

Primitive Neuroectodermal Tumour of Pancreas; Second Case from Asia

Khalid Hamid CHANGAL¹, Mohmad Hussain MIR², Sheikh Aeja AZAZ², Sumyra Khurshid QADRI³, Abdul Rashid LONE²

Submitted: 3 Feb 2014

Accepted: 8 Jun 2014

¹ Department of Internal Medicine, Sher-i-Kashmir Institute of Medical Sciences, Srinagar 190011, India

² Department of Medical Oncology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar 190011, India

³ Department of Pathology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar 90011, India

Abstract

Primitive neuroectodermal tumours (PNETs) are malignant tumours composed of small round cells of neuroectodermal origin that affect soft tissue and bone. PNETs originating in the pancreas are extremely rare; previous to this report, only 14 cases were reported worldwide, making this case the fifteenth in the world and the second in Asia. We present the case of a painful pancreatic lump diagnosed as PNET of the pancreas after a thorough workup. The diagnosis of PNET is made according to the overall clinical picture, imaging, histopathology, cytogenetics, and immunohistochemistry, as in the case we present. It is essential to differentiate primary pancreatic PNET from a secondary involvement. A review of all of the cases diagnosed worldwide thus far is also provided.

Keywords: pancreas, neuroectodermal tumors, primitive, pancreatic neoplasms

Introduction

Primitive neuroectodermal tumours (PNETs) are highly malignant tumours composed of small round cells of neuroectodermal origin. Batsakis et al. divided the PNET family of tumours into the following three groups, based on the tissue of origin (1): central nervous system primitive neuroectodermal tumours; tumours derived from the autonomic nervous system called neuroblastomas; and peripheral primitive neuroectodermal tumours (pPNETs), which are derived from tissues outside the central and autonomic nervous systems.

PNETs usually originate in soft tissues and bone. In rare cases, these tumours have also been found in organs such as the kidney, urinary bladder, uterus, gall bladder, lung, and vagina (2–6). It is extremely rare for PNETs to originate in the pancreas. Previous to this report, only 14 cases were reported worldwide, making this case the fifteenth in the world, the second in Asia, and the first in India.

Case Report

A 60-year-old farmer presented to our hospital with a one-month history of dull, boring pain in the epigastrium that was mild to moderate in intensity. There was no associated jaundice, diarrhea, or vomiting. The clinical examination was significant for a non-tender, firm, fixed lump measuring 3 × 3 cm that was felt in the supraumbilical area. There was no palpable superficial lymphadenopathy. The laboratory data were normal, except for moderately elevated serum amylase and lipase. An ultrasonogram of the abdomen showed a 3.1 × 2.2 cm solid lesion in the region of the pancreatic head, with the main pancreatic duct appearing prominent distal to the mass lesion. Multiple enlarged peripancreatic lymph nodes were also observed. Contrast-enhanced computed tomography (CECT) confirmed a hypodense mass measuring 4 × 3.7 × 2.5 cm in the head region, and multiple enlarged peripancreatic nodes were seen. The fat planes with surrounding tissues appeared normal on the CECT (Figure 1).

Ultrasound-guided aspiration from the pancreatic mass was performed, and microscopy of the aspirated material revealed round tumour cells dispersed individually, mostly with focal clumps. A histopathologic possibility of round cell tumour was made, and an open biopsy was planned to take an adequate sample of the surrounding lymph nodes. Operative findings were multiple enlarged, matted lymph nodes at the root of the mesentery, the celiac axis, and the pancreatic head mass. The transverse mesocolon and omentum were found to be adhered, and the superior mesenteric vein was thrombosed with

multiple collateral vessels. The biopsy from a lymph node showed features of small round cell tumour with pseudorosetting infiltrating the node, suggestive of PNET. A mitotic count of 19/hpf was noted (Figure 2). The growth was found to be too locally advanced for surgical resection and was not excised; only a few surrounding lymph nodes were excised. A clinical examination and imaging showed no evidence of any other metastatic lesion or primary anywhere else in the body, and a bone scan showed normal results.

Immunohistochemistry (IHC) showed the tumour to be positive for membranous expression

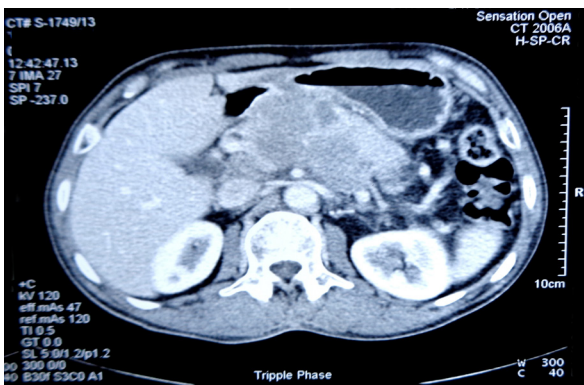


Figure 1: Abdominal contrast-enhanced computed tomography (CECT) showing a hypodense mass measuring $4 \times 3.7 \times 2.5$ cm in the head region of the pancreas.

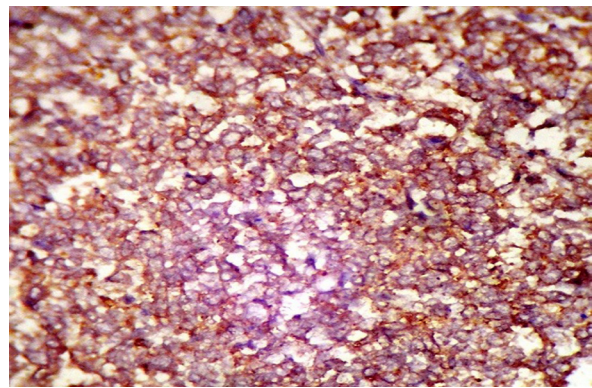


Figure 3: Immunohistochemistry of the tumor, positive for membranous expression of CD99.

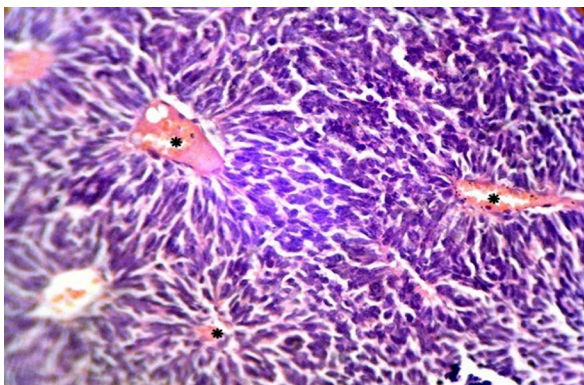


Figure 2: Biopsy showing features of small round cell tumor with pseudorosettes infiltrating the node, suggestive of primitive neuroectodermal tumours (PNET). A mitotic count of 19/hpf was seen. The pseudorosettes are indicated with asterisks.

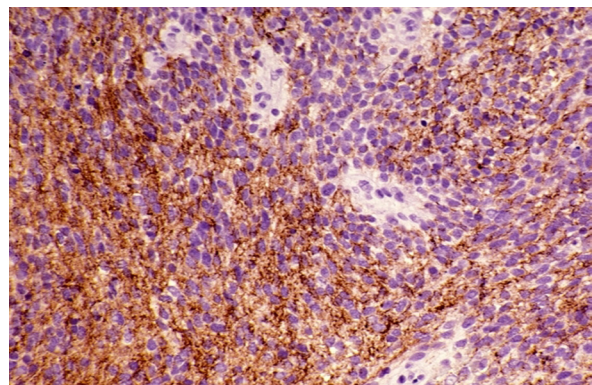


Figure 4: Photomicrograph showing diffuse strong immunostaining for synaptophysin.

of CD99 (Figure 3), NSE, FLI-1, synaptophysin (Figure 4) and cytoplasmic vimentin (Figure 5). Cytokeratin (AE1/AE3) and chromogranin staining were negative. Lymphoid markers LCA, CD3, CD20, CD79a, CD43, CD34, and TdT were negative. Cytogenetic analysis by fluorescence in situ hybridisation confirmed t (11; 22) (q24; q12) translocation.

With this clinical picture, imaging, histopathology, IHC, and cytogenetic analysis, a diagnosis of primary PNET of the pancreas was made. The patient received three cycles of VIDE (vincristine, ifosfamide, doxorubicin, and etoposide) chemotherapy and is planned to undergo three more cycles to reassess for surgery. At three months' follow up, the patient's symptoms improved. A repeat ultrasound after three cycles of chemotherapy showed that the tumour had started to shrink. Prolonged follow up after surgery and reassessment for chemotherapy will be required.

Discussion

Stout first provided a description of PNETs in 1918. At the time, they were thought to originate directly from the nerves (7). PNETs are members of the Ewing's sarcoma family. These neoplasms all exhibit a neural phenotype and express MIC2 protein (CD99), and the same chromosomal translocation between chromosomes 11q24 and 22q12 is observed in approximately 85% of cases (8). Ewing's sarcoma is a primary tumour of bones, and PNETs tend to occur predominantly in soft tissues. Sites favored are the thoracopulmonary region, pelvis, and lower limbs of children and young adults. Most patients are younger than 35 years, and there is a

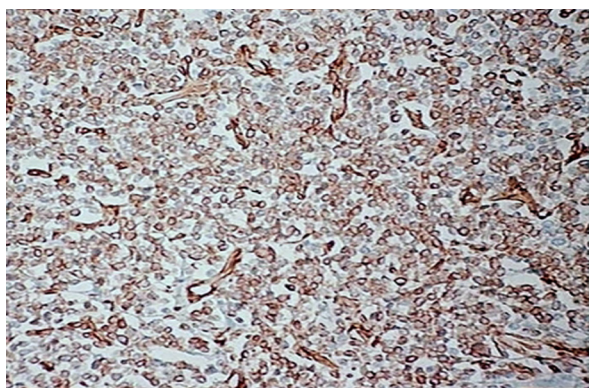


Figure 5: Photomicrograph showing positive immunostaining for vimentin.

slight predominance of males (8). pPNET makes up approximately 1% of all sarcomas (2). When PNET is found in the pancreas, the differential diagnosis includes undifferentiated small cell carcinoma, pancreatoblastoma, pancreatic endocrine tumours, and rarely, lymphoma. Thus, the diagnosis of PNET necessitates histopathologic, immunohistochemical, and if possible, genetic analysis. Translocation t (11; 22) (q24; q12) results in the fusion product EWS-FLI1 and is found in approximately 85–95% of cases. A second translocation, found in approximately 10% of cases, is t (21; 22) (q22; q12) (8).

It is extremely uncommon for PNETs to originate in the pancreas. Luttges found that only two cases among 600 primary pancreatic neoplasms were pancreatic PNETs (6). Previous to our report, there were only 14 cases of pancreatic PNETs reported worldwide (2–6,9,10). In the previous cases, all of the patients were young (6–33 years); eight were male and six were females. Most patients presented with abdominal pain, jaundice, dyspepsia, and vomiting. Only one patient had hyperglycemia. Anemia or upper gastrointestinal bleeding can also be the initial presentation. The lesions varied in size from 3.5 cm to 15 cm. Whipple resections were performed in eight of the 14 patients, and four patients were diagnosed by some form of biopsy. Laparotomy was required in one patient, and resection of the uncinate process was performed in another. Four patients were treated with chemotherapy alone following surgery; one patient had no evidence of disease at 33 months' follow up, one patient died of the disease at 48 months' follow up, and the outcomes of the other two patients were not available. Four patients received radiation and chemotherapy following surgery; one of the patients died of the disease and the other three were alive with the disease, although with not a comparable follow up to each other. Two patients were treated only with a Whipple resection; one patient was alive at 27 months' follow up and the other one died after recurrence at six months' follow up.

Computed tomography (CT) and magnetic resonance imaging are the imaging modalities of choice for visualising tumours. On imaging, the most common lesion is a tumour in the pancreatic head with clear margins. A CT scan of the abdomen may show a tumour of varying density if it is undergoing necrosis. As most of these tumours do not have a close relationship with arteries, they are usually without enhancement in the arterial phase. In cases of advanced disease,

local or remote metastasis may be visualised (11). For pathological diagnosis, direct histological evidence of the PNETs and distinction from other small round cell tumours are important. Homer-Wright rosettes and atypical rosette arrays of the cells are uncommon in pancreatic PNETs. Cell cytoplasm holding neurofilaments and neuronal secretory and pyknic nucleus granules are the significant criteria for the diagnosis of pPNETs (2–6).

Approximately 85% of all Ewing’s tumors display a translocation that includes the EWS gene (22q12) and FLI-1 (11q24). In the other 5–10% of cases, the translocation is found between EWS and ERG (21q22) (14,15). IHC can be used to detect antibodies to FLI-1 in the gene fusion product of EWS (14). pPNETs typically co-express CD99 and vimentin. Other markers are S-100, neuron-specific enolase, synaptophysin, and CD75 (15). A summary of the markers tested in the previous 14 cases of PNET of pancreas is presented in Table 1 (2–6,10).

Thus, the diagnosis is made by taking into account overall clinical picture, imaging, histopathology, and IHC. It is also essential to differentiate between primary pancreatic PNET and a secondary involvement.

The treatment for PNET includes systemic multi-agent chemotherapy along with surgery

and/or radiotherapy. Disseminated disease at the time of diagnosis is associated with a worse outcome compared with localised disease (16). Chemotherapy protocols such as CAV (cyclophosphamide, adriamycin, and vincristine) and neoadjuvant chemotherapy protocol (vincristine, dactinomycin, adriamycin, cyclophosphamide, ifosfamide, etoposide) are usually used, and local radiotherapy is also used with some efficacy. Unfortunately, these treatments are not very satisfactory (17).

Conclusion

To conclude, PNET of the pancreas is an extremely rare condition, but it should be kept in mind. Our case is only the second case reported in Asia, and more work is definitely needed to understand the disease and how to treat it.

Acknowledgement

None.

Conflict of Interest

None.

Funds

None.

Authors’ Contributions

Conception and design, critical revision of the article for the important intellectual content: KHC, MHM, SAA, ARL

Analysis and interpretation of the data: KHC

Drafting of the article: KHC, SKQ

Final approval of the article: MHM, ARL, SAA

Provision of study materials or patient: MHM, SKQ

Administrative, technical or logistic support: KHC, ARL, SKQ

Collection and assembly of data: KHC, MHM

Table 1: The summary of the markers tested in the previous 14 cases of primitive neuroectodermal tumours (PNET) of pancreas. The positive percentage of the markers is mentioned in the brackets

Marker	Number of cases tested	Number of times tested positive
CD99	13	13 (100%)
NSE	13	12 (92%)
AE1/AE3	11	8 (72.7%)
Chromogranin	12	1 (8.3%)
Synaptophysin	14	5 (35.7%)
Desmin	9	1 (11.1%)
S-100	4	2 (50%)
Vimentin	5	1 (20%)
Leu 7	1	1 (100%)
Insulin	4	0 (0%)
Glucagon	4	0 (0%)
Somatostatin	4	0 (0%)

Correspondence

Dr Khalid Hamid Changal

MBBS (India)

Department of Internal Medicine

Sher-i-Kashmir Institute of Medical Sciences

Srinagar 190011

India

Tel: +91-9469049626

Email: khalidchangal@gmail.com

References

- Batsakis JG, Mackay B, el-Naggar AK. Ewing's sarcoma and peripheral primitive neuroectodermal tumor: an interim report. *Ann Otol Rhinol Laryngol*. 1996;**105**(10):838–843.
- Movahedi-Lankarani S, Hruban RH, Westra WH, Klimstra DS. Primitive neuroectodermal tumors of the pancreas: a report of seven cases of a rare neoplasm. *Am J Surg Pathol*. 2002;**26**(8):1040–1047.
- Bülchmann G, Schuster T, Haas RJ, Joppich I. Primitive neuroectodermal tumor of the pancreas. An extremely rare tumor. Case report and review of the literature. *Klin Padiatr*. 2000;**212**(4):185–188. doi: 10.1055/s-2000-9675.
- Perek S, Perek A, Sarman K, Tuzun H, Buyukunal E. Primitive neuroectodermal tumor of the pancreas. A case report of an extremely rare tumor. *Pancreatol*. 2003;**3**(4):352–356. doi: 10.1159/000071776.
- Danner DB, Hruban RH, Pitt HA, Hayashi R, Griffin CA, Perlman EJ. Primitive neuroectodermal tumor arising in the pancreas. *Mod Pathol*. 1994;**7**(2):200–204.
- Lüttges J, Pierré E, Zamboni G, Weh G, Lietz H, Kussmann J, et al. Malignant non-epithelial tumors of the pancreas. *Pathologe*. 1997;**18**(3):233–237.
- Stout AP. A tumor of the ulnar nerve. *Proc NY Pathol Soc*. 1918;**18**:2–11.
- de Alava E, Gerald WL. Molecular biology of the Ewing's sarcoma/primitive neuroectodermal tumor family. *J Clin Oncol*. 2000;**18**(1):204–213.
- O'Sullivan MJ, Perlman EJ, Furman J, Humprey PA, Dehner LP, Pfeifer JD. Visceral primitive peripheral neuroectodermal tumors: a clinicopathologic and molecular study. *Hum Pathol*. 2001;**32**(10):1109–1115. doi: 10.1053/hupa.2001.28247.
- Mao Y, Sang X, Liang NX, Yang H, Lu X, Yang Z, et al. Peripheral primitive neuroectodermal tumors arising in the pancreas: the first case report in Asia and a review of the 14 total reported cases in the world. *Hepatobiliary Surg Nutr*. 2013;**2**(1):51–60. doi: 10.3978/j.issn.2304-3881.2012.08.01.
- Obuz F, Kovanlikaya A, Olgun N, Sarialioglu F, Ozer E. MR imaging of pancreatic metastasis from extrasosseous Ewing's sarcoma. *Pancreas*. 2000;**20**(1):102–104.
- Turc-Carel C, Aurias A, Mugneret F, Lizard S, Sidaner I, Volk C, et al. Chromosomes in Ewing's sarcoma. I An evaluation of 85 cases of remarkable consistency of t (11; 22) (q24; q12). *Cancer Genet Cytogenet*. 1988;**32**(2):229–238.
- Zucman J, Melot T, Desmaze C, J Ghysdael, Plougastel B, Peter M, et al. Combinatorial generation of variable fusion proteins in the Ewing family of tumours. *EMBO J*. 1993;**12**(12):4481–4487.
- Liu BY, Yang Y, DU J, Zhang Y, Wang H, Zheng J. [Application of the in situ hybridization with EWS dual-color break-apart fluorescence probe and anti-CD99 and anti-FLI-1 antibodies in the diagnosis of Ewing's sarcoma/primitive neuroectodermal tumor]. *Beijing Da Xue Xue Bao*. 2008;**40**(4):358–362.
- Armbruster C, Huber M, Prosch H, Dworan N, Attems J. Ewing's sarcoma and peripheral primitive neuroectodermal tumor in adults: different features of a rare neoplasm. *Onkologie*. 2008;**31**(4):179–184. doi: 10.1159/000118034.
- Eralp Y, Bavbek S, Başaran M, Kaytan E, Yaman F, Bilgiç B, et al. Prognostic factors and survival in late adolescent and adult patients with small round cell tumors. *Am J Clin Oncol*. 2002;**25**(4):418–424.
- Zogopoulos G, Teskey L, Sung L, Dix D, Grant R, Greenberg ML, et al. Ewing sarcoma: favourable results with combined modality therapy and conservative use of radiotherapy. *Pediatr Blood Cancer*. 2004;**43**(1):35–39. doi: 10.1002/pbc.20037.