

Pancreatic Neuroendocrine Tumour

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Abstract: Pancreatic Neuroendocrine Tumours (PNET) are extremely rare compared to their exocrine counterparts accounting for approximately 1% of all primary pancreatic tumours. They may be functional or non-functional depending upon the secretion of hormones. The diagnostic grading and prognostic criteria for PNET's have been controversial in surgical pathology and clinical medicine. Most PNET's are sporadic however some of them may occur as part of familial tumors (inherited), such as multiple endocrine neoplasms Type 1 (MEN 1 syndrome), von hippel-lindau syndrome (VHL), neurofibromatosis Type I (nf-I) and tuberous sclerosis. We present a case of 65yr old male who presented with abdominal pain, vomiting and weight loss. CT revealed a mass in the uncinate process of pancreas. Pancreaticoduodenectomy was performed with a clinical diagnosis of pancreatic neoplasm. Histopathological diagnosis of PNET was made. The PNET presents usually with non specific symptoms and has a low incidence, therefore early detection and pathological diagnosis of PNET histologically and immunohistochemically helps in management of the case and may prevent metastasis.

Keywords: Pancreatic Neuroendocrine Tumour (PNET), Whipples resection, Nonfunctional endocrine tumor

INTRODUCTION

In 1902 Nicholls documented an example of a pancreatic neoplasm that was termed as "islet cell adenoma". Fabozzi described a biologically malignant counterpart later [1].

PNET's are rare cancers arising from islet cells of endocrine pancreas which account for 1 to 2% of all pancreatic malignancies and 10% are associated with genetic syndromes such as MEN-I [2]. According to WHO 2010 neuroendocrine tumours are divided into 4 groups in terms of grading, Neuroendocrine tumours G1 (NET G1), Neuroendocrine tumour G2 (NET G2), Neuroendocrine carcinoma (NEC), Mixed Adenoneuroendocrine carcinoma (MANEC) [3]. Pancreatic NeuroEndocrine Tumours are classified as functional or non functional based on the presence or absence respectively of a particular clinical syndrome associated with hormone hyper secretion [4, 5].

PNET's tends to have an indolent behaviour and long term survival. Five year survival is about 55% when tumours are localised and resected. PNETs have a better prognosis compared to exocrine adenocarcinoma of the pancreas [6].

Histopathologically PNET's may be well circumscribed or infiltrative. PNET's have characteristic

"organoid" arrangements of the tumour cells and solid nests, trabecular or ribbon like, gyriform, tubuloacinar/pseudoglandular and mixed patterns morphologically [2, 7].

The cells are relatively uniform with round to oval nuclei, coarsely granular and stippled chromatin and variable from pale to moderately eosinophilic cytoplasm. Abundant neurosecretory granules are produced by the cells. Electron microscopy can identify secretory granules [2, 7].

We present a case of Non functional pancreatic neuroendocrine tumour in a 65 year old male.

CASE REPORT

A 65 year old male presented with nonspecific symptoms of epigastric pain, vomitings and weight loss. The patient was a known alcoholic and not a known diabetic and there was no history of any hypoglycemic spells.

Complete blood picture revealed mild leucocytosis. Blood glucose levels were within normal limits, CA-19.9 levels were normal -3.96U/ml, HbsAg was negative. Other investigations were normal.

Ultrasound abdomen revealed a round to oval hypoechoic lesion measuring 3.2X2.7 cm situated in the head of pancreas. There was no evidence of increased vascularity. CECT was suggested for further evaluation. CT contrast revealed a non homogeneous moderately enhancing well circumscribed mass lesion in uncinata process of pancreas measuring 3X3.1X3.5

cm suggestive of a pancreatic non functioning tumor/ carcinoma.

Patient underwent whipple's resection and we received a specimen of size 20 X 3 cm tumor in the head and uncinata process of pancreas.

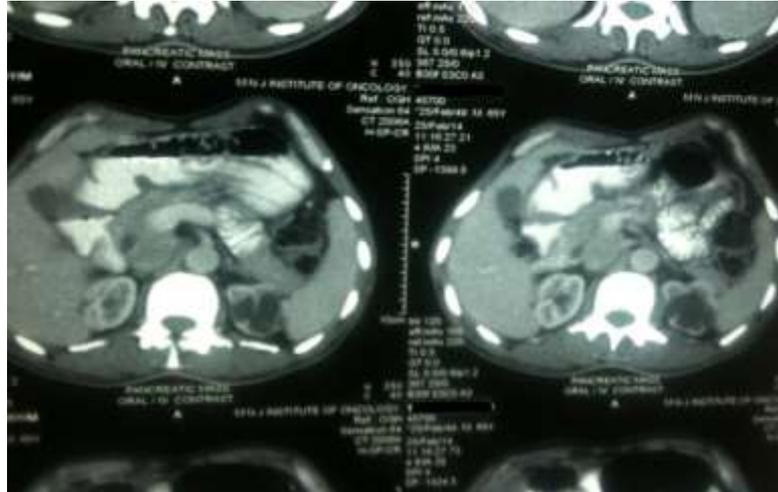


Fig. 1: CECT of abdomen



Fig. 2: Gross image of Whipple resection (Whipple resection with a part of stomach measuring 5 cm, duodenum and jejunum 15 cm , gall bladder 10X 2 cm and part of pancreas 5X3 cm ,duodenum filled with bile)



Fig. 3: Cut section of Tumour. Cut sections showed grey white tumor in the head and uncinata process of pancreas of size 2X3 cm.

Histopathological examination showed native pancreatic tissue along with tumor tissue arranged in nests, lobules and trabecular pattern composed of small round to oval cells with vesicular nucleus, salt and pepper chromatin with moderate eosinophilic cytoplasm. Few cells with eccentric nuclei were also seen. Mitotic index $<2/\text{Hpf}$. Adjacent areas show normal pancreatic tissue which is separated from tumor tissue by a well defined fibrocollagenous capsule. Proximal and, distal resected margins and cystic duct were free from tumour invasion. Gall bladder showed features of chronic cholecystitis. Immunohistochemistry with synaptophysin and chromogranin were positive which confirmed the diagnosis.

Final diagnosis of pancreatic Neuroendocrine tumour grade-I as per WHO 2010 criteria was given. The patient had uneventful clinical course without complications and is currently on follow up.

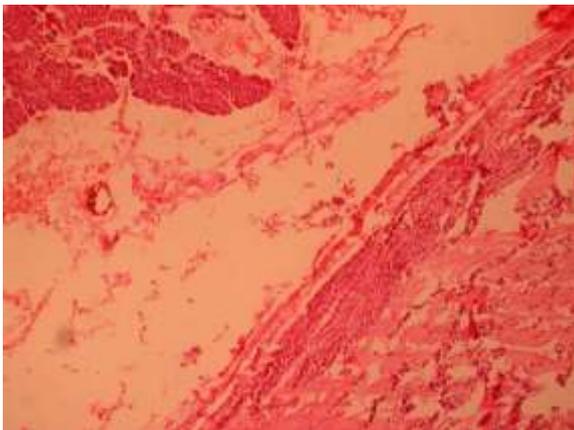


Fig. 4: H&E -Low Power 10X shows normal pancreatic tissue along with the well circumscribed tumour tissue

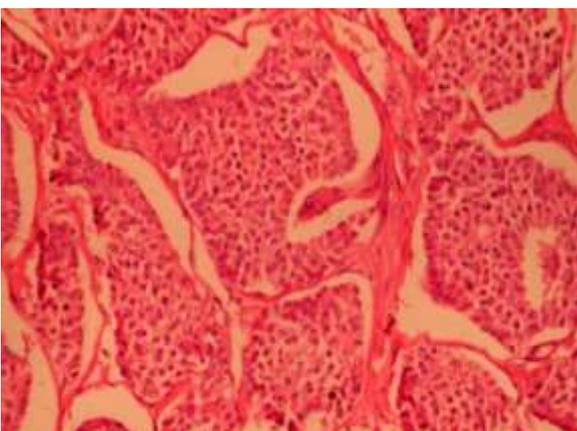


Fig. 5: H&E High Power 40X. Tumour tissue arranged in islands and nests.

Immunohistochemistry: A panel of neuroendocrine markers were done. Synaptophysin, Chromogranin were positive.

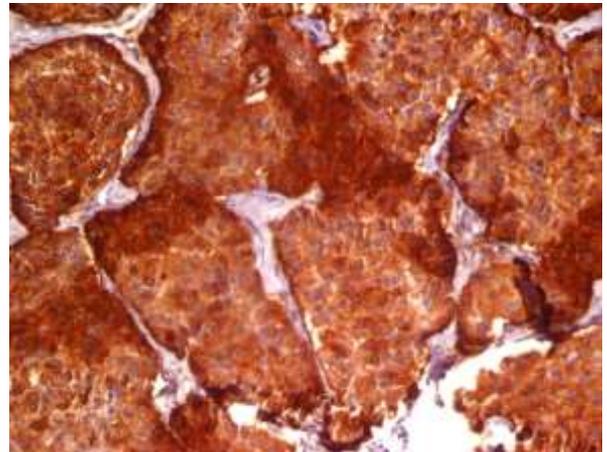


Fig. 6: Chromogranin Positive

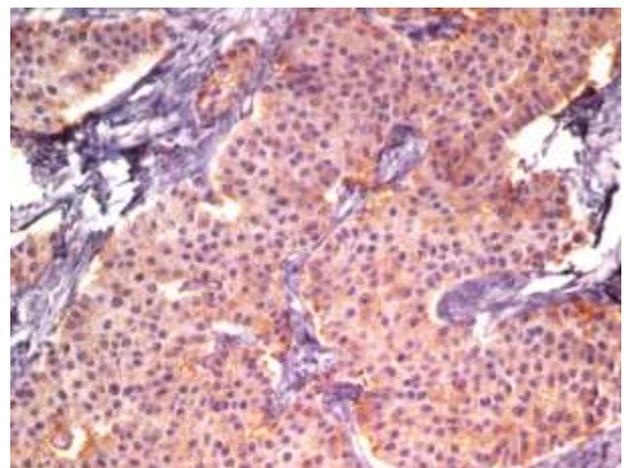


Fig. 7: Synaptophysin Positive.

DISCUSSION

PNETs are rare accounting for only 1-2% of all pancreatic malignancies. PNET's are mostly functional tumors and only 15-30% is Non-functional PNETs [8]. They are a heterogeneous group of neoplasms that are characterised by non specific symptoms leading to delay in their diagnosis. Incidence peaks around 5th decade of life and both the sexes are equally affected. Clinical symptoms usually are abdominal pain 40-60%, weight loss 25-50%, jaundice 30-40%, nausea, vomiting and loss of appetite [9, 10]. Symptoms may vary as per the specific hormone secreted. Our case is a male of age 65 years came with the complaints of abdominal pain and vomitings.

Imaging techniques like CT, Ultrasound and Endoscopic/intraoperative ultrasound are useful for locating most PNETs greater than 2 cm in diameter but

it is difficult to locate the PNETs with size less than 5mm [11]. In our case it was a homogeneously enhanced well circumscribed lesion in the uncinata process of pancreas measuring 3x3.1x3.5cm.on CT.

Histopathologically tumour tissue may show organoid, trabecular and pseudoglandular pattern of arrangement. Individual cells have round to oval nuclei with moderately eosinophilic cytoplasm and salt and pepper chromatin. PNET cannot be distinguished between functional and non-functional tumours on histopathology. Diagnosis is confirmed with positive immunohistochemical staining of neuroendocrine markers chromogranin A, synaptophysin and Neuron specific enolase. Cytokeratin AE1/AE3 is positive for the epithelial component and CA-19.9 is negative. Classifying PNETs has been difficult and bad prognosis includes metastasis and invasion of adjacent structures. Other categories taken into consideration are tumour size, mitotic counts, Ki-67 labeling index.

WHO system 2004 criteria include

Well differentiated pancreatic tumour

- Benign behaviour: Confined to pancreas, no vascular or perineural invasion, <2cm and <2mitotic figures/HPF.
- Uncertain behaviour: Confined to pancreas, vascular and /or perineural invasion, >2cm, or 2-10mitotic figures/HPF.
- Well-differentiated pancreatic endocrine carcinoma
- Gross local invasion or metastasis.

Surgical resection is used for initial management of PNETs. According to Haynes *et al.*, benign tumour of PNET confirmed histopathologically on biopsy should undergo tumor resection and careful post operative surveillance [12]. In our case whipples procedure was performed with clinical improvement in the patient's condition. Chemotherapy with somatostatin analogues can be started for patient diagnosed as metastatic pancreatic endocrine carcinoma.

CONCLUSION

Pancreatic Neuroendocrine tumours are generally indolent neoplasms, even though the majority do present at an advanced stage. Once PNETs are suspected based on the histological features, immunohistochemistry plays a critical role to confirm the diagnosis and start the treatment early as most of these tumours have a benign indolent course. It has to be also kept in mind that all these tumours have the potential to metastasize even after many years requiring a follow up.

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