Archives of Surgical Research | Case Report

Nonfunctioning Pancreatic Neuroendocrine Tumour (NF-PNET) Presenting as Pancreatitis: A Rare Clinical Association

Haseeb Arif, Hamza Azhar, Talat Waseem

IMPORTANCE Pancreatic neuroendocrine tumors are relatively rare tumors. They make up to 2-5% of all the pancreatic tumors. It is important to diagnose them in early stage. They are found incidentally or if malignant with either epigastric pain or distant metastasis. Very rarely PNETs may present with pancreatitis. Only 30 such cases have been reported previously which did present with focal pancreatitis. Here we present such a rare case.

CASE PRESENTATION A 51-year old female presented with history of recurrent epigastric pain for past 4 years. On Ultrasound and CT scan, a 2x2cm well defined mass in the head of pancreas was observed. The findings were confirmed with CT scan. Modified Whipple procedure was done and histopathological report showed WHO grade – I neuroendocrine tumor with chromogramin positive tumor cells.

DISCUSSION & CONCLUSION The association between neuroendocrine tumor and pancreatitis is very rare hence neuroendocrine tumors should be considered as a differential diagnosis while dealing with such cases.

KEYWORDS Nonfunctioning Pancreatic Neuroendocrine Tumour; NF-PNET; Pancreatitis; Whipple procedure; pancreaticoduodenectomy; Modified Whipple procedure

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Case Report

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Pancreatic neuroendocrine tumours are a class of rare neuroendocrine tumours arising from the pancreas. The official WHO (2000) denomination for these tumours is gastroenteropancreatic neuroendocrine tumours[1]. Pancreatic neuroendocrine tumours (PNET) may be functional; producing hormones such as insulin, gastrin, glucagon or somatostatin, or non-functional; which do not produce any hormones. Most Functional tumours tend to be symptomatic whereas non-functional tumours usually get discovered in the later stages when the tumour has greatly increased in size or has metastasised. Non-functional neuroendocrine tumours of the pancreas are more common, making up to 60-90% of all NETs[2,3] . Pancreatic neuroendocrine tumours are rare entities, making up only 2% of all pancreatic tumours[4,5] . Pancreatitis however is an ever rarer manifestation of PNET's. Only 30 cases of this nature had been reported by 2012[6]. Though an uncommon manifestation, recurrent acute pancreatitis could be an early sign of an underlying pancreatic neuroendocrine tumour. This report presents one such case of a patient with recurrent attacks of acute pancreatitis found to have a PNET.

CASE PRESENTATION

The patient was a 51 year old Pakistani female from Mughalpura, Lahore, presented with an episode of severe epigastric pain. She had been having similar episodes of epigastric pain for the past 4 years. The pain was gnawing in character, associated with nausea and vomiting, radiating to the back, relieved on leaning forward and aggravated by the consumption of fatty meals. She had been admitted to various hospitals for similar episodes of epigastric pain in the past. Each time the pain settled over the period of a few days and the patient was discharged without a definitive diagnosis. There was no association with elevated pancreatic enzymes (i.e. Serum Amylase, Serum Lipase) thus the primary diagnosis remained APD. The patient was diagnosed with diabetes Mellitus 1.5 years ago, but had no family history of DM. This was partially controlled with oral hypoglycemics. She was also diagnosed with hypertension 1 year before presentation, which was being controlled with Atenolol. She also complained of pain in the left hip which began 1.5 months ago which was associated with a limp when walking. At presentation, she had mild pallor on

general examination and abdominal examination showed mild epigastric tenderness. Her left hip was painful with reduced range of motion. Several blood tests were ordered including CBC, Urine C/E, LFT's, RFT's, serum electrolytes, Serum amylase, serum Lipase, Hepatitis B and C screening tests and HBA1C. Abdominal ultrasound, CT scan and a chest X-ray were also done. The patient's Hb was low (10.7 gm/dL), urinalysis showed glucosuria and some RBC's were also found in the urine, serum amylase and lipase were raised and HBA1C was also raised (10.5).

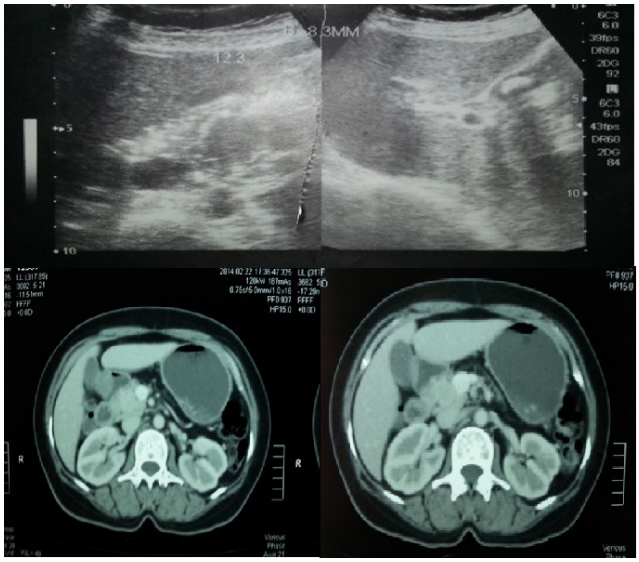

FIG 1: Patient's Abdominal USG (above) and abdominal CT scan (below)

The Ultrasound and CT scan showed a 2x2 well defined rounded growth in the head of pancreas with no vascular encasement and pancreatic atrophy attributed to chronic pancreatitis. An ultrasound guided FNAC was advised but was declined by the patient due to financial constraints. Surgical exploration was planned with curative intent to deal with a resectable symptomatic pancreatic neoplasm (Modified Whipple Procedure). The surgery was performed after; the pancreatitis was settled, adequate glycemic control was provided and cardiovascular disease was ruled out. Intraoperatively a small 2x2 cm mass confined to the head of pancreas was observed with an atrophic pancreas and no regional metastases. The resected tissues included; the pancreatic tumour and head of pancreas (4.2cm x 2.5cm), duodenum, CBD and the gallbladder. The histopathological report of the resected specimen showed a Neuroendocrine tumour WHO grade- I, 2cm in greatest dimension. Tumour cells were found to be chromogramin positive.

DISCUSSION

The association between acute pancreatitis and pancreatic neuroendocrine tumours is very rare. A 1996 study in the American Journal of surgery found only 21 such cases reported in literature [7] while another study in 2012 found only 30 reported cases of this nature as of 2012 [6], with only 11 new cases reported between 1996 and 2012 over the span of 16 years. A Swedish population-based cohort study showed that out of 49,749 individuals with acute pancreatitis only 1% (536 individuals) developed pancreatic cancer[8]. With PNET's making up less than 2% of all pancreatic tumours [5] they are a truly rare entity. The tumour may cause pancreatitis through several different mechanisms though most commonly through the obstruction of the pancreatic duct, pancreatic enzymatic activation and ischemia due to vascular occlusion[4]. In a 2012 case report, S. Tejedor et.al presented 3 such cases of acute pancreatitis secondary to advanced neuroendocrine tumours[6]. Another 2018 study reported a case of an advanced stage pancreatic neuroendocrine tumour presenting as acute pancreatitis with metastases in the paratracheal, anterior cervical and mediastinal lymph nodes [9]. In 2006 Jukemura J. reported the case of a 31y/o patient with weight loss and a history of acute pancreatitis that was diagnosed with a pancreatic neuroendocrine tumour. Jukemura J. concluded that the presence of a pancreatic endocrine tumour should be excluded in the presence of acute pancreatitis of undetermined etiology[4].

Different types of PNET's are associated with different symptoms. Some well recognised forms of functional PNET's in order of incidence include; Gastrinomas, which may lead to Zollinger Ellison syndrome, Insulinomas leading to hypoglycaemic symptoms and glucagonoma which may present as a skin rash, new onset or worsening diabetes mellitus and weight loss. Some rarer types of functional PNET's may release: Erythropoietin; leading to polycythemia, Renin; leading to HTN, GLP-1/IGF-2; resulting in hypoglycaemia and Luteinizing hormone; leading to masculinisation and infertility[10]. Non-Functional PNET's do not release any hormones but their symptoms are related to their size and metastases. These symptoms may include abdominal pain, anorexia, nausea, obstructive jaundice and palpable mass/es[11]. Liver is the most common site of metastasis for these tumours. Yulong Tian et. al. reported a case of PNET's with metastasis in the liver leading to portal vein thrombosis[5].

Neuroendocrine tumours (NETs) arise from neuroendocrine cells, mostly originating from the GI tract

and pancreas. Pancreatic NET's may occur as a part of other disorders such as MEN-I, VHL and NF-1. It is generally assumed that the loss of a tumour suppressor gene or the gain of an Oncogene is the mechanism by which chromosomal alterations cause PNETs; for example abnormalities of the p53 tumour suppressor and the upregulation of the CCND1 (cyclin D1) gene are commonly found in PNET's. Diffuse endocrine cell hyperplasia, dysplasia or microadenomas found in the pancreatic tissue are considered to be precursor lesions for these tumours [12]. Over 1/3 of these tumours are located in the pancreatic head[4,14].

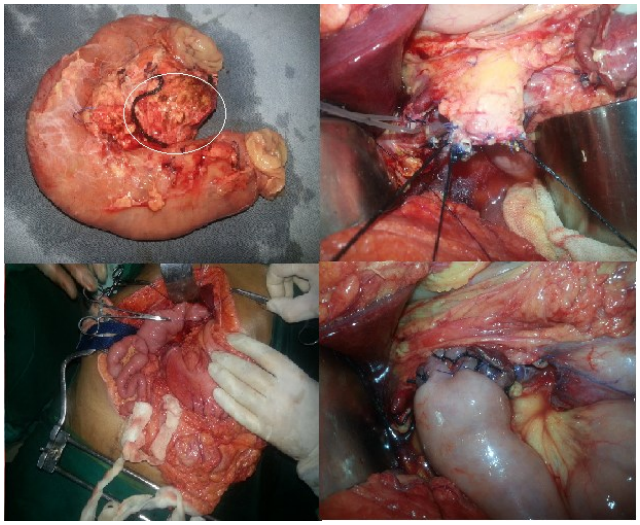

FIG 2: (clockwise) (1) the resected specimen: CBD, duodenum, jejunum, pancreas, (2), (3), (4) photos taken intraoperatively.

The diagnosis of PNET involves endocrine analysis, imaging and histological evaluation. Chromogranin A (CGA), neuron-specific enolase (NSE), and pancreastatin are the most useful PNET markers. Fasting levels of gastrin, proinsulin, insulin, glucagon and vasoactive intestinal peptide (VIP) may be useful for the detection of functional tumours. Imaging techniques such as CT scan and MRI can be useful in localising the tumour and any metastases. Advanced imaging techniques such as Gallium – DOTATOC can be effectively used to identify these tumours. DOTATOC is a somatostatin analogue and this can be radiolabelled with gallium to provide accurate diagnostic information for PNET's. Yulong Tian et .al. used 18F-FDG PET/CT examination to confirm a pancreatic neuroendocrine tumour with multiple liver metastases in 2020[5]. The best predictor of PNET behaviour is the tumour grade. Obtaining a biopsy sample is therefore key, as it can be used to grade the tumour and hence predict the behaviour of the tumour[12]. The malignant potential of pancreatic neuroendocrine tumours can be assessed by their size, Mitotic index, expression of the KI-67 protein, vascular invasion and perineural invasion[13].

The only curative treatment of choice for localized pancreatic tumour is surgical resection. For non-functional NETs which are less than 2cm, an intense follow up with a non-surgical approach should be considered. Absolute indications for surgical intervention include: tumours that have metastasised, tumours more than 2cm in size and/or a yearly increase of more than 0.5cm in size. Decision regarding the type of surgery depends on the site of lesion. For pancreatic head lesions, pancreaticoduodenectomy or whipple procedure is done. In our case, a 2x2cm well defined rounded mass in the head of pancreas was found on ultrasound and CT scan. Due to its size and location modified whipple procedure for the resection of tumour was done.

Other treatment options for NETs includes locoregional ablative therapies like selective (chemo) embolization, radiofrequency ablation and radioembolization. Medical therapy has a role in management of advanced NETs. It include chemotherapy, biological targeted agents (like somatostatin analog IFN – α), targeted molecular therapy (VEGF-R inhibitors, mTOR inhibitors)[15]. Hepatectomy should be done in patients with liver metastasis.

CONCLUSION

Acute pancreatitis is an uncommon symptom of PNETs. 30 cases of acute pancreatitis secondary to neuroendocrine tumours have been reported in medical literature. Hence while dealing with a case of acute pancreatitis; neuroendocrine tumours should also be considered as a differential diagnosis.

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