Extraosseus Ewing's Sarcoma in Pancreas: A Review

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Abstract

Primitive neuroectodermal tumors (PNET, previously referred to as peripheral neuroepithelioma) are rare malignant tumors with various degrees of differentiation belonging to the Ewing's family of sarcomas. They are classified as round cell tumors arising from soft tissues. In rare instances, PNETs may arise from solid organs containing neuroendocrine cells of kidney, bladder, heart, lungs, parotid glands and pancreas. Most cases occur in the second decade of life with a slight preponderance in males. PNET of the pancreas is an aggressive tumor with multiple recurrences and a relatively poor prognosis. These tumors should be considered in the differential diagnosis, especially in a diagnosed pancreatic tumor in individuals less than 35 years of age. Due to the nature of the tumor, surgery with subsequent chemoradiation are widely accepted modalities despite the poor prognosis. In this article, we review 25 cases of extraosseous Ewing's sarcoma (ES) of the pancreas which to the best of our knowledge, enlists most cases reported in the literature thus far.

Categories: Oncology, Orthopedics

Keywords: ewing's sarcoma, pancreas, primitive neuroectodermal tumor, extraosseous

Introduction And Background

Ewing sarcoma is a poorly differentiated, aggressive, malignant, round cell tumor without cellular or structural differentiation more commonly diagnosed in children younger than ten. It is the second most common malignant bone tumor in children, after osteosarcoma. The incidence of Ewing sarcoma is 1 per million for people of all ages in the United States and has remained unchanged for 30 years [1]. It is most common in Caucasians, and less frequently seen in Asians and African Americans [2,3].

The clinical entity of PNET was identified by Stout in 1918, initially seen in the peripheral nerves [3]. Tefft described the extraosseous form of Ewing’s sarcoma (EES) in 1964. PNETs have also been found in other sites such as the kidney, urinary bladder, uterus, gallbladder, lung, and vagina, and vulva [4-9]. Peripheral primitive neuroectodermal tumors rarely arise in organs and it is extremely uncommon for PNETs to originate in the pancreas. Batsakis et al. divided the PNET family of tumors into the following three groups, based on the origin of the tissue-central nervous system tumors including primitive neuroectodermal tumors in the brain and spinal cord, tumors derived from the autonomic nervous system called neuroblastomas, and tumors originating outside the central and autonomic nervous system called Peripheral primitive neuroectodermal tumors (PPNETs) [4].

The ES/PNET family also includes several other related clinicopathologic neoplastic entities such as malignant small-cell tumors of the thoracic pulmonary region (Askin’s tumor, Open Access Review Article DOI: 10.7759/cureus.7505

How to cite this article
Patel D, Nandu N, Reddy A (April 01, 2020) Extraosseous Ewing's Sarcoma in Pancreas: A Review . Cureus 12(4): e7505. DOI 10.7759/cureus.7505
described by Askin in 1979), paravertebral small-cell tumor, atypical ES, PNET of bone, and extraosseous ES. These neoplasms exhibit a neural phenotype, express the MIC2-protein (CD99) and display the same chromosomal translocation t (11; 22) (q24; q12) in about 85% of the cases and hence, can be helpful in diagnosis and have a prognostic value \[1,2\].

PNETs usually originate in soft tissues and bone. Luttges, et al. found that only two cases among 600 primary pancreatic neoplasms were pancreatic PNETs \[9\]. The tumor is of insidious onset and patients usually have no specific clinical symptoms. The most common presentation of an extraosseous tumor is a rapidly growing mass associated with localized pain. The diagnosis of peripheral primitive neuroectodermal tumors of the pancreas encompasses clinical symptoms, pathological characteristics, immunohistochemical features, and molecular genetic analysis. Complete surgical resection followed by radiation and chemotherapy is the currently accepted treatment, although the prognosis remains poor due to the highly aggressive nature of this cancer \[7\]. Chemotherapeutic regimens that have been used in various combinations include vincristine, cyclophosphamide, actinomycin D and doxorubicin. The prognosis of the extraosseous sites of PNETs is poor due to the delay in diagnosis, and also due to the age of the patient, tumor bulk, location and the highly aggressive nature of the tumor \[10\].

**Review**

This literature review talks about Pancreatic Ewing's Sarcoma (ES/PNET). In total, 25 cases have been reported in the literature to our knowledge. From the review of the 25 cases, we observed that ages ranged from 2 years to 60 years while the average age was around 23 years. No significant sexual predominance was identified in the literature review (13 male patients and 12 female patients). The most common symptoms reported were abdominal pain (68%), jaundice (20%), nausea (16 %), and anemia (16 %). Endocrine disorders such as hyperglycemia and precocious puberty were accompanied in some cases \[11\]. Ten patients out of 25 had documented chromosomal translocations t(11; 12) (q24; q12). The most common site for peripheral PNET was the head of the pancreas with the size ranging from 3.5 cm to 11 cm.

Abdominal CT and MRI are the two most common modalities to visualize pancreatic tumors, with MRI being the more sensitive imaging study. Tan et al. reported that the radiographic characteristics of the lesion have an isodense or hypodense on unenhanced CT, isointense on T1WI, and can be either isointense or hyperintense on T2WI as revealed by MRI \[12\]. Pancreatic tumors have ill-defined borders and irregular shapes with heterogeneous enhancement. Due to necrotic areas within the tumor, variable densities have been noticed on the CT scan of the abdomen. Although there is no close relationship 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 into the surrounding organs and metastasis may be seen \[13-15\].

Gene studies have shown that the fusion of the FLI1 gene on chromosome 11 and the ERG gene on chromosome 22 to be associated with PNES. The products of the fusion genes resulting from the translocations are specific to the type of tumors. In reports of ES/PNETs, there are eight cases in which chromosome translocation is t (11;22) (q24;q12) while three cases had t (21;22) (q22; q12). Loss of cosmids F7 and E4 distal of the EWS-R1 breakpoint in nearly all cells was noted in one case \[5,10,16-20\].

ES is an undifferentiated tumor lacking neural differentiation in the primitive cells. However, some tumors have cells with neural differentiation in the form of Homer-Wright rosettes. Histologically, there is a presentation of small round blue cells in the form of monotonous sheets with hyperchromatic nuclei and scant cytoplasm \[16\]. All 25 cases in this review meet these histologic criteria. The tumor consists of extensive necrotic areas with viable tissue usually preserved around blood vessels \[18-21\]. A known marker for the diagnosis of PNET are p30/32MIC2 \[20\]. Nonspecific monoclonal antibodies like CD99, O13, HBA71, 12E7, RFB1 were
also tested, although none of them are specific for PNETs [21]. Neural markers like Neuron Specific Enolase (NSE), Chromogranin A (CgA), Synaptophysin (Syn) can also be positive [22-24].

There are no definite guidelines for the pathological criteria for the diagnosis of the peripheral PNETs. The combination of clinical signs and symptoms such as abdominal pain with an abdominal mass, jaundice, vomiting, dyspepsia, pathological characteristics like sheets of small round blue cells with hyperchromatic nuclei and scant cytoplasm; immune-histochemical features stained positive for CD99, O13, HBA71, 12E7, RFB1 and neural markers like Neuron Specific Enolase (NSE), Chromogranin A, Synaptophysin; cytogenetic analysis for MIC-2 gene and t [11;22] [q24; q12] suggest a 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 is the cell cytoplasm containing neuronal secretory granules, neurofilaments, and pyknic nucleus granules [25,26]. From our present review, neural markers were positive for NSE (10/25 cases), synaptophysin (2/25 cases) and vimentin (6/25 cases).

Differential diagnoses that are considered based on histomorphology are ES/PNET, desmoplastic small round cell tumor (DSRCT), small cell neuroendocrine carcinoma (SNESC) and pancreaticoblastoma. 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, desmoplasia is noticed in the cellular phase which resembles the soft tissue in ES. The tumor cells are positive for Creatine kinase (CK) and desmin [8]. The tumor often stains positive for neuroendocrine markers such as synaptophysin, CD56, and chromogranin. There have been five reported cases of pancreatic PNETs with local recurrence, three cases with lung metastasis and one case with bone metastasis [27-30].

Surgical resection with chemoradiation is the widely accepted treatment protocol for PNETs. The commonly used chemotherapeutic agents include doxorubicin, cyclophosphamide, vincristine, actinomycin-D, ifosfamide, and etoposide. A randomized study by Grier et al. compared treatment with three drug regimen (VDC: vincristine, doxorubicin, and cyclophosphamide) versus a five-drug therapy (VDC plus ifosfamide, and etoposide). Subsequently the five drug regimen was established as the gold standard for treatment of PNET’s [20]. Dactinomycin is no longer used in the United States but continues to be used in the Euro-Ewing studies. Increased dose intensity of doxorubicin during the initial months of therapy was associated with an improved outcome in a meta-analysis done prior to the standardization of ifosfamide and etoposide. Radiation therapy has a role in those patients with residual disease after surgery and chemotherapy. Hyperfractionated radiation therapy has not shown to be of any extra benefit; whereas proton-beam radiation therapy and intensity-modulated radiation therapy (IMRT) treatment seem to be promising but lack randomized data.

The main treatment of the disease from our review was surgery along with chemotherapy with or without adjunctive radiotherapy. 18 out of 25 patients received chemotherapy after surgery. Five out of 25 patients had multiple recurrences after combined surgery and chemotherapy.

There is only a little-reported data on the prognosis and survival of these patients who have ES/PNETS. Improvements in the detection of PNETs and their early surgical removal has had a 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 the liver or unresectable tumor. Advancing age, advanced stage tumors,
non-functioning tumors and those with rapid growth generally have poor outcomes. In patients with advanced PNETs with metastasis, the development of new therapeutic options that arrest tumor growth and progression have shown to be promising [7, 29,30,31,32,33,34]. From our review, 4 out of 25 cases died with the disease within the range of 6 months to 50 months from the time of diagnosis while one died with postoperative complications. The rest were alive with or without disease, with some having multiple metastasis and recurrences. Table 1 summarizes the findings of the 25 cases reviewed.

| Reference         | Age/Sex | Symptoms                          | Physical exam findings | Cytogenetic analysis | Light microscopy and Immunohistochemical(IHC) stain | Diagnosis and Treatment | Metastasis and Recurrence | Clinical follow-up and Outcome |
|-------------------|---------|-----------------------------------|------------------------|----------------------|---------------------------------------------------|-------------------------|-----------------------------|--------------------------------|
| 1 Bulchmann et al [6] | 6/F     | Abdominal pain, Anemia, dizziness | 4.0x5.4x3.0 cm         | 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 diagnosis pancreatoblastoma; later revised after rosettes found in lymph nodes | Surgery with pancreateoduodenectomy | 6 mo; Recurrence | DOD                          |
| 2 Mao Y et al [10] | 13/F    | Dyspepsia, Vomiting                | 22                     | NA                   | NA                                                | Whipple resection, Chemotherapy | NA                          | NA                            |
| 3                  | 31/M    | Abdominal pain, decreased appetite | NA                     | NA                   | NA                                                | Chemotherapy            | NA                          | NA                            |
| 4                  | 17/M    | Abdominal pain                     | 9                      | t(11;12) (q24;q12)   | NA                                                | Radiotherapy, Chemotherapy | N/P                         | 8 months, AWD                 |
| 5                  | 13/F    | Abdominal pain, Diabetes Mellitus type2 | 3.5                     | t(11;12) (q24;q12)   | NA                                                | Resection of the uncinate process, Radiotherapy / Chemotherapy- Four courses of VAC. | 9/36 months, recurrence;12 months, ascites | 41 months; AWD |
| 6 Shoustari et al. [34] | 47/F    | Abdominal pain, abdominal distension, fatigue, weight loss | 10 x 15 | - | Small round and oval cells with scant cytoplasm. The tumor was separated by fibrous connective tissue into the folial parts. Granular nuclear chromatin and karyoskinesis phenomenon with unclear nuclei were found. There were no Homer-Wright rosettes in the tumor cells, positive for CD99, NSE. | Excision of the tumor with a distal pancreatectomy and splenectomy, Alternating IE and VAC | Negative | AWD                          |
|   | **Kumar et al.** [27] | 20/F | Abdominal pain | 11x9 | - | Well-circumscribed tumor with a fibrous pseudocapsule composed of sheets of small round cells with enlarged nuclei, fine stippled chromatin, and moderately clear to amphophilic cytoplasm staining periodic acid Schiff stain positive, positive for CD 99, while negative for cytokeratin (CK), insulin, glucagon, synaptophysin (SYP), and chromogranin (CHR). Whipple resection, VAC along with radiotherapy | bone, liver and lungs | 26 months, DOD. |
|---|---|---|---|---|---|---|---|---|---|
| 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, VDC | NA | 27 months, AWD |
| 10 | 21/F | Abdominal Pain | NA | t(11;12) (q24;q12) | Whipple resection, NA | NA | Died of post-operative complications |
| 11 | Movahedi-Lankarani S et al. [5] | 25/F | Abdominal Pain | NA | NA | Biopsy, NA | NA | NA |
| 12 | 25/F | Jaundice, Abdominal pain | 8 | t(11;12) (q24;q12) | AE1/AE3 and 6 of 7 were positive for NSE | Biopsy, NA | NA | NA |
| 13 | 13/M | Abdominal pain | 6 | NA | Biopsy, NA | N/P | 43 months, NED |
| 14 | 10/M | Jaundice, Abdominal Pain | 3.5 | t(11;12) (q24;q12) | Whipple, VDC | 48 months, Recurrence | 48 months, DOD |
| 15 | Perek et al. [7] | 31/M | Abdominal Pain, fever | 10 | - | Whipple, Radiotherapy, ifosfamide X 6; docetaxel and palliative resection | 4 months, Recurrence; 24mo/36mo lung | 50 months, DOD |
| 16 | Welach et al. [22] | 33/M | One day history of abdominal pain | 18 cm x 18 cm x 6 cm | t(11;12) (q24;q12) | Laparotomy, Resection, Radiotherapy, 6 cycles of of VIDE, VAI, AST Chemotherapy | Simultaneously, liver, spleen | 12 months, AWD |

Cytokeratin (CK), desmin, synaptophysin (SYP), and chromogranin (CHR) were negative.
| Case | Authors | Gender | Age | Symptoms | Mass Size/Location | Pathological Findings | Treatment | Outcome |
|------|---------|--------|-----|----------|-------------------|----------------------|------------|---------|
| 17.  | Teixeira et al. [33] | 28/F | epigastric pain for 14 days, pruritus, jaundice, cholangitis, acholia. | 12.8 × 12.1 × 10.9 cm, hardened palpable mass in the epigastric and right hypochondrium regions. | 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 chorogranins, 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. [21] | 60/M | epigastric Abdominal Pain for 1 month | 3 x 3cm lump in the supraumbilical region without lymphadenopathy | FISH confirmed t(11;22) (q24;q12) translocation. | Small round cell tumor with pseudorosetting infiltrating the node. Positive for CD99, NSE, FLI-1, synaptophysin and cytoplasmic vimentin. Negative for Cytokeratin (AE1/AE3) and chorogranin, LCA, CD3, CD20, CD79a, CD34, and TdT were negative. Biopsy of the peri-pancreatic lymph nodes. Received three cycles of VIDE (vincristine, ifosfamide, doxorubicin, and etoposide), planned for a total of 6 cycles. | - | | A repeat ultrasound after 3 cycles of chemotherapy - tumour shrunk. Prolonged follow up after surgery and reassessment for chemotherapy will be required. |
| 19.  | Schutte et al. [32] | 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 x4 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. | CR without further surgery, hormone levels normalized and pubertal signs regressed. |
| 20.  | Menon et al. [28] | 8/F | Abdominal pain and menstrual bleeding, breast development and pubic hair; | 10 X 6 X 10 NA | Mass occupying whole pancreas and obstructing distal CBD found at laparotomy; no lymph node or other metastases; sheets of small | Laparotomy with biopsies and cholecystectomy; chemotherapy and radiotherapy, cumulative | | | |
| Case | Author et al. | Sex | Age | Presenting Symptoms | Lesion Location | Lesion Size | Initial Diagnosis | FISH Findings | Histological Findings | Initial Treatment | Outcome | Follow-up Details |
|------|---------------|-----|-----|---------------------|----------------|-------------|------------------|---------------|----------------------|------------------|---------|-------------------|
| 21   | Doi et al. [23]| 37/M| NA  | Jaundice            | NA             | 10 x 10 x 8  | NA               | NA            | 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 | FISH showed an EWSR1 rearrangement at 22q12 | Pancreato-duodenectomy 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 | One year after diagnosis, lung and bone tumors had diminished; was in good health at time of writing |
| 22   | Jing et al. [31]| 24/F| NA  | Exophytic PNET      | NA             | 9 X 10 X 8   | NA               | NA            | Surgery, Radiation and chemotherapy for recurrent disease; | NA               | Recurrent PNET    | Doing well at time of report |
| 23   | Bose et al. [24]| 35/M| 3   | Gallstone pancreatitis | NA             | 8.8 X 7.8 X 6.4 | NA               | NA            | 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 | FISH using a probe for the EWSR1 gene located at 22q12 revealed a rearrangement hybridization signal in each of 100 nuclei analyzed | Distal pancreatectomy, splenectomy and cholecystectomy. Adjuvant VAC alternating with IE (no specific evidence of malignancy seen on postoperative PET/CT) | 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. [26]| 11/M| Fatigue, abdominal pain | T(11;22) 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 | NA               | Six months follow up after adjuvant treatment |
| 25   | Saif et al.    | 38/F| Abdominal pain, epigastric | T(11;22) | Sheets of small round cells with enlarged round to oval nuclei, fine stippled chromatin, moderately | Distal pancreatectomy with splenectomy. 2 cycles of ifosfamide, etoposide. And | NA               | NA               | Six month follow up after adjuvant treatment | | | |

markedly elevated estradiol levels
round cells, MIC2 positive and LCA negative
doxorubicin failure 1 month after completing treatment, fatal cardiac arrest 19 months after diagnosis

Doi et al. [23]

37/M jaundice NA
FISH showed an EWSR1 rearrangement at 22q12

Pancreato-duodenectomy 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

One year after diagnosis, lung and bone tumors had diminished; was in good health at time of writing

Jing et al. [31]

24/F Exophytic PNET in pancreatic uncinate process 10 X 10 X 8 NA NA

Surgery, Radiation and chemotherapy for recurrent disease;

Bose et al. [24]

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

Distal pancreatectomy, splenectomy and cholecystectomy. Adjuvant VAC alternating with IE (no specific evidence of malignancy seen on postoperative PET/CT)

Maxwell et al. [26]

11/M Fatigue, abdominal pain 9.8 X 7.8 X 6.4 T(11;22) EWSR1-ERG fusion transcript by RT-PCR

Whipple procedure, VDC alternating with IE

Saif et al.

38/F Abdominal pain, epigastric 8x10 cm T(11;22)
Sheets of small round cells with enlarged round to oval nuclei, fine stippled chromatin, moderately

Distal pancreatectomy with splenectomy. 2 cycles of ifosfamide, etoposide. And No metastasis or recurrence

Six month follow up after adjuvant treatment
TABLE 1: Brief review of case reports on PNETs in Pancreas.

| NA- Not Available; N/P- Not Performed; AWD- Alive with Disease; DWD- Died with Disease; NED- No Evidence of Disease; RT-PCR – Reverse Transcriptase - Polymerase Chain Reaction; VAC- Vincristine, Adriamycin, and Cyclophosphamide; IE- Ifosfamide and Etoposide; VDC- Vincristine, Doxorubicin, Cyclophosphamide. |

Conclusions

PNET is an aggressive malignant tumor with unavoidable recurrences. Our review of 25 reported cases of PNET till date indicates that from the lack of concrete diagnostic pathological criteria, it is easy to misdiagnose PNET. In cases of pancreatic tumors, it is necessary to highlight the importance of considering ES/PNET early on in the differential diagnosis for improved prognosis and better longevity.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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