with ZES are found to have MEN 1. ZES in MEN-1 present at an *earlier age* (mean 32–35 years). *Better prognosis* of ZES in MEN-1 than sporadic gastrinoma with higher 5-year survival (93% v/s 68%). Gastrinomas in both sporadic cases and in patients with MEN 1 are most commonly located in the duodenum followed by head of pancreas (Gastrinoma triangle). As with sporadic cases, gastrinomas are highly malignant (90%).
- **Insulinomas and MEN-1:** Occur in *younger age* (<20yrs) compared to sporadic cases (>40yrs). Metastases are reported in up to 50% of patients with MEN1-associated insulinomas, but less than 10% of non-MEN1 insulinomas.
- **Glucagonomas and MEN-1:** 5–17% of glucagonomas occur in patients with MEN 1 (rare PanNEN otherwise with majority being sporadic). Typically, large tumors, > 5.0 cm. Metastasis to liver, lymph nodes, bone, and lung frequent.

Other abdominal manifestations of MEN-1:

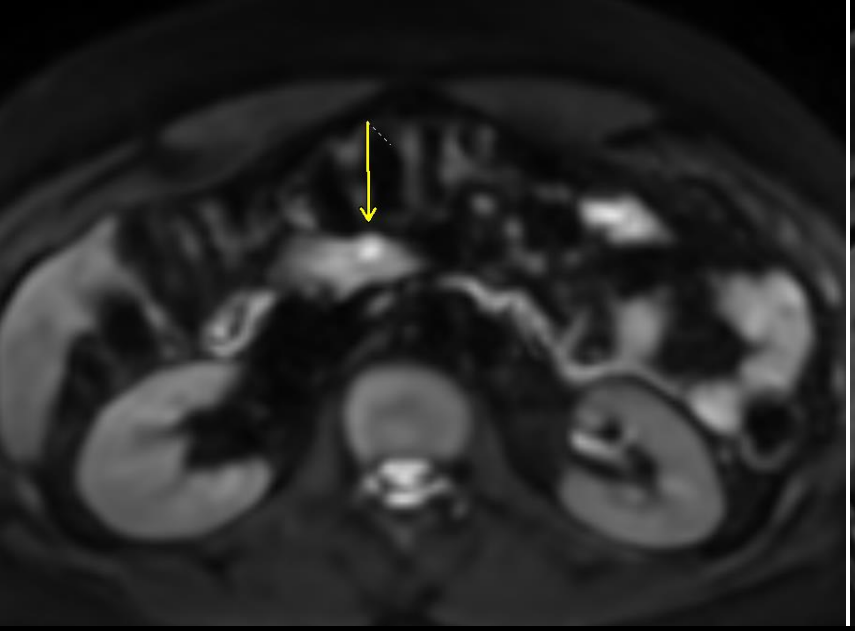
- Gastrointestinal neuroendocrine tumours (also bronchial and thymic carcinoids)
- Adrenal tumours : 20% to 73%. Higher risk of adrenal cortical carcinoma in lesions >1cm (than in general population). Higher association with hyperaldosteronism.

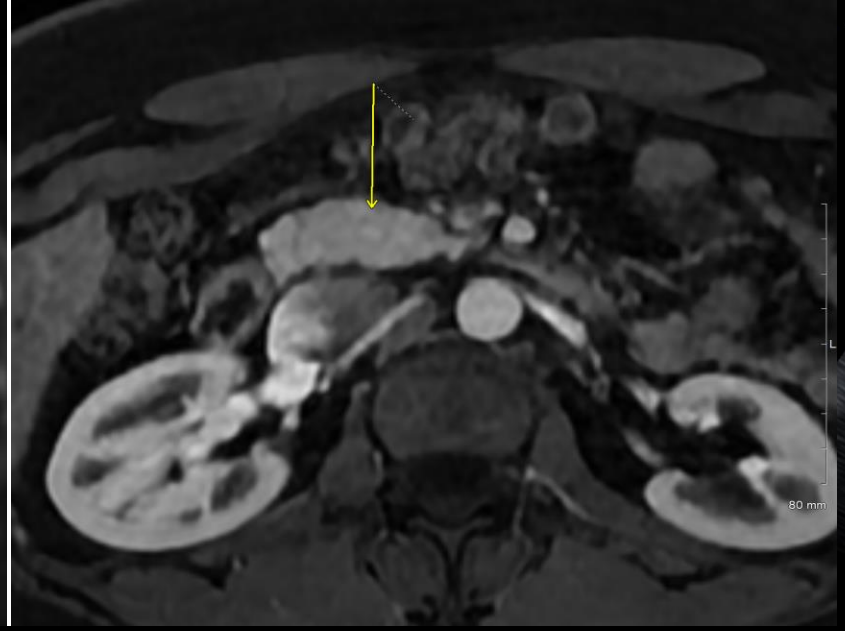
IMPACT OF PanNEN IN MEN-1 PATIENTS:

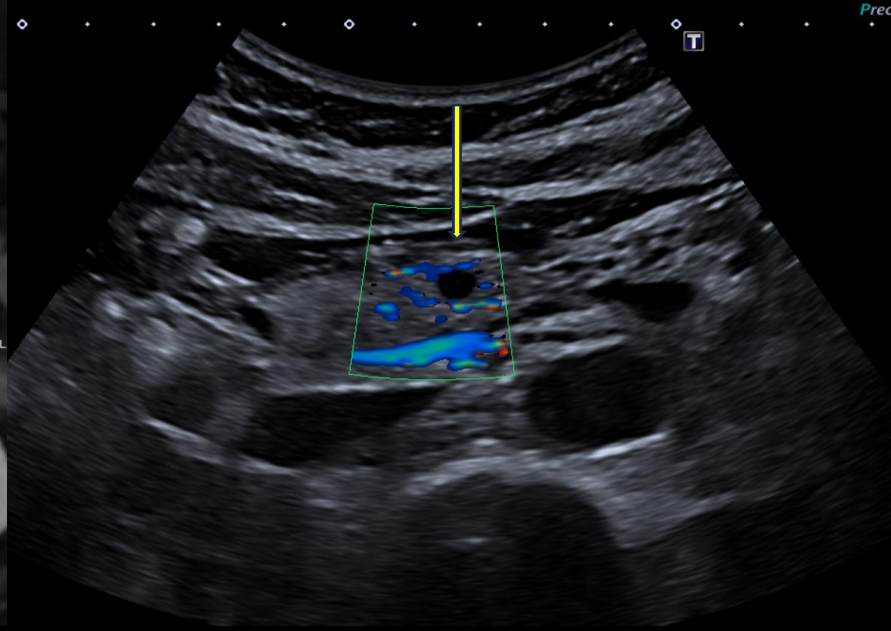
- **Earlier age** of onset. **More than one hypersecretion syndrome** can develop over the years.
- In addition to a functioning pancreatic endocrine tumor, patients with MEN 1 often have several small coexisting multihormonal tumors measuring up to 5mm, termed "**microadenomas**".
- MEN1-associated tumors may be **larger, more aggressive, and resistant to treatment** than sporadic endocrine tumors.
- The mean age at death in patients with MEN-1 is 55–60 years with 50–70% dying of causes directly related to MEN1. Whereas in early series patients often died as a result of complications of hormonal effects of the tumors such as upper gastrointestinal bleeding resulting from ZES or renal complications as a consequence of hyperparathyroidism, today there is a **shift toward death from malignancy**.



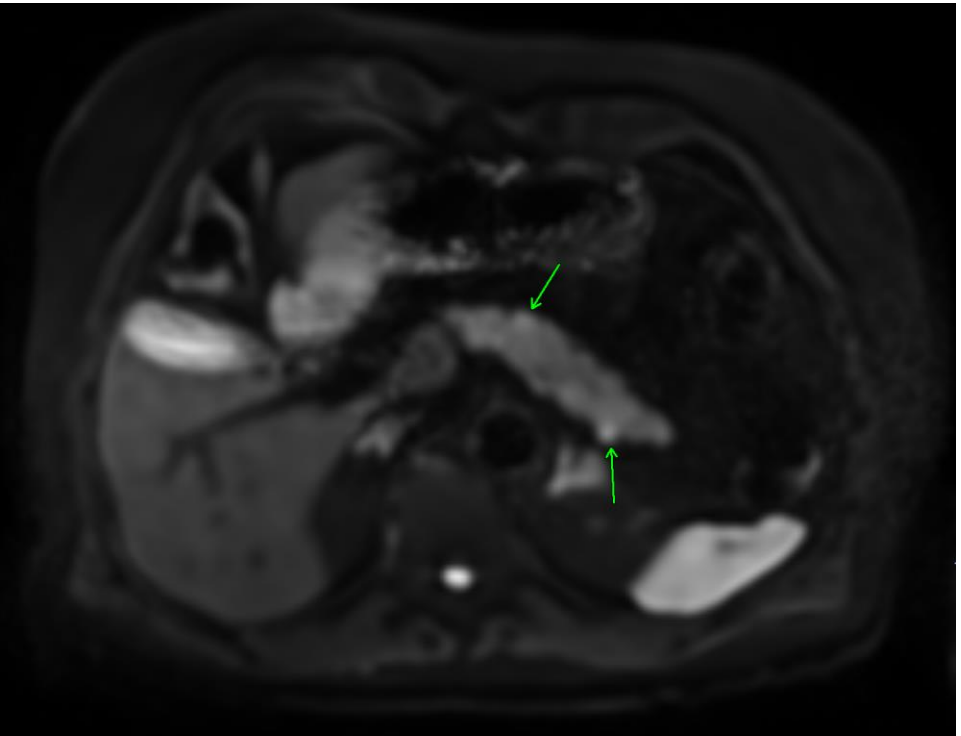
MEN –1 with synchronous lung mass (carcinoid) and PanNEN with liver metastases and bilateral adrenal nodules.





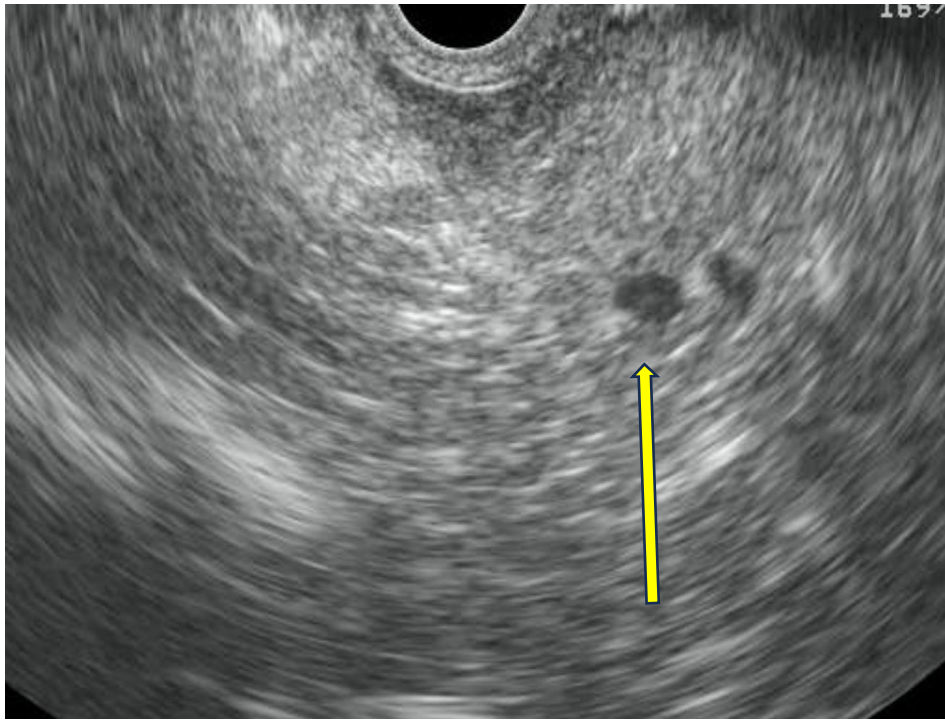


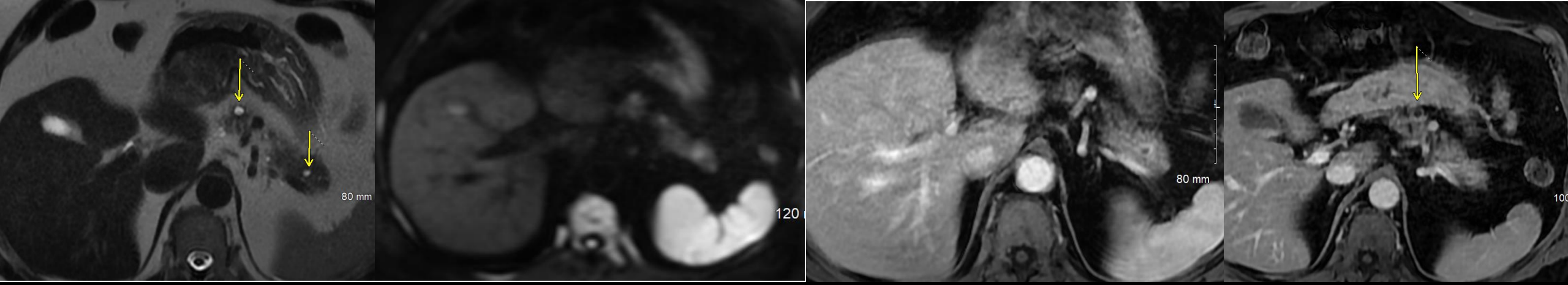
Small PanNEN in uncinate process - DWI hyperintense, arterial enhancement. Well defined and hypoechoic on US.



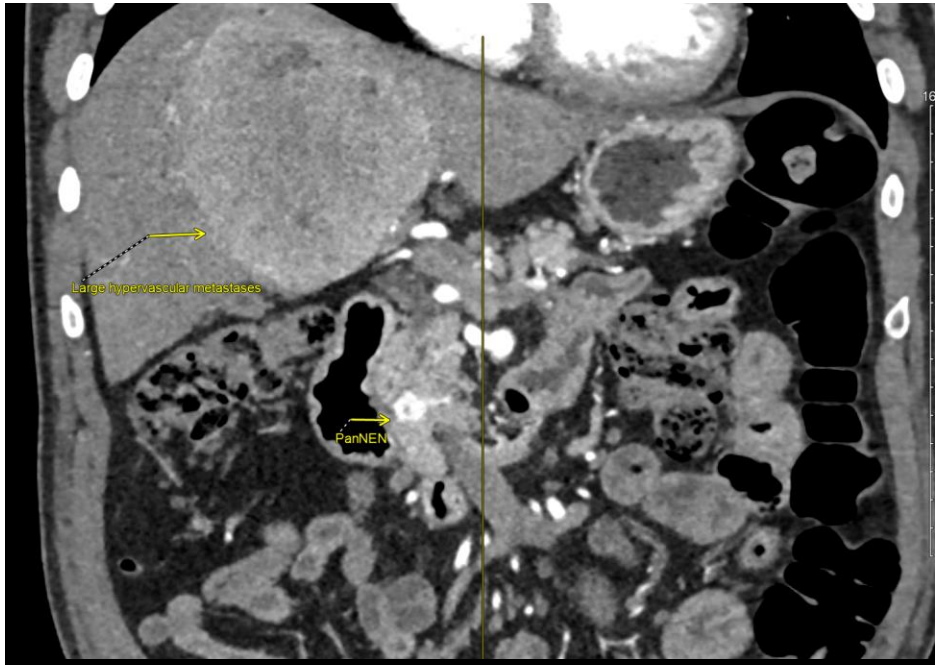
Lesions are often detected early due to regular surveillance. They may only be visible on DWI with faint hyperintensity as in this case with no other correlate. Bilateral adrenal hyperplasia.

EUS is often helpful in doubtful cases.

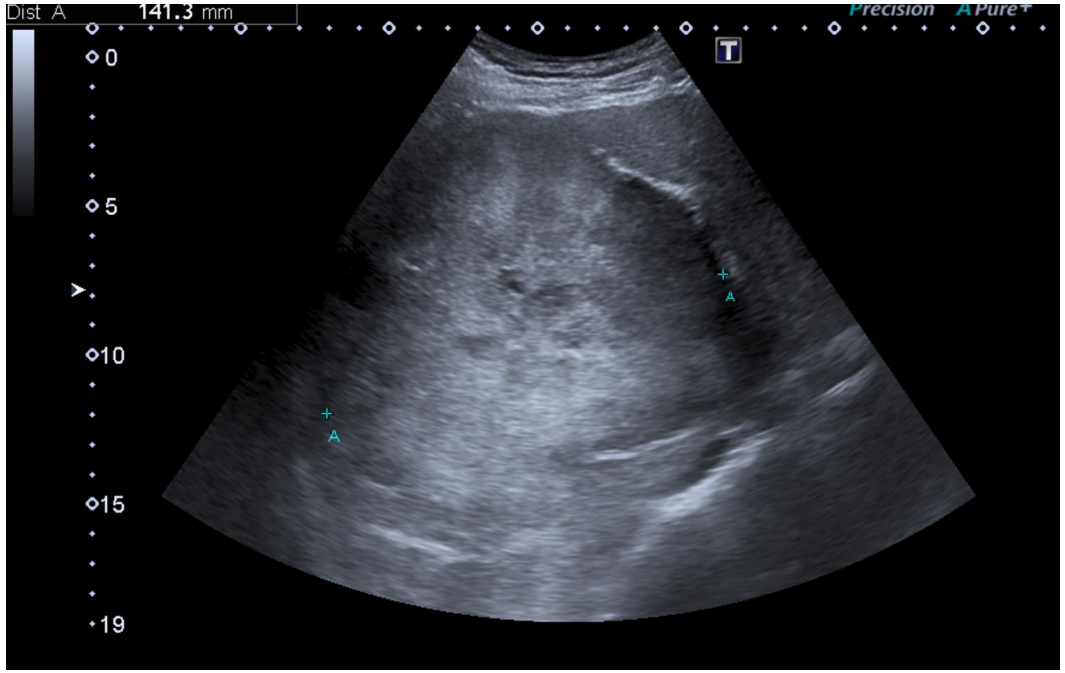




Multiple cystic PanNEN in MEN-1 - Well defined, rounded T2 hyperintense lesions with DWI hyperintensity and rim enhancement on post contrast T1 .

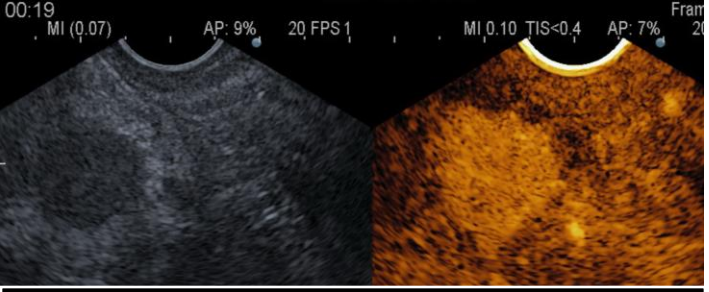


PanNEN in head with large hypervascular liver metastases. Prior distal pancreatectomy and splenectomy for PanNEN.



Same patient: liver metastases on US

PanNEN in Von Hippel-Lindau syndrome

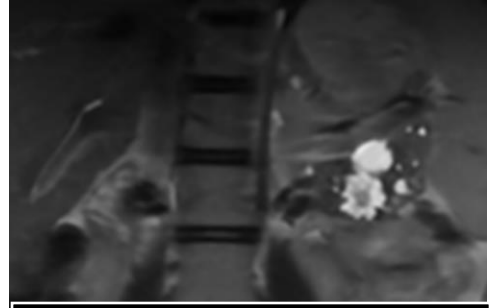


Contrast EUS – homogeneously enhancing hypoechoic HOP mass

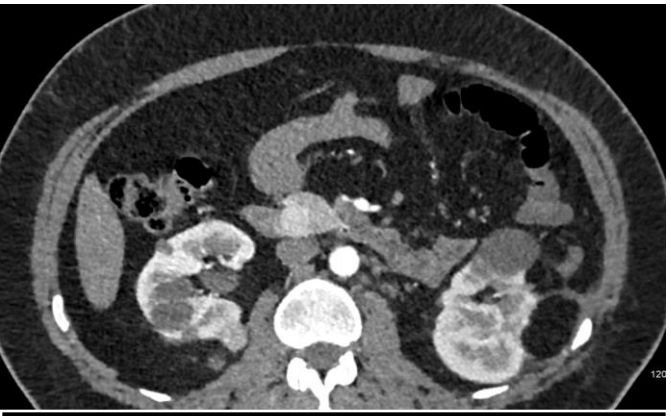
- PanNENs were established as ***VHL component tumors*** in 1998.
- Incidence of PanNEN in VHL = 5 to 18%.
- ~3% of deaths in VHL is due to pancreatic tumours (MC due to RCC and cerebral hemangioblastoma).
- Pancreatic lesions (may be the earliest manifestation)
  - pancreatic cysts: ~40%
  - pancreatic neuroendocrine tumours (PanNEN) - 5-18%
  - pancreatic serous cystadenoma: 9-17%
  - pancreatic adenocarcinoma: rare
- PanNEN in VHL – Asymptomatic, multiple, typically non-functioning, occurs in younger age and have a slow growing pattern.

Other abdominal manifestations of VHL:

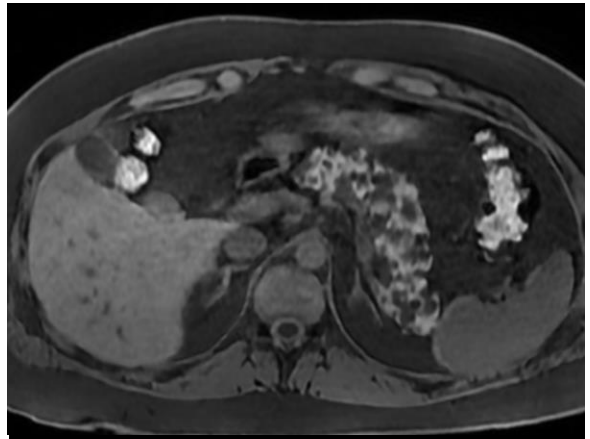
- Kidneys: RCC, cysts, AML
- phaeochromocytoma, paraganglioma
- Liver: cysts



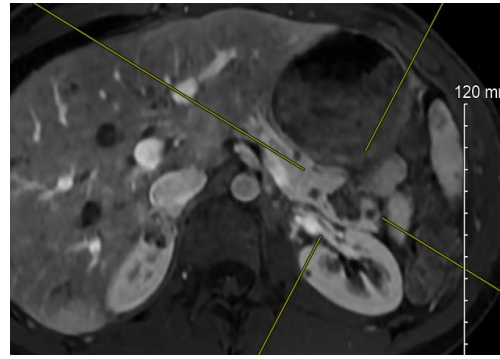
Coronal T2: serous cystic neoplasm and cysts in tail of pancreas



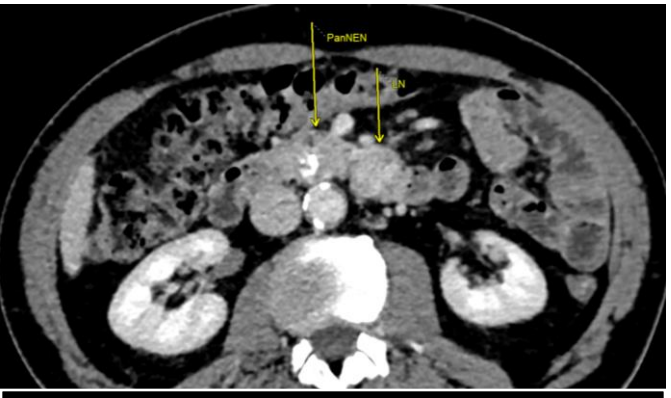
CECT Arterial phase : homogeneously enhancing uncinate process mass. Prior left partial nephrectomy, bilateral renal cysts and right RCC.



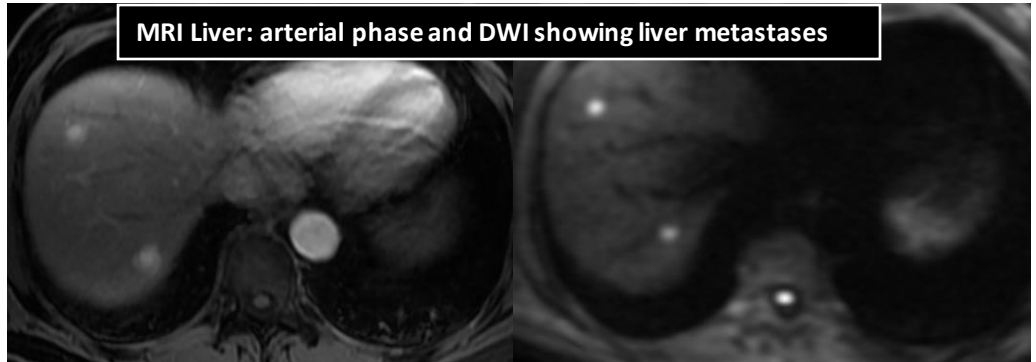
Multiple pancreatic cysts in VHL showing the difficulty in identifying PanNEN in this background! [no PanNEN here]



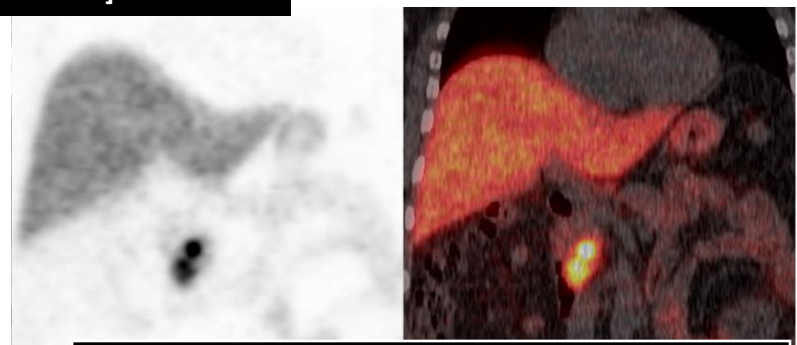
Oblique axial T1 arterial : Rt RCC, Serous cystic neoplasm in tail of pancreas



CECT Portal phase: enhancing calcified uncinate process mass with adjacent lymph node.

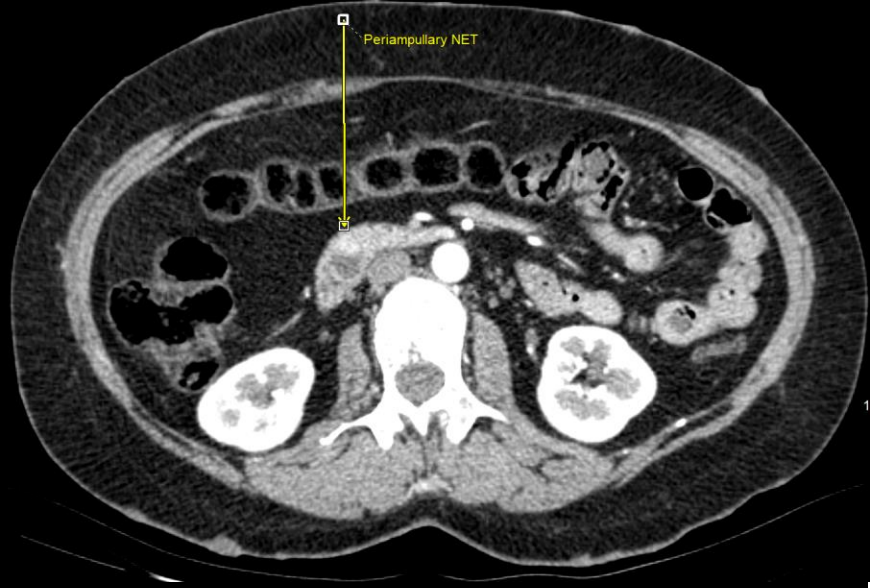


MRI Liver: arterial phase and DWI showing liver metastases

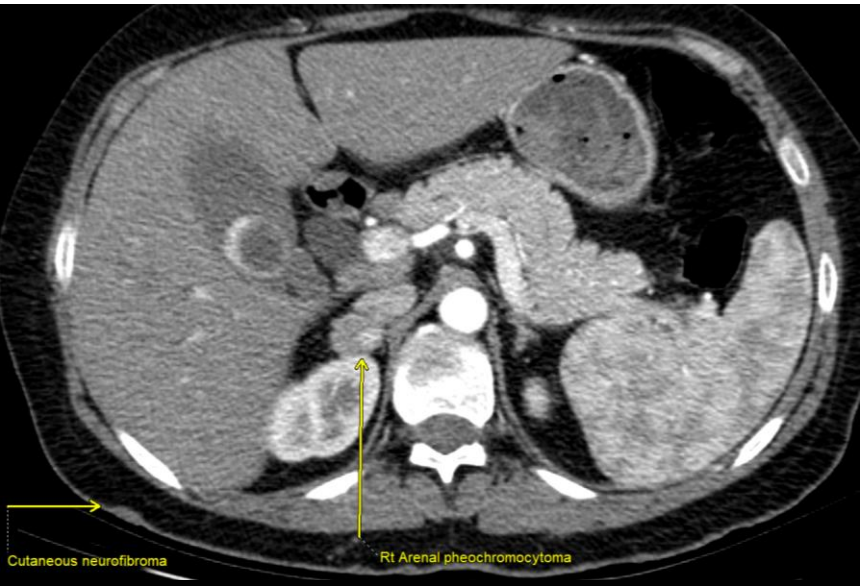


DOTATATE PET: Multifocal uptake in head of pancreas

PanNEN in Neurofibromatosis -1



CECT abdomen arterial phase – hyper-enhancing periampullary lesion

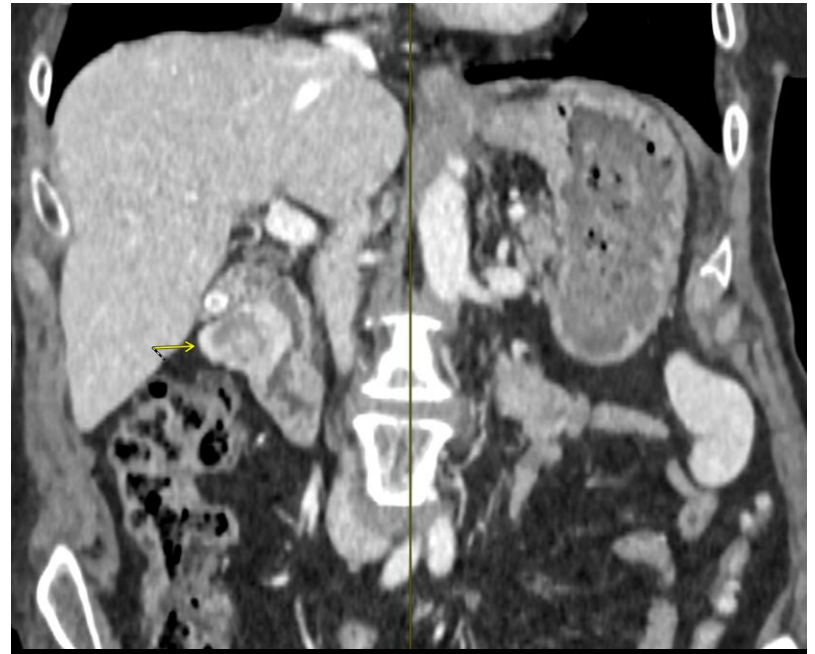


CECT abdomen of the same patient with right adrenal phaeochromocytoma and cutaneous neurofibroma.

- Gastrointestinal manifestations of NF-1 usually arise during midlife or later; generally, later than the appearance of the cutaneous manifestations of the disease. Rarely maybe the first presentation of disease.
- 1% patients with NF1 develop PanNEN.
- Most common subtype is a ***somatostatinoma*** in periampullary location (2/3rd pancreas, 1/3rd duodenum). Periampullary somatostatinoma and GIST are pathognomonic of NF-1.
- Majority non-functioning = somatostatin syndrome is absent in NF1 individuals. Symptoms are the result of the mass effects: jaundice and non-specific abdominal pain.
- Diagnosis relies on CT, endoscopic ultrasound (EUS), and measurement of chromogranin A (CgA) and urinary 5-HIAA. Very rarely metastasize in NF1.

Abdominal manifestations in NF-1:

- Neurogenic neoplasms: Cutaneous and retroperitoneal neurofibroma, plexiform neurofibroma, malignant peripheral nerve sheath tumour.
- GIST
- phaeochromocytoma and paraganglioma.
- Vascular dysplasia of aorta / renal arteries etc.
- Leiomyoma of uterus and GI tract.



Different NF-1 patient with duodenal GIST.

PanNEN in Tuberous sclerosis

- Majority of NETs in TSC are PanNEN (1 to 9%).
- Most common pancreatic pathology in TSC is also PanNEN (others are cysts and AML)
- Occur at a younger age and are more frequently *cystic*.
- Most common subtype is non-functioning PanNEN, followed by insulinomas and gastrinomas (like sporadic PanNEN)
- Most lesions are *solitary* (unlike multifocal in other syndromes)

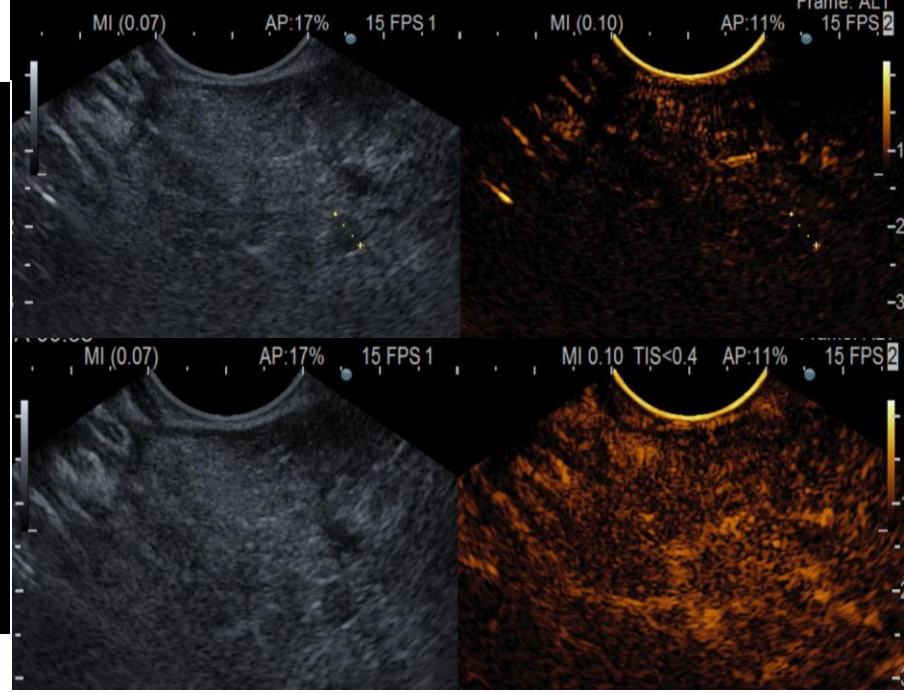
Abdominal manifestations of Tuberous Sclerosis:

Renal - cysts, angiomyolipomas, RCC.

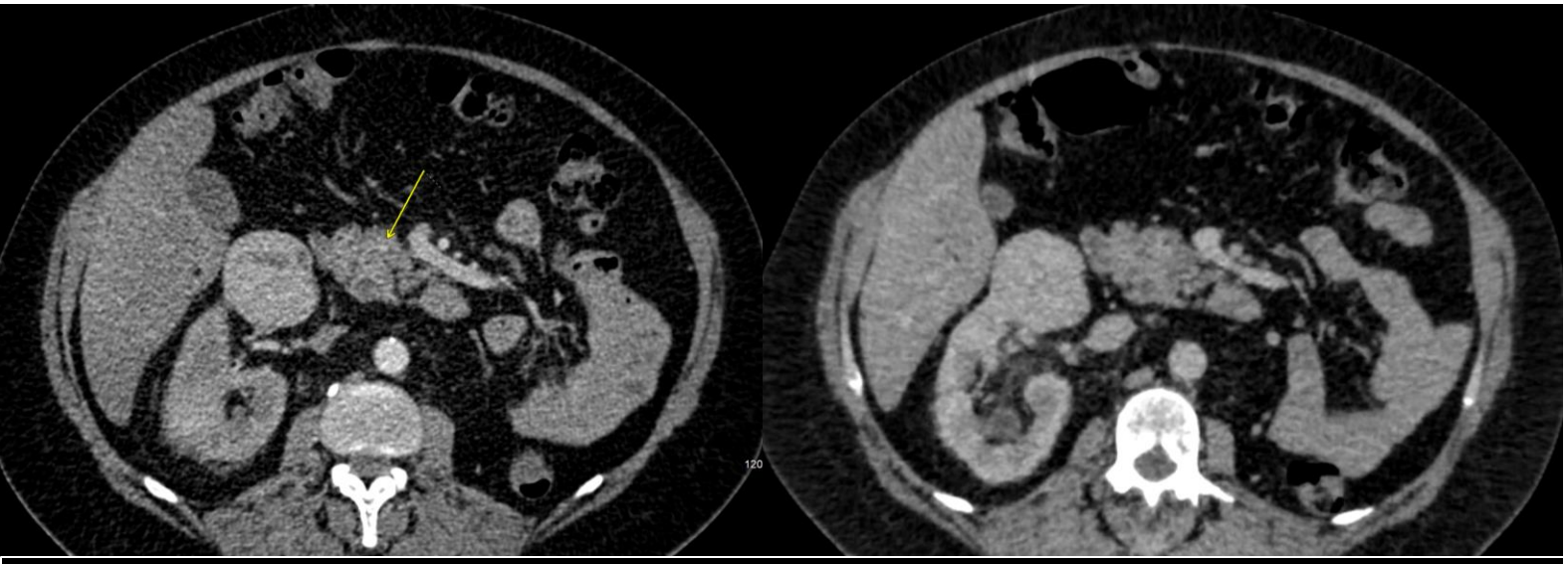
Liver – angiomyolipomas

Bones - sclerotic bone lesions, periosteal new bone formation

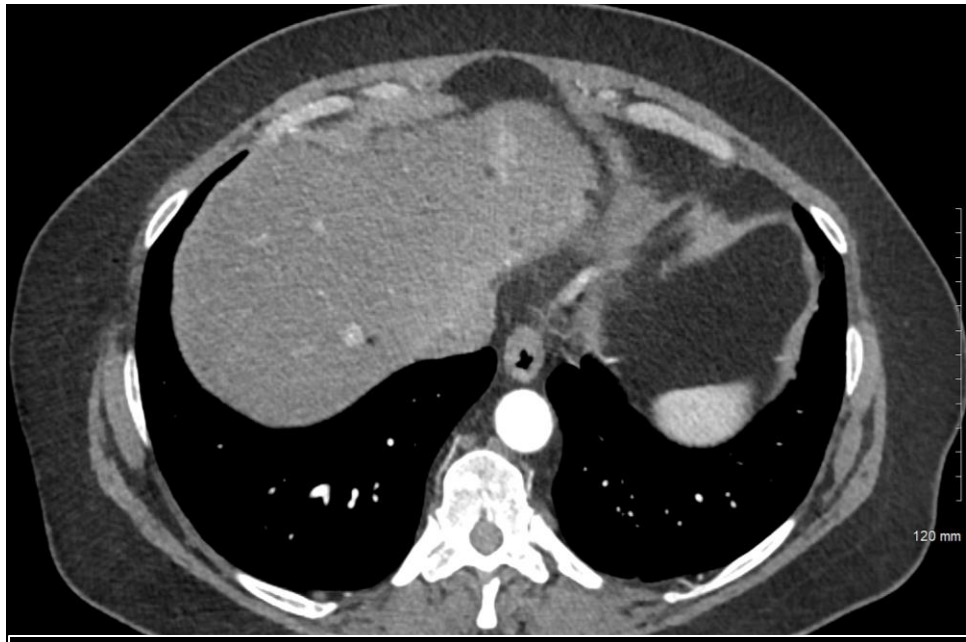
Splenic - hamartomas



Pre and post contrast enhanced EUS: well defined, rounded, hypoechoic lesion in the head of pancreas which is isoenhancing to parenchyma post contrast.



CECT arterial and portal venous phases : subcm subtle hyper-enhancing lesion in head of pancreas. Right RCC.

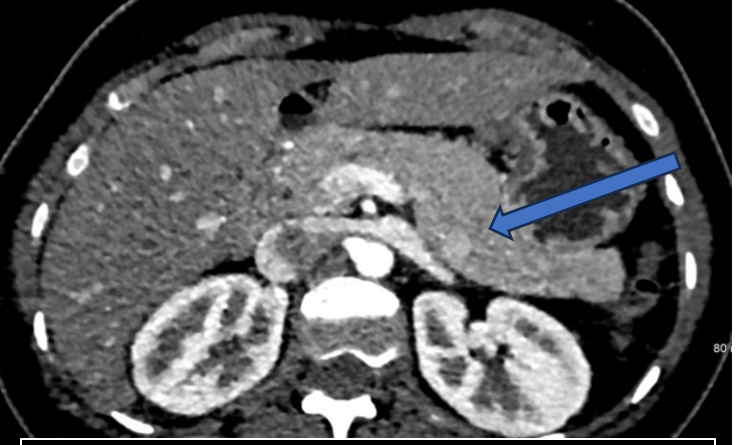


CECT abdomen arterial phase: hyperenhancing metastases in the liver. Fat containing hypodense lesions in the liver – angiomyolipomas.

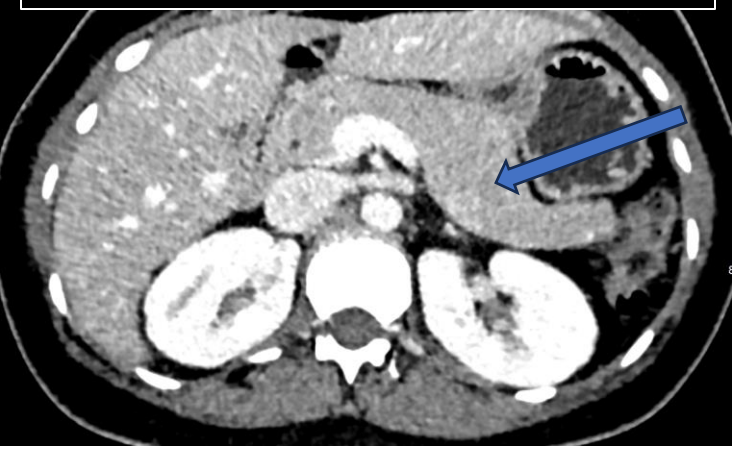
PanNEN in Mahvash disease

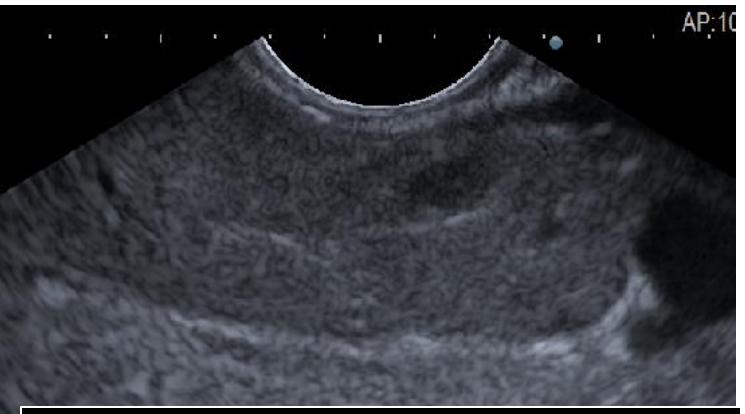
- Mahvash disease is an *autosomal recessive, hereditary pancreatic neuroendocrine tumor syndrome* caused by inactivating glucagon receptor mutation in the liver and reactive pancreatic α cell hyperplasia (which leads to PanNEN development).
- Rare, estimated prevalence is approximately 4 per million
- *Marked hyperglucagonemia (many-fold elevation) without glucagonoma syndrome* (due to inactive glucagon receptor gene) is an essential feature. All PanNENs in Mahvash disease are clinically nonfunctioning (even though majority of tumors are glucagonomas).
- The symptoms at presentation are nonspecific and may include abdominal pain.
- Histology = coexistence of profound and diffuse α cell hyperplasia, dysplasia, micro-PanNENs, and gross PanNENs.
- *Imaging = pancreatomegaly with or without masses. Fatty liver +/- features of portal hypertension.*
- Somatostatin receptor–based nuclear imaging - entire pancreas and the masses may be positive.
- All known patients have undergone partial or total pancreatectomy. Management of PanNEN is as per MEN-1 guidelines.
- Natural history of untreated Mahvash disease can only be extrapolated from that of the GCGR−/− mice = fail to thrive in adulthood, develop bulky PanNENs with remote metastasis and premature death.

MAHVASH DISEASE

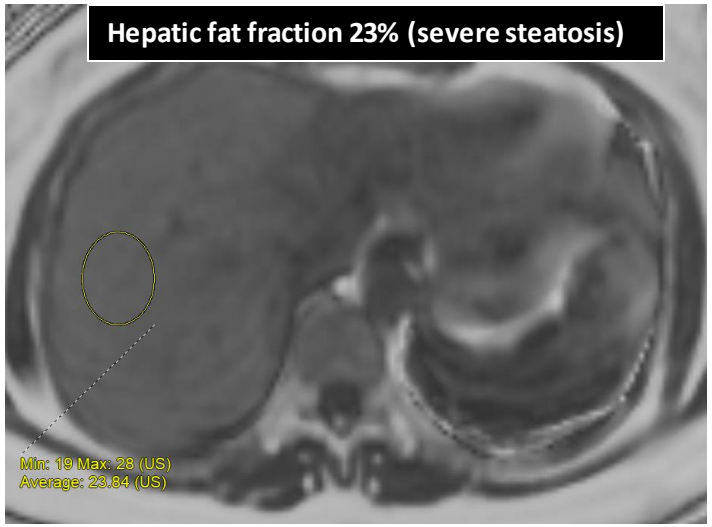


CECT abdomen, arterial and portal venous phases: pancreatomegaly. Hyperenhancing lesion in tail.

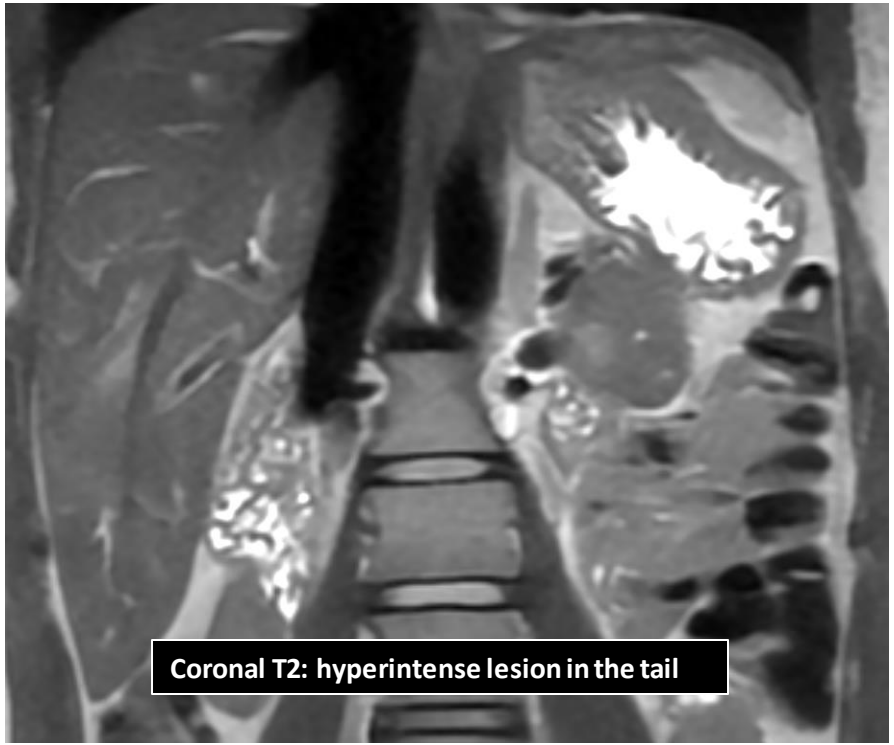




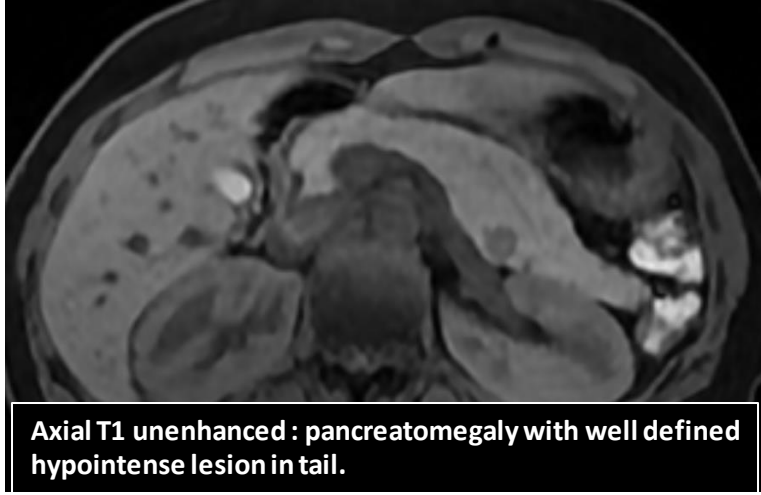
EUS: Well defined, hypoechoic lesion in tail of pancreas



Hepatic fat fraction 23% (severe steatosis)

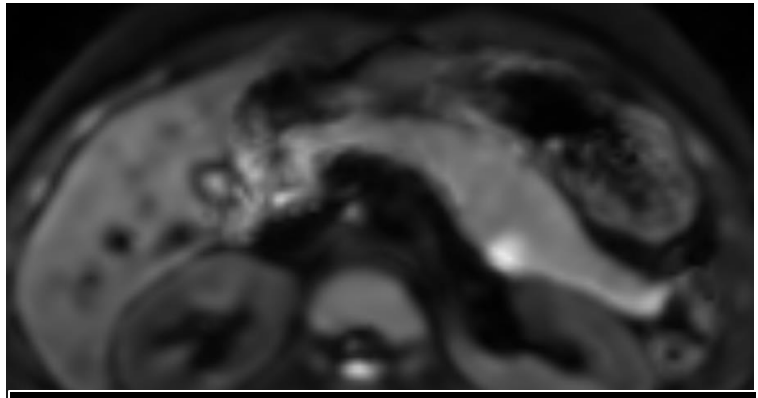


Coronal T2: hyperintense lesion in the tail



Axial T1 unenhanced : pancreatomegaly with well defined hypointense lesion in tail.

Axial T1 portal phase: mild-moderate enhancement of the lesion.



DWI: Restricted diffusion (with low ADC, not shown)

Syndromes with less frequent PanNEN prevalence:

Insulinomatosis:

- Insulinomatosis is characterized by multiple insulinomas (predominantly micro-insulinomas) scattered throughout the entire pancreas .
- Less than 5% of all patients with hyperinsulinemic hypoglycemia have insulinomatosis. Mostly sporadic, rare cases of familial insulinomatosis documented.
- Presents with Whipple's triad. It occurs more frequently in females, and the mean age at the diagnosis is 39.5 years
- Typically, along with a few macrotumors (usually 0.5–1 cm), multiple microtumors are found throughout the entire pancreas, all secreting insulin. Although these multifocal insulinomas are usually benign, rare occurrence of metastases has been reported.

Multiple Endocrine Neoplasia –type 4:

- The prevalence of gastrinomas and nonfunctional pancreatic tumors in MEN4 is approximately 25% (This is much lower than in MEN1). No case reports of other PanNEN tumors exist in MEN4 cases.

Summary

SYNDROME	PanNEN and other pancreatic manifestations	Other abdominal manifestations
MEN-1	Incidence Upto 80%. MC nonfunctioning > gastrinoma > insulinoma. Multiple.	Duodenal gastrinomas. Features of hypergastrinemia – gastric wall thickening, duodenal ulcerations. Adrenal cortical tumours.
VHL	Incidence ~ 15%. MC pancreatic findings are cysts, serous cystic neoplasm and PanNENs. Mutiple non-functioning PanNENs.	Renal cysts, RCC, AML. Liver cysts. phaeochromocytoma, paraganglioma.
NF-1	Incidence ~1%. MC periampullary somatostatinomas. No somatostatin syndrome	Neurogenis tumours, GIST, phaeochromocytomas
Tuberous sclerosis	Incidence ~1%. PanNENs are the most common pancreatic manifestations followed by AML and cysts. Solitary. Frequently cystic.	Renal cysts, AML and RCC. Hepatic AML. Sclerotic bone lesions. Splenic hamartomas.
Mahvash disease	Diffuse pancreatomegaly, heterogeneous parenchyma, PanNENs.	Fatty liver +/- portal hypertension (presinusoidal)

CONCLUSION:

- Syndromic pancreatic neuroendocrine neoplasms are rare tumours overall, but PanNENs are quite often the dominant / frequently occurring pathology in them contributing to increased morbidity and also mortality in some cases.
- While the imaging appearance of individual PanNEN in these syndromes is indistinguishable from that of sporadic PanNEN, their natural history and biology tend to be unique to each syndrome.
- Not uncommonly, abdominal manifestations may be the first presentation of these syndromes OR they may be incidentally diagnosed on abdominal imaging for other indications.

Hence radiologists must be aware of these associations of PanNENs – so that these syndromes do not slip through our NETs!

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THANK YOU!