Pancreatic Neuroendocrine Tumours

PNET

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Also called islet cell tumours/Pancreatic Carcinoids

- Are well differentiated ,low or intermediate grade tumours
- Arise from endocrine or islet cells
- Secrete various peptides or hormones like insulin,Gastrin.
- Better prognosis than pancreatic adenocarcinomas.

Functional

- Hormone producing
- Clinical symptoms of hormone excess

Non functional

- May or may not produce hormones
- No clinical symptoms of hormone excess

- They are rare tumours.
- May occur sporadically or in association with syndromes like MEN1,Von Hippel Lindau amd Tuberous sclerosis
- Mostly malignant except Insulinoma (95% benign)
- Malignant types differentiated by locoregional spread and distant and nodal metastasis.
- May be localised,locoregional involvement or distant metastasis
- Due to delay in diagnosis,metastatic percentage is more
- Survival has improved over last decades especially in metastatic tumours .

Classification and pathology

- Different types of pancreatic endocrine cells
- B cells --------- insulin
- A cells --------- glucagon
- D cells ---------- somatostatin
- PP cells producing pancreatic polypeptide
- Rare cells produce serotonin and ghrelin.
- IHC markers used to identify PNET.
- General endocrine markers: NSE(neuron specific enolase),chromagranin A,synaptophysin
- Specific for PNETs: NSEP 55 (neuroendocrine secretory protein 55) and PDX 1 (pancreatic duodenal homeobox 1).

WHO tumour grading

- Well-differentiated neuroendocrine neoplasms: neuroendocrine tumours
- **MITOTIC INDEX** **Ki-67**
- pNET G1 <2 ≤2%
- pNET G2 2–20 3%–20%
- pNET G3 >20 >20%
- Poorly differentiated neuroendocrine neoplasms: pancreatic neuroendocrine carcinoma (pNEC)
- pNEC (G3)
- Small-cell type
- Large-cell type >20 >20%
- Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)
- *aPer 10 high-power fields = 2 mm2; at least 50 fields in areas of highest mitotic density.*
- *bMIB1 antibody; percentage of 500 to 2,000 tumor cells in areas of highest nuclear labeling.*

- **American Joint Committee on Cancer 8th Edition Staging**
- Primary Tumor (T)
- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor limited to the pancreas, 2 cm or less
- T2 Tumor limited to the pancreas, 2–4 cm
- T3 Tumor limited to the pancreas, >4 cm; or tumor invading the duodenum or bile duct
- T4 Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery)

- Regional lymph nodes (N)
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

- Distant metastases (M)
- M0 No distant metastasis
- M1 Distant metastasis
- **T N M Stage Group**
- T1 N0 M0 I
- T2 N0 M0 II
- T3 N0 M0 II
- T4 N0 M0 III
- Any T N1 M0 III
- Any T Any N M1 IV

Diagnosis and management of PNETs
NON FUNCTIONAL TUMOURS

- Do not cause hormone excess clinical syndrome
- Usually asymptomatic
- Large tumours may cause pain,biliary or gastric obstruction.
- Rarely G I bleed due to duodenal involement or spleenic vein thrombosis leading to gastric varices
- Absense of weight loss,cachexia or back pain as compared to adenocarcinoma (even if small in size)
- Diagnosed as incidental masses on imaging.contrast CT is MC investigation. Hypervascular tumours
- DOTATATE PET CT better ,MRI for small liver mets
- EUS for FNAC if indicated

Treatment

- Surgery is the treatment of choice.(Whipples procedure/distal pancreatectomy)
- Unresectable tumours: biopsy is done to d/d adenoca
- Metastatic tumours: Role of metastatectomy,debulking surgery . other liver directed therapies like RFA,Cryoablation,and transarterial therapies TACE,TARE.
- Systemic therapy for advanced,metastatic disease :
- Somatostatin analogues,octreotide,lanreotide
- Tyrosine kinase inhibitors:Sunitinib
- m-tor inhibitors: Everolimus
- PRRT-Ytrium or lutetium labelled somatostatin analogs.

FUNCTIONAL TUMOURS
INSULINOMA

- Most common functioning neuroendocrine tumors of the pancreas. However, they are rare tumors. Insulinomas can occur at any age with a mean around 50years.

- Majority of these tumors are benign, solitary, and relatively small in size (< 2 cm). Most are located in the pancreas with an even distribution throughout the pancreatic head, body,and tail.
- The majority of insulinomas are sporadic; however,5–10 % are associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome.

Clinical presentation

- Patients present with episodes of hypoglycemia with associated symptoms. Common after physical exertion.
- Symptoms categorized into adrenergic and neuroglycopenic symptoms.

Adrenergic (B.S <50mg/dl)	Neuroglycopenic (BS < 45 mg/dl)
Anxiety	Headache
Diaphoresis	Dizziness,confusion
Tremors	Behaviour /personality changes
Palpitations	Insomnia
Hunger	Seizures,coma

- Weight gain is common ,as patients tend to eat more to prevent hypoglycemic symptoms

Diagnosis

- Whipple's triad:

1. Fasting hypoglycemia (plasma glucose < 50 mg/dL)
2. Neuroglycopenic symptoms
3. Relief of symptoms after administration of glucose

. Gold standard biochemical diagnosis consists of the 72-h fast requiring hospitalization with measurement of plasma glucose, insulin, C-peptide, and proinsulin. It is able to detect 99 % of insulinomas .

Localisation: CT scan,MRI,DOTATATE PET CT

If imaging fails to localise,calcium stumulation with hepatic venous sampling.

Treatment

- Surgery is the main treatment.
- As majority are benign,enucleation is adequate
- Some require extensive suregry,Whipples,distal pancreatectomy.
- MEDICAL MANAGEMENT.
- For hypoglycemia : Diazoxide.
- Octreotide.

- Advanced/metastatic cases: Cytoreductive surgery,metastatectomy
- Liver directed treatments: RFA,Cryoablation.
- Arterially directed therapy: TACE,TARE
- PRRT: Ytrium/lutetium .

GASTRINOMA/Zollinger – Ellison syndrome

- ZES is a rare disease , the second most common functional PNET following insulinoma.
- Most occur sporadically, 20–25 % of patients with ZES have underlying MEN1.
- Most common functional NET in patients with MEN1, as half of patients with MEN1 have ZES.
- Hypersecretion of gastrin leads to stimulation of parietal cells causing refractory peptic ulcer disease.

Clinical presentation

- Most patients present with chronic diarrhea, refractory peptic ulcer disease, or complications of hyperacidity, such as GI hemorrhage, esophagitis and stricture, and peptic ulcer perforation .
- Presently,diagnosis is often delayed due to use of PPIs.

- Diagnosis is made by raised Serum gastrin levels in absence of achlorhydria.(gastric PH should be <2)
- Elevated levels of gastrin can also be seen in H.pylori infection,achlorhydria,pernicious anaemia,atrophic gastritis,
- Gastrin> 1000pg/ml,gastricPH<2 is diagnostic
- If gastrin 100 – 1000pg/ml and PH>2: calcium or secretin stimulation test is done,gastrin >200pg on secretin test>diagnostic.

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- LOCALISATION: commonly located in Gastrinoma triangle.Intraop Exploration is mandatory.
- CT scan/MRI

  EUS

  DOTATATE PET CT SCAN

TREATMENT:

- Surgery is the main treatment.(Whipples/distal pan)
- Medical management for acid suppersion: high dose PPIs.
- Advanced /Metastatic : debulking surgery,metastatectomy,
- Liver guided therapy: RFA,cryoablation,TACE,TARE
- PRRT

VIPoma

- Verner –Morrison syndrome
- Rare tumour caused by VIP secreting PNET leading to
- WDHA syndrome:watery diarrhoea,hypokalemia,achlorhydria.
- Severe diaarhoea,.20 movements/day
- Diagnosis /Localisation: CT,MRI,DOTATATE PET CT
- Treatment options:

  Medical management of diarrhoea.

  Surgical resection

Advanced /metastatic cases: Cytoreductive surgery,metastatectomy,RFA etc

Glucaganoma

- Presents with syndrome that includes diabetes and typical rash called necrolytic migratory erythema (NME)- painful,bulous dermatosis,pruritis and ulceration
- Thes patients also have weight loss,diarhoea,glossitis.
- Surgery is the main treatment
- Advanced,unresectable cases: somatostatin analogs may control symptoms
- Insulin is used for hyperglycemia.

Other rare forms

- Somatostatinoma: present with diabetes,diarhoea.management is similar to other PNETs

- ACTH producing tumours: ectopic ACTH production leads to cushins syndrome.

Summary

- PNETs are rare tumours.
- Symptoms depend on size and site of tumours and also on hormone production
- Localisation is important before surgery
- DOTATATE PET CT has improved the localisation
- Cytoreductive suregry,metastatectomy has a role and has shown better survival .
- Unresectable metastatic tumours are treated by various options like RFA,Cryoablation,Arterial guided therapies like TACE,TARE.

Thank You