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Non-Functional Pancreatic Neuroendocrine Tumor: an Enigma

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ABSTRACT

Pancreatic neuroendocrine tumors (PNET) are rare and complex neoplasms. They can either present as a sporadic tumor or as part of various familial syndromes. Clinical presentation depends on whether the tumor expresses hormones and also whether the hormones expressed, can produce symptoms. Diagnosis can be delayed in non-functional PNET and can have metastatic disease at the time of presentation. Management depends on the location and extent of the tumour. This article presents a case series of non-functional neuroendocrine tumors managed in our institute.

Keywords : neuroendocrine tumor, pancreas, non functional

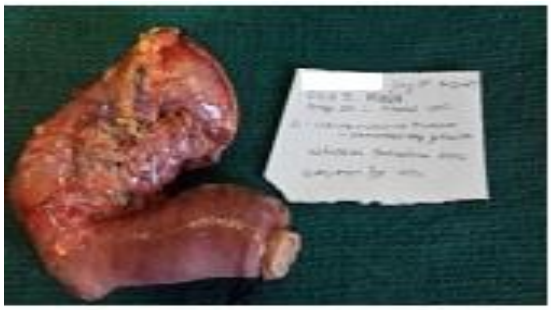
INTRODUCTION

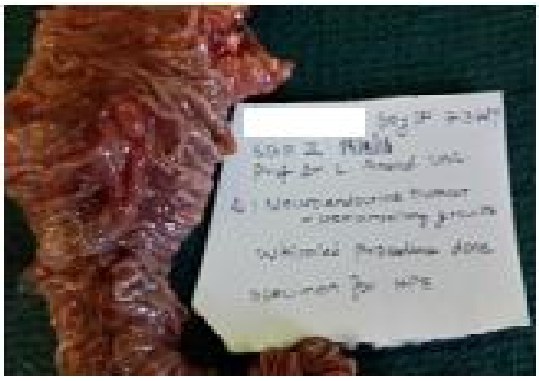
Neuroendocrine tumors of the Pancreas (PNET) are relatively rare neoplasms. They constitute a heterogenous group of tumors having unique clinical behaviour due to the expression of various hormones which result in characteristic clinical syndromes. Although, certain neuroendocrine tumors can be non-functional, without the secretion of any hormonesthat can produce symptoms [1]. Non-functional neuroendocrine tumors (NF-PNET) are usually slow growing, but, a subset of neoplasms can have aggressive behaviour and can be metastatic at the time of presentation. This article presents a case series of NF-PNETs that had varied presentations and were managed in our institute from the year 2016 to 2017.

Case 1

A 60 years old female presented with yellowish discoloration of sclera, pruritus, loss of appetite and weight. Patient was icteric, with scratch marks all over the body. Abdominal examination revealed a palpable gall bladder. Biochemical investigations indicated raised bilirubin (Total- 14.8 mgs%, Direct- 7.5 mgs%) and alkaline phosphatise (294 U/L). Ultrasonography showed dilatation of the intrahepatic biliary radicles (IHBR) and common bile duct (CBD) with suspicious obstructive lesion at the periampullary level. Contrast enhanced computed tomographic (CECT) scan of the abdomen showed suspicious soft tissue density lesion at the level of distal CBD. CA 19-9 level was 39.6 U/ml. Upper GI Endoscopy (UGI scopy) demonstrated an ulcero proliferative growth arising from the periampullary region. Biopsy of the lesion suggested neuroendocrine tumor of pancreas. Whipple‘s pancreatico-duodenectomy was done (Fig. 1). Histopathologic report of the operative specimen came as moderately differentiated neuroendocrine carcinoma with lymphovascular invasion.

Figure 1: pancreatico-duodenectomy specimen showing ulcerative growth (white arrow) involving the periampullary region





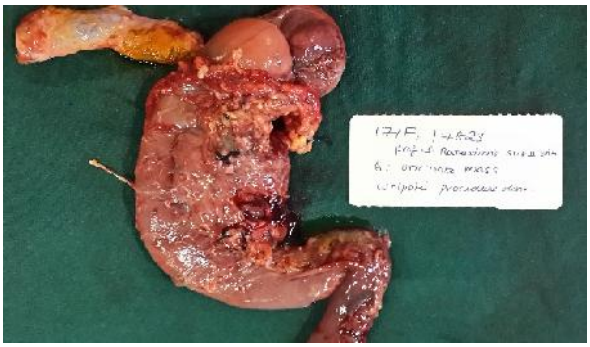


Figure 3: Pancreatico-duodenectomy specimen of the uncinate tumor

Case 2

A 17 years old female, known case of tuberous sclerosis diagnosed 5 months back with angiomyolipoma of both kidneys. Patient underwent angioembolisation and subsequently partial nephrectomy of the right kidney. During the evaluation, a mass lesion was identified at the uncinated process of the pancreas and intraoperative biopsy of the lesion was done during the previous laparotomy. Biopsy of the lesion came as cellular atypia. Laboratory investigations including liver function tests and renal parameters were normal. Magnetic resonance imaging (MRI) of the abdomen revealed 11x8 mm well defined arterial phase enhancing lesion in the uncinated process of the pancreas suggestive of neuroendocrine tumor (Fig. 2). Portal venous Doppler was done which showed an uninvolved portal vein. Patient underwent Whipple's pancreatico-duodenectomy (Fig. 3). Histopathologic report suggested well differentiated neuroendocrine tumor. Immunohistochemistry showed synaptophysin positivity in the lesion.

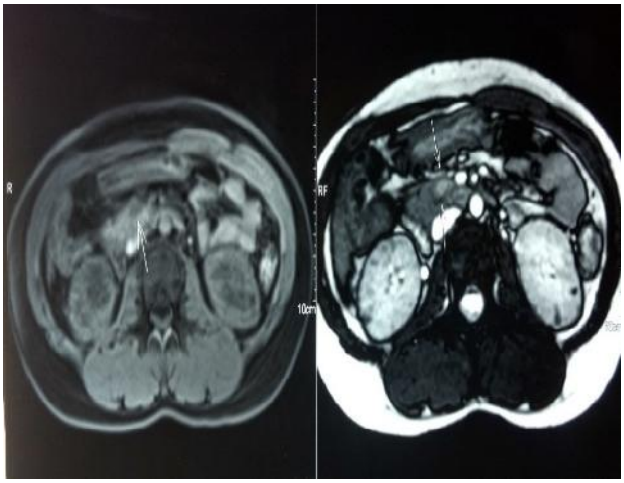


Figure 2: MRI Abdomen T1 & T2 weighted images showing well defined lesion (white arrow) in the uncinate process of pancreas

Case 3

A 52 years old female presented with left upper abdominal pain of 2 months duration. Examination of the patient was normal. Lab tests were also normal. CECT of the abdomen showed 3x4.4x4.9 cm heterodense lesion with minimal necrotic areas and confluent foci of coarse calcification in the distal body and tail of pancreas (Fig. 4). Multiple enlarged perigastric and peripancreatic nodes were noted along with multiple heterodense lesion in both lobes of the liver. (68)Ga DOTONOC PETCT was done which showed DOTONOC avid lobulated soft tissue density lesion in the tail of the pancreas. Peripancreatic nodes and the lesions in both lobes of the liver also showed DOTONOC avidity (Fig. 5). Palliative distal pancreatectomy and splenectomy was done considering the metastatic nature of the disease (Fig. 6&7).

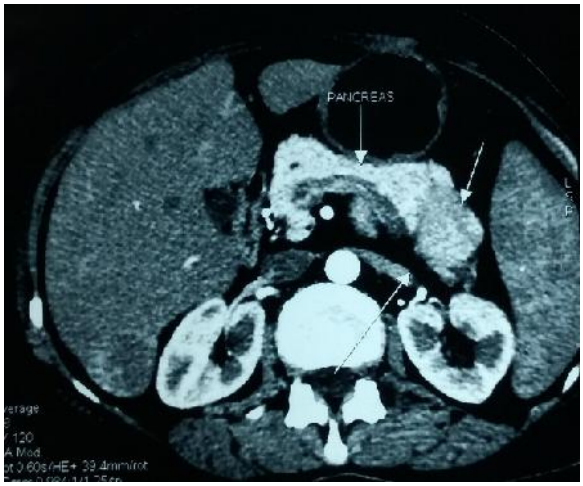


Figure 4: CECT Abdomen images showing well defined hyperdense lesion (White arrows) in the tail of pancreas

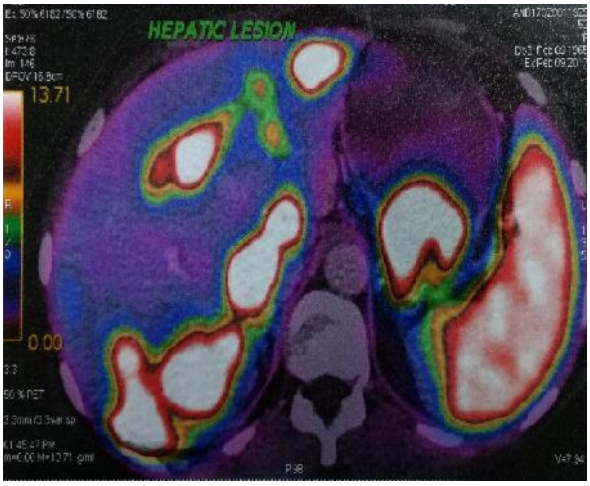


Figure 5: (68)Ga DOTONOC PET scan showing PET avid pancreatic tail lesion with multiple PET avid metastatic lesions in both lobes of liver

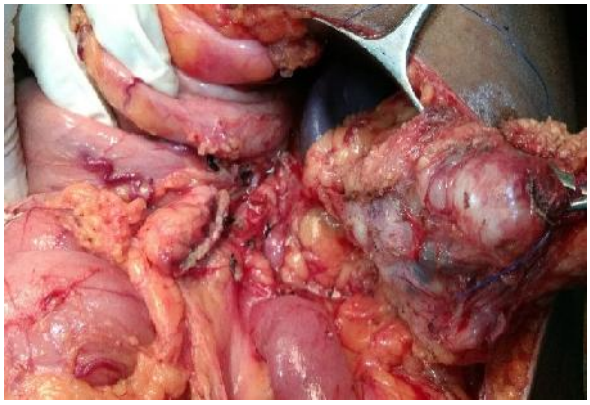


Figure 6: Distal pancreatectomy done for the NET tumor in the tail of pancreas

Figure 7: Distal pancreatectomy & splenectomy specimen

DISCUSSION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), also known as carcinoids and islet cell tumors, are tumors derived from neuroendocrine cells that can occur anywhere along the gastrointestinal tract. The annual incidence of NETs has been increasing worldwide. Whereas early studies have reported incidence rates of 1 per 100,000 persons per year, recent studies have shown a significant, more than fivefold increase in NETs [2].

Approximately 85% of NETs are sporadic and the remainder occur as part of familial cancer syndromes including multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau disease (VHL), von Recklinghausen's disease (neurofibromatosis 1, NF1), and tuberous sclerosis (TS)[3]. Recent large, epidemiologic studies have shown that majority of NETs (60–90%) are clinically non-functioning, well-differentiated, slow-growing neoplasms diagnosed, in most instances, incidentally during unrelated procedures or diagnostic tests [4].

The new WHO 2010 classification of NETs applies to all GEP-NETs. In this classification, tumour grade is based on the proliferation index(Ki-67 Index) and mitotic count (Table 1).

In general, well-differentiated, low or intermediate grade NETs have a relatively indolent behavior with slow progression, but, poorly differentiated tumors may exhibit highly aggressive behavior with rapid metastatic spread that is clinically indistinguishable from pancreatic adenocarcinoma [5].

F-PNETs present with symptoms caused by the specific hormone produced. Common F-NETs include insulinoma, which presents with hypoglycemia, and gastrinoma, which presents with peptic ulcer disease, gastroesophageal reflux disease or secretory diarrhoea. Unlike other solid tumors (including F-PNETs), NF-PNETs can remain asymptomatic before they reach a significant tumor burden. When they become symptomatic, their symptomatology is typically related to mass effect from the primary tumor or the metastasis. Many PNETs occur in the head of the pancreas where symptoms may include jaundice, abdominal pain, or weight loss. Other less frequent symptoms may include anorexia, nausea, intra-abdominal bleeding or a palpable mass. Liver metastases more frequently occur with non-functional tumors and presents with symptoms. When liver metastases occur, most are multifocal and bilobar in nature[6].

Table 1. WHOClassification of Neuroendocrine Tumors (2010)			
Histological Classification	**Well Differentiated (Low Grade, G1)**	**Moderately Differentiated (Intermediate Grade, G2)**	**Poorly Differenti-ated (High Grade, G3)**
Mitotic Rate	<2	2–20	>20
Ki-67 Index	<3%	3–20%	>20%
Prognosis	Prolonged survival	Intermediate	Poor

The most important general circulating tumor marker is chromogranin A, expressed in 80-90% of all patients with GEP-NETs. Chromogranin A determination is also useful for staging, prognosis and follow up, since the serum concentration correlates to the tumor mass. Histopathologically, NF-PNET cannot be distinguished from functional tumors byimmunohistochemistry. In general, positive staining with chromogranin A and synaptophysin confirms the diagnosis and these are elevated in 60-100% of NF -PNETs, although a negative chromogranin result does not completely rule out an endocrine tumor.

Imaging modalities include conventional radiology, such as transabdominal ultrasonography, computerized tomography (CT) and magnetic resonance imaging, selective angiography, nuclear imaging including somatostatin receptor (SSTR) scintigraphy with single-photon emission CT, bone scintigraphy, endoscopic ultrasonography and various intraoperative methods.

Positron emission tomography (PET) with 18-fluorodeoxyglucose ([18F] FDG) is mainly useful for highly aggressive GEP-NETs. For this reason, other hybrid systems of diagnosis are under evaluation. Among these, PET with (68)Ga-DOTATATE, (68)Ga-DOTATOC or (68) Ga-DOTANOC, all with a high affinity to the SSTR subtype 2 [7], enables diagnosis of NET with a very high sensitivity.

Curative surgery should be considered whenever possible even in the presence of metastatic disease, including localizedmetastatic disease to the liver if considered potentiallyresectable and the patient can tolerate the surgery. The type of surgery, the form of pancreatico-duodenal resection, distal pancreatic resection orenucleation in combination with resection, depends on the location of theprimary tumor. As the malignancy is frequent in pancreatic NETs, adequate lymph node clearance is mandatory[8]. Cytoreductive surgery should be considered when metastatic disease is localized or if >70% of tumor load is thought resectable [9].Streptozocin based combination chemotherapy in pancreatic NETs may help control symptoms and achieve tumor response in 40% cases.

CONCLUSION

Neuroendocrine tumours, though rare neoplasms, are increasing in incidence. Delay in diagnosis is common, especially in NF-NETs, resulting in increased probability of metastatic disease at the time of presentation. Assessment of the location and extent in these heterogeneous tumors is crucial for management and it can also provide prognostic information. Curative resection of localised tumors offer excellent prognosis while cytoreductive surgery should always be considered in metastatic disease.

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