International Surgery Journal
Saxena P et al. Int Surg J. 2022 May;9(5):1094-1100
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20221164

Case Report

A rare case of malignant pancreatic non-functional neuroendocrine tumor presenting as huge abdominal lump

Pradeep Saxena*, Swastik Bhardwaj, Tarun Sutrave, Ankit Lalchandani

Department of Surgery, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India

Received: 06 March 2022
Accepted: 28 March 2022

***Correspondence:**
Dr. Pradeep Saxena,
E-mail: pradeep@bhopalsurgery.com

ABSTRACT

We present a case of an exceptionally large size non-functioning pancreatic neuroendocrine tumor (PNET) in a young female. The tumor occupied the whole abdomen and pelvis and was clinically masqueraded as an ovarian tumor. Imaging with contrast enhanced CT scan and magnetic resonance imaging of the abdomen aided in preoperative diagnosis of origin of the tumor from the pancreas. Distal pancreatectomy with splenectomy and left hemicolectomy was done. Primary colocolic anastomosis was done for reconstruction. Postop course was uneventful, and patient was discharged with advice to undergo adjuvant chemotherapy. Surgical excision of large size locally advanced non-functional PNET should be done with curative intention/ to treat symptoms and improve patient survival

Keywords: Neuroendocrine tumor of pancreas, Non-functioning PNET, Malignancy of pancreas, Distal pancreatectomy

INTRODUCTION

Pancreatic neuroendocrine tumors (PNET), also called as islet cell tumors, account for 1% of all pancreatic tumors. Although PNETs are rare overall, they have a better prognosis than the more common pancreatic exocrine tumors. PNETs are classified into different categories like: Functioning or non-functioning, localized or with distant metastasis, well differentiated or poorly differentiated and sporadic or familial.

The more common non-functioning tumors account for 50% of PNETs and are defined as tumors without specific symptoms due to elevated hormone levels. These tumors may be detected incidentally on imaging or when they grow to a large size and cause mass effects, obstructive symptoms, and metastatic disease. Functioning NETs present early with endocrine related symptoms. Most PNETs occur sporadically, but some may be associated with genetic syndromes like MEN-1, Von Hippel-Lindau, neurofibromatosis type 1, and tuberous sclerosis.[1-3] We present a rare case of an exceptionally large size, non-functioning PNET in a young female which on initial evaluation looked like the more frequently seen ovarian tumor. Such a large sized pancreatic mass has never been reported in the literature and thus we think it pertinent to report the case. The literature for clinical presentation and management of PNETS is also reviewed.

CASE REPORT

A 22-year female presented with a lump in the abdomen for 3 months. As per the patient, the lump was progressively increasing in size and occupied the whole abdomen. The patient had dull aching pain in the abdomen which was not related to meals. She also complained of loss of appetite for the last 1 month which was associated with weakness and loss of weight. She also complained of prolonged cycles and painful menses for the last 3 cycles. There was no history of tuberculosis, diabetes, or any other major illness in past.

The patient had undergone appendicectomy 4 years back and had a normal delivery 3 years back. Her bowel and

bladder habits were normal. Her age at menarche was 13 years. Family history was not significant.

On clinical examination, the patient was afebrile, pallor was present, and there was no icterus, cervical lymphadenopathy, or edema over foot. On abdominal examination, there was a large lump occupying the left hypochondrium, left lumbar region, epigastrium, umbilical region. The lump extended 20 cm below the costal margin in the left midclavicular line and crossed the midline on the right side for about 5 cm. The lump was firm in consistency, the surface was smooth, and the margins were well defined. There was some side-to-side mobility but no movement with respiration. Per rectal and prevaginal examination were insignificant.

Investigations

On routine hematological work-up Hb was 7.8 gm%, WBC count was 5820, and platelet count-2.49×105. Liver function and renal function test normal. Carcinoma embryonic antigen-5.68 ng/ml and AFP was 3.11 ng/ml.

USG of abdomen showed a large well-defined solid cystic heterogenous mass lesion of size 25×21×5 cm (CC×TR×AP) in abdominal cavity extending from epigastrium to the pelvic cavity with mild internal vascularity. There was no free fluid in peritoneal cavity.

Contrast enhanced CT scan (CECT) of the abdomen revealed a large infra pancreatic retroperitoneal solid cystic focus which was poorly circumscribed and heterogeneously enhancing (Figure 1 to 4). It was abutting the body and tail of the pancreas which were not seen separately from the lesion. It measured 24×22×10.2 cm (craniocaudal×transverse×anterio-posterior diameter). Claw sign on CECT could be appreciated as sharp angles on either side of the mass, which the surrounding normal pancreatic parenchyma formed suggesting the mass has arisen from the pancreas rather than just located adjacent to it. It extended in the bilateral iliolumbar, umbilical, and hypogastric regions. The splenic vein was thrombosed with opened portosystemic collaterals. The adjacent bowel loops were displaced inferiorly.

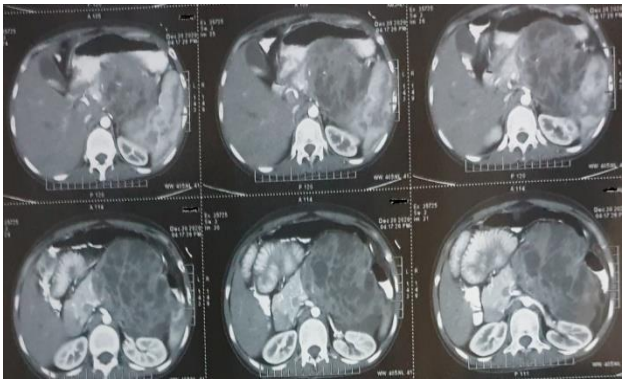

Figure 1: CECT upper abdomen showing claw sign suggesting origin from pancreas.

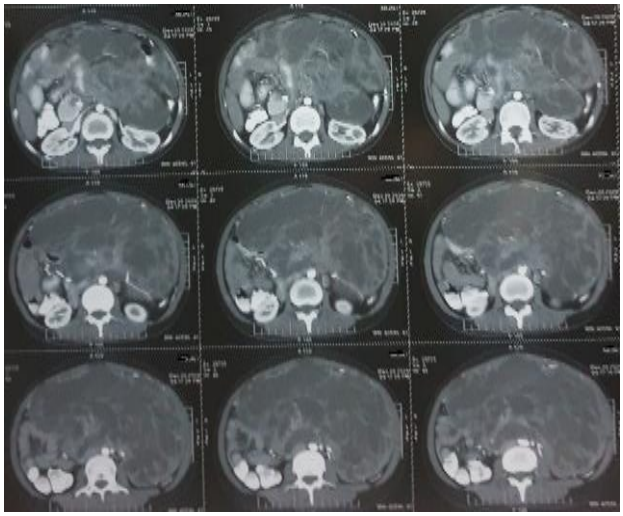

Figure 2: CECT mid abdomen showing tumor crossing midline with displacement of small intestines to right.

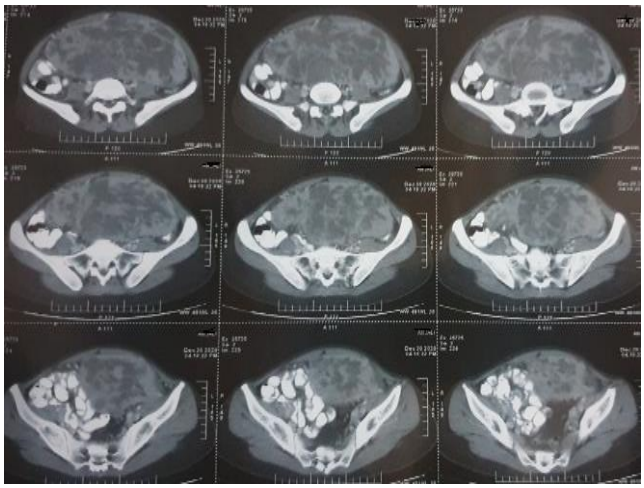

Figure 3: CECT lower abdomen showing extent of tumor in pelvis.

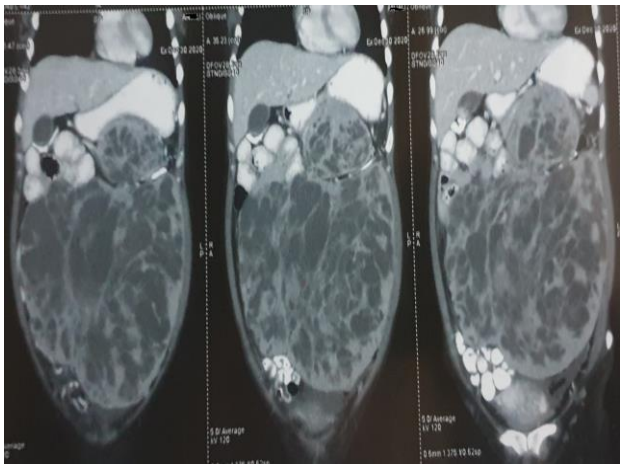

Figure 4: CECT showing the complete supracolic and infracolic extent of tumor in coronal section. The intestines are displaced in lower abdomen and pelvis.

Differential diagnosis

Based on clinical evaluation and imaging studies, a preoperative diagnosis of pancreatic neoplasm was made. Pancreatic mucinous cystadenoma and non-functioning PNET were the main differential diagnosis. Other large size tumors kept in differential diagnosis were ovarian tumor, retroperitoneal teratoma, liposarcoma, and neuroblastoma.

Treatment

The patient was optimized preoperatively by giving three units of packed RBC and planned for exploratory laparotomy for excision of the tumor. Abdomen was opened by a generous midline incision. A large heterogenous abdominal mass with solid and cystic components, covered with and adherent to the overlying omentum was seen. The mass was occupying the supracolic as well as infracolic compartments and extending from the left hypochondrium to the pelvis with all small bowel displaced to the right side and pelvic cavity.

Transvers colon was displaced anteriorly by the mass and mesocolic blood vessels were adherent to the mass. In the pelvis, both the ovaries, adenexa, and uterus were normal and separate from the mass. The lesser sac was widely opened and the supracolic part of the mass was seen merging imperceptibly with the pancreas. The whole pancreatic mass along with spleen and left colon were excised by performing a distal pancreatectomy with splenectomy and left hemicolectomy (Figure 5).

A primary colocolic anastomosis was done to establish gastrointestinal continuity. No blood transfusion was required intra-operatively and post-operatively.

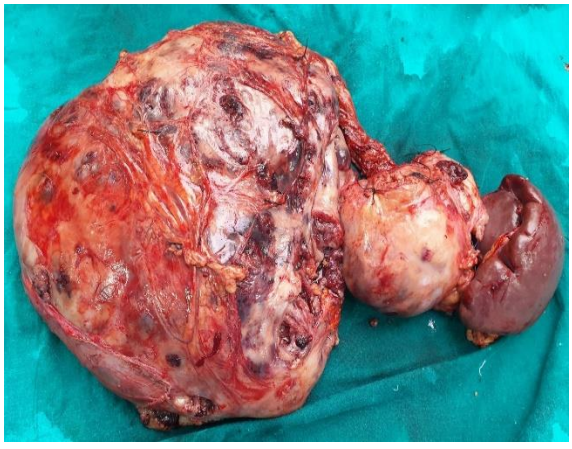

Figure 5: Excised specimen of nonfunctional PNET.

Outcome and follow-up

Postoperative course was uneventful. The patient was vaccinated for pneumococcus and meningococcus after a week. The excised distal pancreatectomy specimen with spleen and left colon were sent for histopathology.

Histopathology reports: Grossly, excised specimen consisted of 2 lobular masses with spleen and a left hemicolectomy specimen. The supracolic smaller nodular mass measured 10×7.5×8 cm with attached spleen. Extending to its inferior aspect was a larger abdominal mass measuring 23×20×8 cm. On serial slicing of whole of the mass, it showed variable grey-white to grey-brown to dark areas. Focal necrotic areas were seen.

Representative sections examined showed a large mass arising from the pancreas. This mass was cellular, and had an attenuated capsular aspect, the tumor was arranged in diffuse sheets with areas of hemorrhagic infarction and infarction necrosis. The tumor cells were small with high nucleocytoplasmic ratio, hyperchromatic round to oval nuclei, stippled chromatin, and scant cytoplasm. Few of the cells showed nuclear grooves and scant eosinophilic cytoplasm (Figure 6). Mitotic activity with an average of 2-3 mitotic figures per high power field was seen. Apoptosis was seen. The residual pancreatic tissue was seen on one side, the tumor was seen to infiltrate the pancreatic parenchyma. The tumor was seen to entrap nerve bundles. No definite lympho-vascular invasion was seen in routine-stained sections. No definite papillary configuration /eosinophilic hyaline globules were seen. No definite squamous nests were seen.

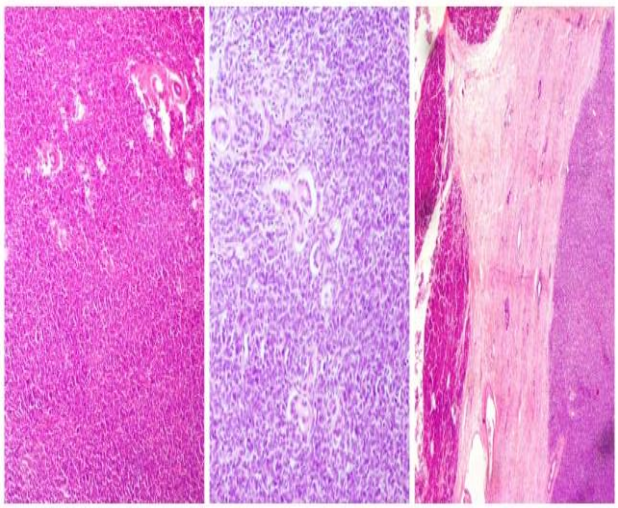

Figure 6: Histopathology nonfunctional PNET-tumor cells showing atypia, hyperchromatic nuclei with high nucleocytoplasmic ratio.

Spleen did not show any significant pathological changes, no definite metastatic tumor deposits were seen. No lymph nodes were seen in the hilar region. Sections taken from the submitted colonic segments showed submucosal edema and submucosal prominence of lymphatics, hypertrophy of muscularis, and hypertrophy of neural plexus. There was no evidence of tumor infiltration. Resection limits and the entire length of the submitted

colon was free of tumor. Lymph nodes isolated from pericolic tissue did not show any evidence of metastasis (0/2).

Immunohistochemistry tests were done for confirmation of neuroendocrine origin of tumor (Table 1).

Table 1: Immunohistochemistry findings.

Chromogranin	Negative
Synaptophysin	Cytoplasmic granular positivity
CD 99	Show intense membranous positivity in tumor cells
Bcl 2	Some expression of bcl2 seen
CD 45, CK 20, CD 10, CD 99 and CD 34	Negative
PR	Negative
CK7	Negative
WT1	Negative
EMA	Negative
SMA, vimentin	No definite expression in tumor cells, vessels, and connective tissue

Based on histopathology and immunohistochemistry the diagnosis of malignant PNET (Grade 3) was made. Attached spleen and colon were free of tumor. Possible staging: pT3NoMx

The patient was discharged on the 14th post-operative day with advice to seek consultation for adjuvant chemotherapy. The patient was last seen six months after surgery and is doing well and is in our regular follow-up.

DISCUSSION

The term 'carcinoid' (carcinoma-like) was first proposed over 110 years ago by Obendorfer to describe functional neuroendocrine tumors in the gastrointestinal tract with a slow-growing nature. Clinically, the term 'carcinoid' was restricted to describe neoplasms that secrete serotonin (5HT). The term neuroendocrine was accepted due to the recognition of the neural and epithelial elements present such as expression of neuron specific enolase, chromogranin A/B/C, and synaptophysin.

PNETs are rare neoplasms of pancreas (<3%). The prevalence of PNETs has been increasing recently due to more frequent radiological imaging.

PNETs are classified as functional or non-functional. These tumors have no gender preference and patients are typically between the ages 30-60 years. These neoplasms are usually sporadic, and sometimes they may be associated with genetic syndromes like multiple endocrine neoplasia-1, Von Hippel-Lindau (VHL), neurofibromatosis type 1 and tuberous sclerosis.[1-3]

MEN1 is an autosomal dominant genetic disease caused by an inactivating mutation of the tumor suppressor gene (MEN1) on chromosome 11q13. The most common MEN1 neoplasm is parathyroid hyperplasia (98%), followed by islet cell tumors of the pancreas (50%), and pituitary adenomas (35%). Only about 50% of MEN1 patients harbor gross PNETs. Endocrine cell hyperplasia, dysplasia, and micropnets are present in all MEN1 patients. Gastrinoma, Insulinoma, and non-functioning PNETs are commonly seen.[2,3]

VHL is an autosomal dominant inherited disorder characterized by the development of multiple benign and malignant tumors and cysts. In patients with VHL, the non-functioning PNET is usually associated with cerebellar haemangioblastoma or renal cell carcinoma. PNETs associated with VHL have a much lower rate of metastatic spread (11-20%). These non-functioning PNETs in patients with VHL should be closely observed and resected only if the diameter is >1 cm, as the other associated conditions in VHL are life threatening.[2,3]

PNETs may present with signs and symptoms related to hormone hypersecretion or due to mass effect or as an asymptomatic incidental radiographic finding. Clinically functional PNETs present more often with symptoms caused by secretion of an excess of hormones and are thus further sub classified based on the hormone produced. The hormone expressed depends on the type of neuroendocrine cell within the PNET: Alpha cells with glucagonoma, beta cells with insulinoma, delta cells with somatostatinoma, and PP with pancreatic polypeptide and VIPoma. Uncommon hormones that are reported are calcitonin, neurotensin, growth hormone releasing factor, adrenocorticotropic hormone, and serotonin.[3]

Non-functional PNETs are functionally inactive pancreatic tumors. They often secrete peptides such as chromogranin A, neuron-specific enolase, neurotensin, pancreatic polypeptide, ghrelin, and subunits of alpha-hCG. These peptides can be detected in the serum, but do not cause hormonal syndromes. Non-functional PNETs are more common and account for 50% of the PNETs. Non-functioning PNETs remain asymptomatic until they present clinically due to abdominal pain, fullness, or symptoms related to mass effect. Symptoms due to mass effect may be because of compression or obstruction such as pain abdomen, nausea, steatorrhea, anorexia, weight loss, or jaundice. Patients may also present with tumor-related complications like bleeding. Our patient was a young female (22 years) and she presented with a very large sized abdominal solid cystic mass. While large ovarian tumors are well known in young females, such a large sized pancreatic mass are very rare.

Non-functioning PNETs may be benign or malignant and its clinical differentiation may be difficult. Tumors <2 cm are more likely to be benign, 2-4 cm are of uncertain behavior, and >4 cm are more likely to be malignant. Larger tumors are more often associated with

angioinvasion, perineural infiltration, nodal, and liver metastases.

Differential diagnosis of large size pancreatic mass lesions includes adenocarcinoma (70-95%), mucinous and serous cystadenomas, PNETs, pseudopapillary tumors, pancreatoblastoma and pancreatic lymphoma. The diagnosis and management of these lesions can be challenging. Diagnosis of PNETs requires endocrine testing, imaging, and histological evidence. It is important to ascertain the functioning nature of the PNET by endocrine testing, identify the primary and metastatic loci on imaging studies, and determine the tumor grade by histology. Pancreatic polypeptide (PP), gastrin, proinsulin, insulin, glucagon, and vasoactive intestinal peptide (VIP) are the hormones most frequently produced by functioning PNETs and should be measured as per clinical requirements. Neuron specific enolase (NSE), and pancreastatin are the most useful PNET markers. In our patient there were no hormone related symptoms despite a huge pancreatic mass. The pancreatic origin of the mass was ascertained by CT imaging and diagnosis of PNET was further substantiated by histological and immunohistochemical findings.

Contrast enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) of the abdomen are useful for evaluating the pancreatic origin of tumor, lymph node, and liver metastasis. Our patient on clinical and USG evaluation was initially sent to gynecologists with a suspicion of ovarian tumor. However, CECT abdomen revealed a solid cystic mass merging imperceptibly with the pancreas with positive claw sign, and thus she was referred to us.

Nuclear imaging with octreotide may be useful to identify occult tumors not detected by CECT. Tumor biopsy is essential for PNET diagnosis, tumor grading, and immunocytochemical staining. Liver masses should be biopsied transcutaneous by ultrasound or CT guidance. Pancreatic masses can be biopsied with endosonographic guidance.

Macroscopically the PNETs display well demarcated solid masses. Fibrous capsule may be present and although the tumor is in the pancreatic parenchyma, it may protrude into the abdominal cavity without any infiltrative features. In our patient the smaller supracolic part of the tumor was in the distal pancreas, whereas the larger infracolic part protruded into the abdominal cavity posterior to the transverse mesocolon.

On histology characteristic features of PNET are tumor cells arranged in solid nests or trabecular ribbon like or gland like formations. Perivascular pseudorossette arrangement is very specific of PNET. Nuclear atypia, pleomorphism, amyloid deposition and microcalcification (psammoma bodies) may be seen. The current WHO classification for PNET is based on the mitotic index and Ki-67 labeling index.[4]

When histology is unclear in poorly differentiated tumors, immunohistochemistry may be useful in confirming diagnosis and deciding treatments. The cytoplasm of PNET tumor cell contain neuroendocrine granules which can be demonstrated by staining with chromogranin A (ChA) and synaptophysin (SYN). Expression of ChA and/or SYN. ChA has a high specificity and sensitivity in well-differentiated NETs. However, ChA may not be expressed in poorly differentiated NECs. SYN displays high sensitivity but is not necessarily specific for PNETs.[4] In our case the tumor was negative for chromogranin but was positive for synaptophysin. Markers for other tumors on immunohistochemistry were negative. Detection of somatostatin receptor (SSTR) by immunohistochemistry was not available and thus could not be done.

PNETs are potentially malignant, and treatment is recommended according to tumor size, extent of spread, and patient's fitness for surgery. Surgical resection is the primary treatment for symptomatic PNETs and removal of primary, nonmetastatic PNET is curative for the patient. Asymptomatic PNETs of <1 cm diameter without any evidence of lymph node enlargement can be kept in surveillance. Tumors with a diameter of 1-2 cm have lymph node metastases in 6 to 33%. Thus, tumors <2 cm located in the periphery of the pancreas are candidates for enucleation or local resection with lymph node sampling. Important consideration in decision making is patient fitness with acceptable surgical risk, tumor with a Ki67 >10% on endoscopic ultrasound biopsy, and whether the patient is symptomatic or is willing for resection. Malignant non-functioning PNET tumors >2 cms should be aggressively resected. Thus, tumors >2 cm should be resected with a negative margin including adjacent organs and lymph nodes. As per location of the tumor distal pancreatectomy with splenectomy or pancreaticoduodenectomy may be required. Aggressive surgical resection is also recommended in locally advanced PNETs as previous reports showed survival benefits if no residual disease is left and tumor grade is G1 or G2.[5-7] Laparoscopic resection is also recommended if negative margins and adequate lymphadenectomy can be achieved.[8]

Most of the primary metastasis of PNET is to the liver. Surgical resection of liver metastasis of non-functioning PNETs is recommended in selected patients with good performance status without life-threatening comorbidities, when complete resection is achievable and liver tumor burden is less than 25%.[9-11] While resection of liver metastasis may give a survival advantage of 60-80% at five years, the other purpose of resection may be for treating symptoms. Surgical debulking of tumor reduces the mass effect and resection of liver PNET metastases reduces the hormone secretion in functioning PNETs.

In our patient, the tumor was very large and caused mass effect, thus an aggressive approach to resect the primary

tumor and metastatic nodes was planned with an intention for locoregional control and decreasing the tumor burden. The pancreatic tumor had enlarged and protruded to the infra-colic compartment through the mesocolon of the transverse colon. Although the transverse colon was not directly infiltrated by the tumor, the blood vessels of the left colon were adherent to the mass. Thus, a left hemicolectomy was also done along with distal pancreatectomy and splenectomy.

Tierney et al evaluated the outcomes of 6548 patients with metastatic gastro-entero-pancreatic NET. In their study, they reported that patients with pancreatic NETs who underwent resection of their primary tumor demonstrated a statistically significant increase in the median overall survival; 63.6 vs 14.2 months in those who did not undergo resection.[6] A recent systematic review and meta-analysis by Zhou et al which included 10 studies with a total of 2489 patients with PNET and unresectable liver metastasis, showed that palliative resection of the primary tumor can increase overall survival.[12] Even as there is no level 1 evidence, many retrospective studies from Europe and North America have demonstrated improvement in symptom control and overall survival following debulking liver surgery in PNET patients with lymph node metastasis.

Advanced symptomatic PNETs are treated by a multimodality approach with palliative resection of primary, metastatectomy, ablative therapies (radiofrequency ablation (RFA), transcutaneous alcohol ablation, and microwave ablation), locoregional therapy of liver metastases given by radioactive polymer microspheres, chemoembolization, and bland embolization, systemic chemotherapy etc.

Mayo et al in their propensity matching analysis examining the relative efficacy of surgical management versus intraarterial therapy (IAT) observed that asymptomatic patients with a large (>25%) burden of liver disease benefited least from surgical management and IAT may be a more appropriate treatment strategy.[13] Liver directed therapies with transarterial embolization and selective intraarterial radiotherapy, have higher rates of objective response for liver tumor burden than systemic therapies. Systemic therapies used to control the tumor burden in well-or moderately differentiated metastatic PNETs include long-acting octreotide analogs, chemotherapy, or vascular endothelial growth factor inhibition (everolimus or sunitinib).[14,15] While somatostatin analogues are useful in the management of functioning PNETS, they most likely restrain tumor growth in non-functioning PNETs as well. Two somatostatin analogs, octreotide and lanreotide, are currently available. Chemotherapy is reserved for intermediate and high-grade tumors. Cisplatin and etoposide or 5 fluorouracil and streptozocin are recommended treatment combinations for patients with high grade PNETs. Other chemotherapy drugs used are capecitabine and temozolomide. Targeted therapies such as everolimus or sunitinib has prolonged progression-free survival for about 11 months.

Peptide receptor radiotherapy (PRRT) by coupling somatostatin analogues with radionuclides yttrium-90 or lutetium-177 has shown a response rate of 10-40%. It carries bone marrow and renal toxicity and should be reserved for cases not responsive to less toxic systemic therapies.

These tumors progress along different pathways from indolent to aggressive and have differing outcomes. Syndromic PNETs usually behave aggressively in contrast to their sporadic counterparts. Important prognostic factors for PNETs are metastatic spread, large tumor size, hormonal hypersecretion, age, and histopathological high-grade angioinvasion, pancreatic capsular invasion and Ki67. The 5-year survival reported is 65%, and 10-year survival is 45%.

Post operatively, the patient is to be kept in active surveillance for the first 5 years as most recurrences occur within 5 years of resection. The patients will be followed up clinically and with imaging studies either CECT or MRI abdomen every 6 monthly in the first year and then annually for the next 4 years.

CONCLUSION

Patients with PNETs should be managed aggressively, preferably at academic centers with a multidisciplinary team. Surgical excision of locally advanced non-functional PNET with curative or palliative intent is done with the intention to treat the symptoms and improve patient survival. Locally advanced large size non-functioning PNETS can be resected in selected patients with good performance status and without life threatening comorbidities.

ACKNOWLEDGEMENTS

The authors would like to thanks for contribution to Prof. Vaishali Waindesker, professor and head, department of anesthesia and critical care, AIIMS Bhopal in patient management. Prof. Dr. Vaishali A Walke, professor, department of pathology and lab medicine, AIIMS Bhopal contributed in microscopic and immunohistochemical evaluation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Saxena P, Bhardwaj S, Sutrave T, Lalchandani A. A rare case of malignant pancreatic non-functional neuroendocrine tumor presenting as huge abdominal lump. Int Surg J 2022;9:1094-100.