REVIEW ARTICLE

A Review of a Rare Entity in Pancreas- Extraosseous Ewing's Sarcoma

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ABSTRACT

Extraosseous Ewing's sarcoma/primitive neuroectodermal tumor is a rare malignant tumor with poor outcome. It is mostly reported in the second decade of life with equal in males and females. It is an aggressive tumor with unavoidable multiple recurrences and relatively poor prognosis. These tumors can be easily misdiagnosed for different tumors due to lack of established diagnostic pathological criteria. Hence, in the cases of pancreatic tumors, it is necessary to highlight the importance of considering Ewing's sarcoma/primitive neuroectodermal tumor in the differential diagnosis. For the better management, and improved prognosis and survival of these patients, it is necessary to understand the biological characteristics of this tumor in detail. We here present a review of 24 cases of extraosseous Ewing's sarcoma. Chemotherapy combined with surgery showed relatively better outcome with 5 year survival rate of 80%.

INTRODUCTION

Ewing's sarcoma (ES), a malignant osteolytic tumor, characterized as small round cell tumors was first documented by James Ewing in the year 1921 as diffuse endothelioma of bone. Rarely, it also has extra osseous manifestations which resemble intraosseous ES. This extra osseous forms of ES was first described by Tefft in 1969 [1]. Ewing's sarcoma (ES) family of tumors include: classical ES (osseous origin), atypical ES (extra osseous), Primitive neuroectodermal tumor (PNET) and Askin tumor [2]. All these tumors have common morphology, immunophenotypic features and cytogenetics, hence included in the same family of tumors. These tumors were believed to be derived from a primitive cell. The primitive cell can be either the neural crest or mesenchymal stem cells. The definitive origin is yet to be determined [3]. ES occurs due to cytogenetic alterations – t (11:22) translocation which led to the formation of the fusion protein (EWS-FLI1). Osseous ES are more commonly found in the diaphysis of long bones of pelvis, distal femur, proximal tibia, femoral diaphysis, and proximal humerus. Rarely, ES/PNETs can also have extra osseous manifestations. Similar cases have been reported to arise from solid organs like lung, gall bladder, kidney, urinary bladder, uterus, and vagina. Extra osseous manifestation of PNETs in the pancreas is extremely rare.

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DISCUSSION

We aimed to focus on Pancreatic Ewing's Sarcoma (ES/PNET) in this literature review. In total, only 24 cases have been reported world-wide up-to-date **(Table 1)**. From the review of all 24 cases, we found that the age ranged from 2 years to 60 years. The average age was 23 years. There was no significant difference in the sex within these reported cases. The most common signs and symptoms of these patients were abdominal pain, jaundice, abdominal mass, vomiting, and dyspepsia. 10 patients out of 24 showed positive cytogenetic analysis t(11; 12) (q24; q12). The main treatment of the disease from our review was surgery along with chemotherapy +/- radiotherapy. 17 out of 24 patients received chemotherapy after surgery. 5 out of 24 patients had multiple recurrences after combined surgery and chemotherapy.

The incidence of Ewing sarcoma is 1 per million for people of all ages in the United States and it has remained unchanged for 30 years [4, 5]. It is most common in whites, less frequently seen in Asians [5, 6]. The occurrence of extra osseous Ewing's Sarcoma in the Pancreas (ES/PNET) is very rare. From the world-wide literature review, only 24 cases of have been reported up to date.

The fusion partner of EWS is FLI1 gene on chromosome 11 and ERG gene on chromosome 22 in approximately 90% and 10% respectively. Rarely, many other genes from the

Table 1. Review of case reports on extra-osseous Ewing's Sarcoma in Pancreas.

Case no.	Reference	Age/ Sex	Symptoms	Size (cm)	Cytogenetic Analysis	Light microscopy and Immunohistochemical (IHC) Stain	Diagnostic Procedure	Treatment	Metastasis and Recurrence	Clinical follow-up and Outcome
1	Bulchmann *et al.* [2]	6/F	Abominal pain, Anemia	5.5	Postmortem FISH demonstrated loss of cosmids F7 and E4 distal of the EWSR1 breakpoint in nearly all cells	Atypical small round cells positive for pancytokeratin, NSE, gamma-enolase and squamoid corpuscles; negative for desmin and chromogranin, focally positive for S100 and MIC2; initial diagnosi pancreatoblastoma; later revised after rosettes found in lymph nodes	Whipple resection	N/P	6 mo; Recurrence	6 months; DOD
2		13/F	Dyspepsia, Vomiting	22	NA	NA	Whipple resection	Chemotherapy	NA	NA
3		31/M	Abdominal pain, loss of appetite	NA	NA	NA	Biopsy	Chemotherapy	NA	NA
4	Mao *et al.* [12]	17/M	Abdominal pain	9	t(11;12)(q24;q12)	NA	Whipple resection	Radiotherapy, Chemotherapy	N/P	8 months, AWD
5		13/F	Abdominal pain, Diabetes Mellitus type2	3.5	t(11;12)(q24;q12)	Small round and oval cells with scant cytoplasm. The tumor was separated by fibrous connective tissue into the folial parts. Granular nuclear chromatin and karyokinesis phenomenon with unclear nucleoli were found. There were no Homer-Wright rosettes in the tumor cells. positive for CD99, NSE.	Resection of the uncinate process	Radiotherapy / Chemotherapy-Four courses of VAC.	9/36 months, recurrence;12 months, ascites	41 months; AWD
6	Rao *et al.* [25]	47/F	Abdominal pain	10×15	-	Sheets of small round cells with enlarged round to oval nuclei, fine stippled chromatin, PAS positive clear cytoplasm. Areas of necrosis with focal peritheliomatous proliferation of tumor cells around the blood vessels, increased mitosis, nuclear moulding were noted. In some areas, tumor islands were surrounded by desmoplastic stroma. CD99 positive, while cytokeratin (CK), desmin, synaptophysin (SYP), and chromogranin (CHR) were negative	Excision of the tumor with a distal pancreatectomy and splenectomy	Alternating IE and VAC	Negative	AWD
8		17/M	Jaundice, abdominal pain	9	t(11;12)(q24;q12)		Whipple resection	VDC	NA	33 months, NED
9		20/M	Jaundice, abdominal pain	3.5	+ t(11;12) (q24;q12)		Whipple resection	N/P	NA	27months, AWD
10	Movahedi-Lankarani *et al.* [13]	21/F	Abdominal Pain	NA	t(11;12)(q24;q12)		Whipple resection	NA	NA	Died of post-operative complications
11		25/F	Abdominal Pain	NA	NA	Sheets and lobules of small cells with round to oval nuclei and scant cytoplasm, no Homer Wright rosettes, strong membrane positivity for CD99, 5 of 6 cases diffusely expressed cytokeratin AE1/AE3 and 6 of 7 were positive for NSE	Biopsy	NA	NA	NA
12		25/F	Jaundice, Abdominal pain	8	-		Biopsy	NA	NA	NA
13		13/M	Abdominal pain	6	NA		Biopsy	NA	N/P	43 months; NED
14		6/M	Jaundice, Abdominal Pain	3.5	t(11;12)(q24;q12)		Whipple	VDC	48 months; Recurrence	48 months; DOD
15	Perek *et al.* [28]	31/M	Abdominla pain, fever	10	-	No lymph node metastases or Homer Wright rosettes, pseudopapillae present. Tumor cells positive for vimentin, CD99, Leu 7 and focally for synaptophysin	Whipple	Radiotherapy, ifosfamidex6; docetaxel and palliative resection	4months, Recurrence; 24mo/36mo lung	50 months, DOD

16	Welsch *et al.* [14]	33/M	Abdominal pain	15	t(11;12)(q24;q12)	Nests of medium-sized round or oval tumor cells with enlarged round or oval nuclei and scant cytoplasm surrounded by fibrovascular septae; focal Homer Wright rosettes, consistent and strong membranous expression of CD99, strong cytoplasmic staining for vimentin	Laparotomy	Radiotherapy, Chemotherapy	Simultaneously, liver, spleen	12 months, AWD
17	Teixeira *et al.* [19]	28/F	Abdominal pain, pruritus, jaundice, choluria, and acholia	13×9	-	Small round blue cells with scant cytoplasm arranged in nests with fibrovascular stroma. Few mitosis pictures and several areas of necrosis were also found. Strongly positive for CD99, vimentin, automated CKM (creatine kinase, muscle), and CD56. Negative for chromogranins, synaptophysin, neuroblastoma, myogenin, automated CD10, β-catenin, automated RP (ribosomal protein), and LCA (leucocyte common antigen).	gastroduodenopancreatectomy	-	-	discharged on the 13th day after surgery, no recurrence
18	Changal *et al.* [15]	60/M	Abdominal Pain	3×3	FISH confirmed t (11; 22) (q24; q12) translocation.	Small round cell tumour with pseudorosetting infiltrating the node, suggestive of PNET. Positive for membranous expression of CD99, NSE, FLI-1, synaptophysin and cytoplasmic vimentin. Cytokeratin (AE1/AE3) and chromogranin staining were negative	Biopsy	Three cycles of VIDE (vincristine, ifosfamide, doxorubicin, and etoposide)	-	A repeat ultrasound after 3 cycles of chemotherapy - tumour shrinked. Prolonged follow up after surgery and reassessment for chemotherapy will be required.
19	Schutte and Knight *et al.* [20]	2/F	Pubic hair, breast development, vaginal bleeding for 6 months and an upper abdominal mass, markedly elevated estrogen levels and a prominent, large uterus	6×4	NA	Tumor invaded pancreatic surface, but not adjacent structures; resected lymph nodes not involved, but LVI present; examining pathologist's "best diagnosis" was PNET with divergent differentiation	Distal pancreatectomy	adjuvant chemotherapy with VDC alternating with cisplatin and etoposide	-	hormone levels normalized by 1 month after surgery, CT scans showed NED at 1 year follow-up and all pubertal changes regressed
20	Menon and Juraida *et al.* [21]	8/F	Abdominal pain and menstrual bleeding, breast development and pubic hair; markedly elevated estradiol levels	10×6×10	NA	Mass occupying whole pancreas and obstructing distal CBD found at laparotomy; no lymph node or other metastases; sheets of small round cells, MIC2 positive and LCA negative	Laparotomy with biopsies and cholecystostomy	chemotherapy and radiotherapy; cumulative doxorubicin	-	CR without further surgery, hormone levels normalized and pubertal signs regressed; presented with cardiac failure 1 month after completing treatment, fatal cardiac arrest 19 months after diagnosis
21	Doi *et al.* [16]	37/M	Jaundice	NA	"FISH showed an EWSR1 rearrangement at 22q12" an EWSR1 rearrangement at 22q12	Atypical small round cells with scant cytoplasm and round nuclei with distinct nuclear membranes, positive for vimentin, CD99 (MIC2), CD56 and NSE; one lymph node was involved	Pancreatoduodenectomy and hepatic resection,	7 cycles of VDC alternating with IE, as well as radiation therapy to bone metastases plus RFA of one hepatic lesion found on FDG-PET/CT after resection	multiple liver and lung metastases; Bone metastasis	One year after diagnosis, lung and bone tumors had diminished; was in good health at time of writing
22	Jing *et al.* [30]	24/F	Exophytic PNET in pancreatic uncinate process	10×10×8	NA	NA	Surgery (tumor nvading the transverse colon, capsule of right kidney and mesentery)	Radiation and chemotherapy for recurrent disease;	Recurrent PNET	Doing well at time of report

23	Bose *et al.* [17]	35/M	Gallstone pancreatitis	3	FISH using a probe for the EWSR1 gene located at 22q12 revealed a rearrangement hybridization signal in each of 100 nuclei analyzed	Small, round and undifferentiated hyperchromatic tumor cells with oval to round nuclei, coarse chromatin and scant cytoplasm arranged in trabeculae, sheets and lobules, strongly and diffusely immunoreactive to vimentin and CD99	Distal pancreatectomy, splenectomy and cholecystectomy	Adjuvant VAC alternating with IE (no specific evidence of malignancy seen on ostoperative PET/CT)	NA	Doing well at time of writing (18 months from diagnosis) with no evidence of recurrence on PET/CT performed at completion of adjuvant treatment
24	Maxwell *et al.* [18]	11/M	Fatigue, abdominal pain	9.8×7.8 ×6.4	EWSR1-ERG fusion transcript by RT-PCR	Biopsies from duodenal ulcer showed a small blue cell tumor with strong diffuse membranous staining for CD99; also positive for broad-spectrum cytokeratin and vimentin	Whipple procedure	VDC alternating with IE	NA	CT after 3 months of chemotherapy showed significant shrinkage of mass and LAD; EGD showed resolution of ulcer

AWD alive with disease; DWD died with disease; IE ifosfamide and etoposide; NA not available; NED no evidence of disease; N/P not performed; RT-PCR reverse transcriptase - polymerase chain reaction; VAC vincristine, adriamycin, and cyclophosphamide; VDC vincristine, doxorubicin, cyclophosphamide

family members of ETS have also been identified as the fusion partners of EWS [7]. According to Lin *et al*. 95% of cases of ES occur from EWS/FLI1 fusion gene formation as a result of transformation. Due to the difference in the locations of the EWS and FLI1 genomic breakpoints, it resulted in the existence of alternative forms of the chimeric gene. There are two most common forms, type 1 and type 2 accounting to 60% and 25% of the cases respectively. Type 1 consists of the first 7 exons of EWS joined to exons 6-9 of FLI1 and type 2 includes FLI1 exon 5 also [8]. The prognosis of type 1 fusion is significantly better prognosis than the other fusion types as observed by Lin *et al*. a less active chimeric transcription factor is encoded by the type 1 fusion gene explaining the heterogeneous forms of ES at the molecular level. Particular chromosomal translocations are strongly associated with the development of PNET. The products of the fusion genes resulted from the translocations are specific to the type of tumors. In ES/PNETs, karyotype of t(11;22)(q24;q12), which results from the EWS-FLII gene infusion and t(21;22)(q22;q12), which results from EWS-ERG gene infusion account for 85% and 10% respectively [9, 10, 11]. In reports of ES/PNETs, there are eight cases which chromosome translocation are t(11;22)(q24; q12) while three cases with t(21;22)(q22;q12) and loss of cosmids F7 and E4 distal of the EWS-R1 breakpoint in nearly all cells in one case [2, 12, 13, 14, 15, 16, 17, 18].

ES is an undifferentiated tumor lacking neural differentiation in the primitive cells, but some tumors have cells with neural differentiation as they contain Homer-Wright rosettes. The classic ES appears like that of a primitive, undifferentiated neoplasm morphologically. Histologically, there are small round blue cells in the form of monotonous sheets with hyperchromatic nuclei and scant cytoplasm [8]. All the 24 cases in this review satiate these histologic criteria **(Table 1)** [19, 20, 21]. The tumor consists of extensive necrotic areas but viable tumor is usually preserved around blood vessels. Some tumor cells can also invade blood vessels. Some features are absent typically like nuclear atypia, palisading, and formation of rosettes (where the tumor cells are arranged in a circle about a central fibrillary space, indicative of neural differentiation or pseudo rosettes. The markers like P30/32MlC2 and at least two kinds of neuronal markers are the immunohistochemical criteria for the diagnosis of PNET [12]. Monoclonal antibodies like CD99, O13, HBA71, 12E7, RFB1 are also tested although none of them are actually specific for PNETs [12]. The neural markers like Neuron Specific Enolase (NSE), Chromogranin A (CgA), Synaptophysin (Syn) are usually positive but markers such as desmin, actin, S-100, insulin, glucagons, somatostatin are rarely positive.

In extra osseous Ewing's sarcoma, the mean age is 20(0-39), male: female is 53%: 47%. Other characteristics are 85% in whites, 73% in axial primary sites, and 20% in pelvic primary sites [22]. ES clinically presents with abdominal pain with abdominal mass. They can also have associated jaundice, vomiting, dyspepsia, severe anemia, hemorrhage of the upper gastrointestinal tract, hypoglycemia **(Table 1)**. Ewing sarcoma is not restricted to any particular location, it can occur anywhere. They may also have back pain indicating a para-spinal, retroperitoneal, or deep pelvic tumor and patients with metastatic disease often have systemic symptoms of fever and weight loss [23]. ES/PNETs do not have specific signs and symptoms different from ES in general. Head of the pancreas is the most common site for peripheral PNETs (pPNETs) and the size ranged from 3.5 cm to 11 cm **(Table 1)**. Due to the necrotic areas in the tumor, a tumor of variable density is noticed on the CT scan of the abdomen. Although there is no close relationship of the tumors with the arteries, some tumors may have intensification in the focal areas on CT in the arterial phase. In the advanced stages of the tumor, invasion to the surrounding organs and metastasis may be seen [24].

There are no established pathological criteria for the diagnosis of the pPNETs. The combination of clinical symptoms like abdominal pain with abdominal mass, jaundice, vomiting dyspepsia, pathological characteristics like sheets of small round blue cells with hyperchromatic nuclei and scant cytoplasm; immunohistochemical features positive for CD99, O13, HBA71, 12E7, RFB1 and neural markers like Neuron Specific Enolase (NSE), Chromogranin A, Synaptophysin; and cytogenetic analysis for MIC-2 gene

and t(11;22)(q24;q12) suggest the diagnosis of PNETs. Histological features and distinction from other small round cell tumors are the principle criteria for the diagnosis of PNET. In pancreatic PNETs, specific characters of PNET like Homer-Wright (H-W) rosette or atypical rosette array of the cells are rarely present under light microscopy. The important criteria for the diagnosis of ES/PNETs are the cell cytoplasm containing neuronal secretory granules, neurofilaments, and pyknic nucleus granules [12]. From our present review, neural markers were positive for NSE (10 cases), synaptophysin (2 cases), vimentin (6 cases) out of 24 cases.

Differential diagnosis based on histomorphology is ES/PNET, Desmoplastic Small Round Cell Tumor (DSRCT), Small Cell Neuroendocrine Carcinoma (SNSC) and pancreatoblastoma. The ES family of tumors consists of small monomorphic round cells histologically, with small nuclei and scant cytoplasm. The same pattern is observed in a large group of tumors. In DSRCT's, which are multicentric tumors, desmopasia is noticed in the cellular phase which resembles the soft tissue in ES. The tumor cells are positive for CK and desmin [25]. World Health Organisations defined small cell carcinomas as malignant epithelial tumors consisting of small cells with scant cytoplasm, ill-defined borders, granular nuclear chromatin, absent nucleoli with extensive necrosis, and high mitotic count [26]. The tumor often stains positive for neuroendocrine markers such as synaptophysin, CD 56, and chromogranin A. Cell to cell molding is usually seen in SCNC [25]. Pancreatoblastomas are typically solid, soft masses. When observed under the microscope, cells with "acinar" differentiation and cells forming small "squamoid" nests are noticed [27].

pPNETs are known to be extremely malignant tumors with unavoidable relapse and metastasis. There have been reported cases of metastasis to lung, liver, bone marrow, lymph nodes and other organs. There have been five reported cases of pancreatic PNETs with local recurrence [2, 12, 13, 28, 29] and three cases with lung metastasis [16, 28, 30], one case with bone metastasis [16]. High dose radiation therapy and surgical resection with chemotherapy have been present acceptable treatments for pPNETs. The acceptable forms of chemotherapy protocols that promote the efficiency of the treatment are CAV (cyclophosphamide, adriamycin, vincristine) and neoadjuvant chemotherapy (vincristine, actinomycin, adriamycin, cyclophosphamide, isophosphamide, etoposide). Radiation therapy is used with some therapeutic efficacy. There is no appropriate treatment protocol yet for these tumors and unfortunately, all of the above mentioned treatments are unsatisfactory [31].

ES/PNETs being rare, there is only a little reported data on the prognosis and survival of these patients. Improvements in the detection of PNETs and their early surgical removal had significant impact on the survival rate of these patients. From the literature, it has been observed that patients treated with surgery combined with chemotherapy were alive after 5 years of treatment in 80% of individuals. The 5 year survival rate dropped to 29% in patients with metastasis to liver or unresectable tumor. Advancing age, tumors in advanced stage, non-functioning tumors and those with rapid growth generally have poor outcome. In patients with advanced PNETs with metastasis, the development of the new therapeutic options that arrest the tumor growth and progression have shown to be promising [32]. From our review, 4 out of 24 cases deceased with disease within the range of 6 months to 50 months from the time of diagnosis. One case deceased with post-operative complications. Rests of the cases were alive with or without disease, with some patients having multiple metastasis and recurrences.

CONCLUSION

PNET is a very rare malignant tumor with unavoidable recurrences. Being rare, we only have 24 reported cases of PNET up-to-date from our review. Due to lack of established diagnostic pathological criteria for this tumor, it is possible to misdiagnose this tumor. Hence, in the cases of pancreatic tumors, it is necessary to highlight the importance of considering ES/PNET in the differential diagnosis. For the better management, and improved pronosis and survival of these patients, it is necessary to understand the biological characteristics of this tumor in detail.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. De Alava E, Gerald WL. Molecular biology of the Ewing sarcoma/primitive neuroectodermal tumor family. J Clin Oncol 2000; 18:204-213. [PMID: 10623711]

2. 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; 212:185-188. [PMID: 10994548]

3. Randall L, Calvert G, Spraker H, Lessnick S. Ewing's sarcoma family of tumors. ESUN 2011; 3-4.

4. Esiashvili N, Goodman M, Marcus RB Jr. Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: Surveillance Epidemiology and End Results data. J Pediatr Hematol Oncol 2008; 30:425-30. [PMID: 18525458]

5. Jawad MU, Cheung MC, Min ES, Schneiderbauer MM, Koniaris LG, Scully SP. Ewing sarcoma demonstrates racial disparities in incidence-related and sex-related differences in outcome: an analysis of 1631 cases from the SEER database, 1973-2005. Cancer 2009; 115: 3526-36. [PMID: 19548262]

6. Beck R, Monument MJ, Watkins WS, Smith R, Boucher KM, Schiffman JD, Jorde LB, et al. EWS/FLI-responsive GGAA microsatellites exhibit polymorphic differences between European and African populations. Cancer Genet 2012; 205:304-12. [PMID: 22749036]

7. Khoury JD. Ewing sarcoma family of tumors. Adv Anat Path 2005; 12:212-220. [PMID: 16096383]

8. Barr FG, Meyer WH. Role of Fusion Subtype in Ewing Sarcoma. J Clin Oncol 2010; 28:1973-1974. [PMID: 20308653]

9. Pagani A, Macrí L, Rosolen A, Toffolatti L, Stella A, Bussolati G. Neuroendocrine differentiation in Ewing's sarcomas and primitive neuroectodermal tumors revealed by reverse transcriptase-polymerase chain reaction of chromogranin mRNA. Diagn Mol Pathol 1998; 7:36-43. [PMID: 9646033]

10. Sandberg AA, Bridge JA. Updates on cytogenetics and molecular genetics of bone and soft tissue tumors: Ewing sarcoma and peripheral primitive neuroectodermal tumors. Cancer Genet Cytogenet 2000; 123:1-26. [PMID: 11120329]

11. Grier HE. The Ewing family of tumors. Ewing's sarcoma and primitive neuroectodermal tumors. Pediatr Clin North Am 1997; 44:991-1004. [PMID: 9286296]

12. Mao Y, Sang X, Liang N, Yang H, Lu X, Yang Z, Du S, 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; 2:51-60. [PMID: 24570916]

13. 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; 26:1040-7. [PMID: 12170091]

14. Welsch T, Mechtersheimer G, Aulmann S, Mueller SA, Buechler MW, Schmidt J, Kienle P. Huge primitive neuroectodermal tumor of the pancreas: report of a case and review of the literature. World J Gastroenterol 2006; 12:6070–6073. [PMID: 17009412]

15. Changal KH, Mir MH, Azaz SA, Qadri SK, Lone AR. Primitive Neuroectodermal Tumour of Pancreas; Second Case from Asia. Malays J Med Sci 2014; 21:65–69. [PMID: 25897286]

16. Doi H, Ichikawa S, Hiraoka A, Ichiryu M, Nakahara H, Ochi H, Tanabe A, et al. Primitive neuroectodermal tumor of the pancreas. Intern Med 2009; 48:329–333. [PMID: 19252356]

17. Bose P, Murugan P, Gillies E, Holter JL. Extraosseous Ewing's sarcoma of the pancreas. Int J Clin Oncol 2012; 17:399–406. [PMID: 21892669]

18. Maxwell L, Hederman A, Jackson C, Sawaya D, Giles H, Nowicki MJ. Uncommon presentation of rare disorder-duodenal ulcer secondary to invasive pancreatic primitive neuroectodermal tumor: case report and review of the literature. J Pediatr Hematol Oncol 2011; 3:543-8 [PMID: 21716138]

19. Teixeira U, Goldoni M, Unterleider M, Diedrich J, Balbinot D, Rodrigues P, Monteiro R, et al. Primitive neuroectodermal tumor of the pancreas: a case report and review of the literature. Case Rep Surg 2015; 2015:276869. [PMID: 26101685]

20. Schutte WP, Knight PJ. Precocious puberty because of a pancreatic neuroectodermal tumor. J Pediatr Surg 2006; 41:1916–1918. [PMID: 17101370]

21. Menon BS, Juraida E. Pancreatic primitive neuroectodermal tumor associated with precocious puberty. Pediatr Blood Cancer 2009; 53:518–519. [PMID: 19418542]

22. Ewing Sarcoma Treatment–for health professionals (PDQ®). Available at http://www.cancer.gov/types/bone/hp/ewing-treatment-pdq

23. Jeffrey A Toretsky, Robert J Arceci. Ewing Sarcoma Clinical Presentation. Available at http://emedicine.medscape.com/article/990378-clinical

24. Obuz F, Kovanlikaya A, Olgun N, Sarialioğlu F, Ozer E. MR imaging of pancreatic metastasis from extraosseous Ewing's sarcoma. Pancreas 2000; 20:102-4. [PMID: 10630390]

25. Rao L, Monappa V, Rodrigues G, Suresh BP. Ewing's sarcoma of the lesser sac masquerading as a pancreatic tumor. Korean J Intern Med 2012 Mar; 27:91–94. [PMID: 22403505]

26. Travis WD, Garg K, Franklin WA, Wistuba II, Sabloff B, Noguchi M, Kakinuma R, et al. Bronchioloalveolar carcinoma and lung adenocarcinoma: the clinical importance and research relevance of the 2004 world health organization pathologic criteria. J Thorac Oncol 2006; 1:S13–S19. [PMID: 17409995]

27. Savastano S, d'Amore ES, Zuccarotto D, Banzato O, Beghetto M, Famengo B. Pancreatoblastoma in an adult patient. A case report. JOP 2009; 10:192-5. [PMID: 19287117]

28. Perek S, Perek A, Sarman K, Tuzun H, Buyukunal E. Primitive neuroectodermal tumor of the pancreas. A case report of an extremely rare tumor. Pancreatology 2003; 2:352–356. [PMID: 12891000]

29. Jing H, Li F, Chen L, Zhang T, Zhao Y. (2011) Detection of recurrent pancreatic primitive neuroectodermal tumor by Tc-99m hydrazinonicotinyl-Tyr3-octreotide scan. Clin Nucl Med 2011; 36:54–55. [PMID: 21157213]

30. Kumar J, Agrawal S, Agarwal R, Khoiwal S. Pancreatic Ewings Sarcoma- A Dreadful Tumor. American J Can Prev 2013; 3:24-26.

31. Zogopoulos G, Teskey L, Sung L, Dix D, Grant R, Greenberg ML, Weitzman S. Ewing sarcoma: favourable results with combined modality therapy and conservative use of radiotherapy. Pediatr Blood Cancer 2004; 43:35-9. [PMID: 15170887]

32. Pancreatic Neuroendocrine Tumour (PNET). Available at http://www.myvmc.com/diseases/pancreatic-neuroendocrine-tumour-pnet/#Prognosis.