CASE REPORT

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# Pancreatic Ewing's Sarcoma Synchronously Diagnosed in a Patient of Carcinoma Cervix: A Case Report and Literature Review

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## ABSTRACT

Extraosseous Ewing's sarcoma is a rare neoplasm. It has been reported in several sites such as the prostate, lungs, kidney, biliary tract, oral cavity, uterus, gonads, stomach, cervix, urinary bladder, vagina, and salivary glands. However, Ewing's sarcoma/primitive neuroectodermal tumors (ES/PNET) of the pancreas is an extremely unusual finding. Although there are a handful of pancreatic ES/PNET cases in the literature, our case intensifies the importance as it was diagnosed in a patient with carcinoma of the cervix. Our case aims to add value to the body of literature considering a second primary neoplasm of a rare entity at an unusual site.

**Keywords:** Pancreas, Ewing's sarcoma, synchronously, carcinoma, cervix

## INTRODUCTION

Ewing's sarcoma/primitive neuroectodermal tumour (ES/PNET) is an unusual malignant neoplasm. In rare cases, PNETs may arise in solid organs that contain neuroendocrine cells. James Ewing first described Ewing's sarcoma (ES) in 1921, while the extra osseous Ewing's sarcoma or PNET was first described by Tefft in 1969.[1,2] ES/PNET comprises four subtypes: peripheral primitive neuroectodermal tumour (pPNET), Ewing's sarcoma of bone (ESB), Askin's tumour, and extraosseous Ewing's sarcoma (EES). ES/PNET has been reported in several case reports and series with unusual sites such as the salivary glands, oral cavity, adrenal gland, jejunum, pericardium, lung, stomach biliary tract, kidney, heart, prostate, cervix, vagina, gonads, uterine corpus, and pancreas.[3] Here, we report a rare case of ES/PNET in the pancreas of a 51-year old woman with synchronous carcinoma cervix. Reporting on such a rare form will help us in improving the characterization of the pathology, while contributing to cancer treatment advancement. In the future, it will also serve as guidance in the treatment of such rare cases.

## CASE PRESENTATION

A 51-year-old female presented to our hospital in July 2018 with a history of vaginal bleeding accompanied with leukorrhea. She also complained of lower back pain.

Her speculum examination showed an ulceroproliferative growth over the cervix which bled on touch. Computed tomography (CT) revealed a large 7x6.8x6.6 cm mass lesion involving lower uterine segment and upper vagina with multiple iliac nodes. A biopsy was carried out. The patient was diagnosed with squamous cell carcinoma of the cervix (Figure 1A). On immunohistochemistry, tumour cells showed strong nuclear positivity for P40 (Figure 1B).

The patient completed concurrent radiotherapy (50 Gray in 25 fractions) along with five cycles of cisplatin. The patient also received three fractions of intracavitary brachytherapy.

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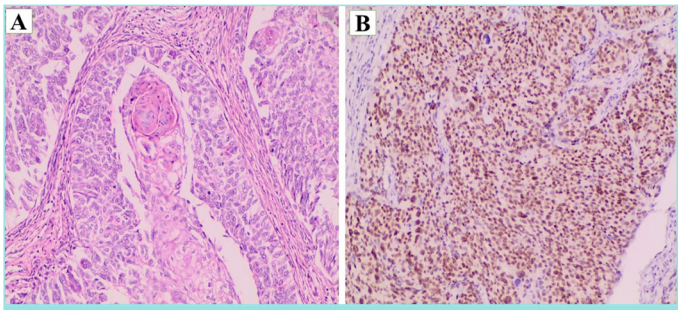


**Figure 1. (A)** H and E (20x) image from cervix showing diffuse sheets of cells having squamous differentiation infiltrating into surrounding connective tissue. **(B)** p40 IHC on cervix lesion showing nuclear positivity in the tumor cells.

Magnetic resonance imaging (MRI) was performed on routine follow-up after two months. A regression in the previously visualized cervical lesion was noted. There was a resolution of the previously mentioned pelvic nodes. A well-defined altered signal intensity heterogeneously enhancing tissue lesion measuring 58x44x50mm in size arising from the tail of the pancreas was noted. The possibility of a second primary of neoplastic origin rather than a metastatic one was suspected.

A whole body PET-CT scan showed a large FDG avid mass involving the tail of pancreas with metabolically active left para-aortic nodes just below the level of left renal hilum [maximum standardized uptake value ($SUV_{max}$): 12.7].

Tumour markers, CA-19.9 and carcinoembryonic antigen (CEA test) were tested to rule out pancreatic adenocarcinoma and were found to be within normal limits. Fine needle aspiration cytology (FNAC) was positive for malignant cells.

The patient underwent laparoscopic distal pancreatic splenectomy. Gross analysis of the specimen showed a pancreatic segment of 13x12x7.5 cm infiltrated by a vague nodular grey mass measuring 6.2x5.5x4 cm at the tail end.

On histology, the tumour showed diffuse sheets of round cells (Figure 2A). The tumour cells exhibited small round cells with a large central nucleus and scanty cytoplasm. (Figure 2B). The tumour cells showed minimal nuclear pleomorphism. Brisk mitosis was noted.

On immunohistochemistry, these tumour cells showed perinuclear dot-like positivity for Pan-CK (Figure 2C); CD99 (Mic-2) showed cytoplasmic membranous positivity (Figure 2D), and Fli-1 showed strong nuclear staining (Figure 2E). Immunohistochemically, the cells were negative for CD-56, Desmin, LCA, AR, ER, Cyclin D1. Hence the diagnosis of Ewing/PNET was made.

The patient had received one cycle of vincristine, doxorubicin (Adriamycin), and cyclophosphamide (VAC) and one cycle of ifosfamide and etoposide (IE). The patient is scheduled for three cycles of VAC and three cycles of IE followed by radiation therapy with vincristine. The patient is currently doing well.

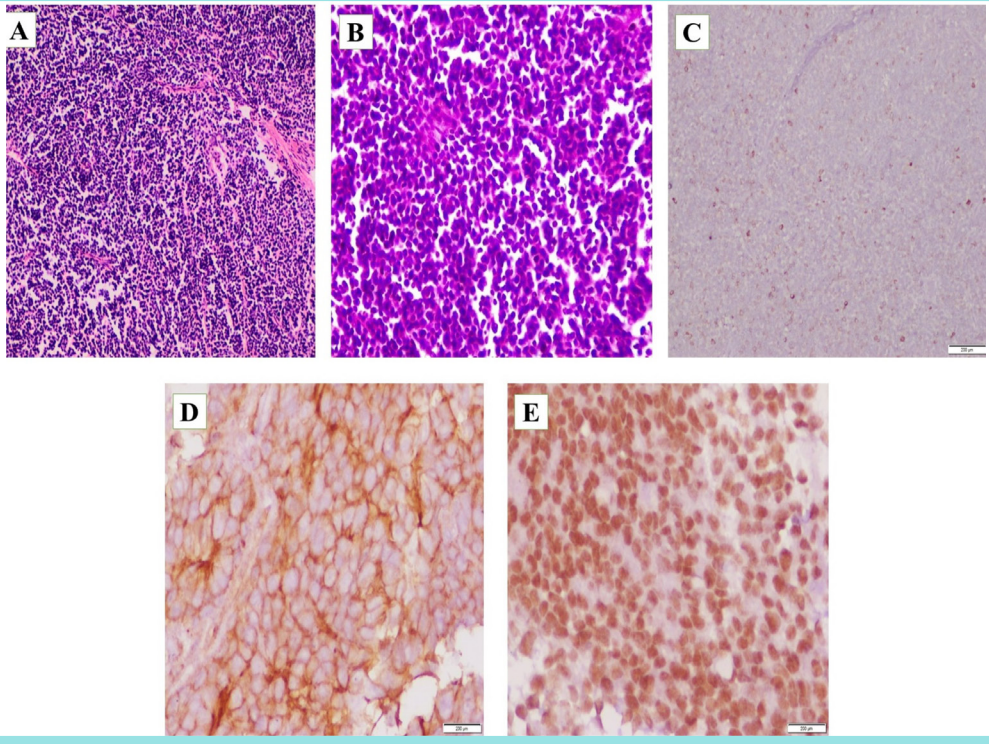


**Figure 2. (A)** H and E (10x) of pancreatic tumor showing diffuse sheets of round cells. **(B)** H and E (40x) of pancreatic tumor showing small round cells with large central nucleus and scanty cytoplasm. **(C)** PAN-CK: Tumor showing perinuclear dot like positivity. **(D)** CD99 showing cytoplasmic membranous positivity. **(E)** Fli-1 showing nuclear positivity.

p40 IHC: p40 Immunohistochemistry, PAN-CK: pan-CK, pan-cytokeratin

**Table 1. Present and previous reported reports of Ewing sarcoma/peripheral primitive neuroectodermal tumours**

| No | Reported by (study type) | Site and nature | Clinical presentation | Radiologic diagnosis | Pathological | Immunohistochemistry | Diagnostic procedure | Cytogenetics |
|---|---|---|---|---|---|---|---|---|
| 1. | Schutte and Knight[4] (case report) | Upper abdominal mass | Pubic hair, breast bud development, and vaginal bleeding | Enhancing mass lesion in the body of the pancreas | Venous and lymphatic vessel invasion | Negative - AEI/AE3. Moderate – EMA. Strong - Strong - SOM, Chromogranin A, S-100, VIM, CD99, ER, PR, and INB | Distal pancreatectomy | NR |
| 2. | Movahedi-Lankarani et al.[6] (case series) | Head of the pancreas | Jaundice and/or abdominal pain | NR | Typical morphologic features of PNETs | Expressed O13 (CD99, p30/32MIC2) | Whipple resection, biopsy | Evidence of t(11;22)(q24;q12) chromosomal translocation |
| 3. | Mao et al.[8], (case report) | Tumor grown superiorly to the infrahepatic space, postero-lateral aspect of the duodenum, and inferiorly to the hepatic flexure of colon | Mild abdominal pain, anorexia, polyuria, polydipsia, weight loss, and immobile firm mass that was tender to deep palpation | A large mass was seen between the liver, the pancreas and the right kidney with focal irregular intensification in the arterial period | a thin and flat neoplasm which was seen in the uncinate process of pancreas | Negative – SOM, $^{131}$I-MIBI | Surgical resection | NR |
| 4. | Kim et al.[9] (case series) | Body of the pancreas | Incidentally detected | Pancreatic cancer/ metastatic tumour/ neuroendocrine tumour | INR | INR | Biopsy/chemotherapy | INR |
| 5. | Rao et al.[14] | Body and tail of the pancreas | Abdominal pain | Exophytic pancreatic mass or exophytic gastrointestinal stromal tumour (GIST) from the posterolateral wall of the stomach was proposed | Peripherally compressed pancreatic tissue was seen and no tumour infiltration was discerned | Positive - CD99, Negative - AE1/AE3, DES, SYP, and CHR | Distal pancreatectomy | NR |
| 6. | Teixeira et al.[17] (case report) | Pancreatic head and body | Epigastric pain, cutaneous pruritus, jaundice, choluria, and acholia | A voluminous expansive lesion in pancreatic head and body, with well delimited borders was observed | Neoplasm of small round blue cells with scant cytoplasm arranged in nests with fibrovascular stroma was seen | Positive - CD99, VIM, automated CKM, and CD56. Negative - CHR, SYN, NBL, MYG, automated CD10, $\beta$-catenin, automated RP (ribosomal protein), and LCA | GDPSx | NR |
| 7. | Welsch et al.[12] (case report) | Pancreatic tail | Acute abdominal pain | A mass arising from the pancreatic tail compressing the stomach and spleen | Nests of medium-sized round or oval tumour cells with enlarged round or oval nuclei and scant cytoplasm surrounded by fibrovascular septae and focally, Homer-Wright rosettes were observed | Positive – CD99, VIM, cytokeratin (KL-1,18), cytokeratin 18, EMA, SYN, CD56, and CD117. Negative - Cytokeratins (7, 8 and 19), CEA, AFP, ⊠1ACT, protein S100, melan A, and HMB-45. | Left pancreatic resection | Tumour cell nuclei showed one fused signal and one dislocated hybridization signal on on chromosome 22q12, indicative of a chromosomal translocation involving the EWS gene |

**Table 1. Present and previous reported reports of Ewing sarcoma/peripheral primitive neuroectodermal tumours**

| No | Reported by (study type) | Site and nature | Clinical presentation | Radiologic diagnosis | Pathological | Immunohistochemistry | Diagnostic procedure | Cytogenetics |
|---|---|---|---|---|---|---|---|---|
| 8. | Khuri et al.[18] (case report) | Pancreatic tail | Upper abdominal pain and coffee ground vomiting | Mass at lesser curvature of the stomach, with compression on the splenic vein was observed | Mass invading the gastric wall, pancreas, and splenic hilum was observed | Positive – CD99, FLI1, VIM, and Ki67.<br>Negative - Cytokeratin, S100, CD20, CD3, CD79A, PAX5, CD30, CD43, DOG-1, CD68, CD163, CD33, MPOX, and DES | Distal pancreatectomy | Positive for EWSR1 gene rearrangement (11:22 translocation) |
| 9. | Nishizawa et al.[19] (case report) | Pancreatic head | Upper abdominal discomfort and nausea | Giant tumour with mild enhancement occupied the pancreatic head | Atypical small round cells with scant cytoplasm, and each had a round nucleus with a distinct nuclear membrane | Positive - CD99, NSE, NEAM, VIM, SYN, and CAM5.2.<br>Negative - CHR A, AE1/AE3, cytokeratin (7 and 20), carbohydrate antigen 19-9, and CD10 | PD | Breakpoint region 1 gene, 22q12 rearrangement was proven |
| 10. | Perek et al.[20] (case report) | Head and the body of the pancreas | Malaise and fever | Subhepatic, hypodense, solid mass with hyperdense borders and focal necrotic areas | Irregular nuclear membranes with occasional cleaving, round or oval nuclei without any distinctive cytoplasm; coarser chromatin pattern and more prominent nucleoli | Positive – CD99, and ß2-microglobulin | Surgical resection | Inconclusive |

AE1/AE3: cytokeratin AE1/AE3, NSE: neuron-specific enolase, CHR: chromogranin, SYN: synaptophysin, EMA: epithelial membrane antigen, CKM: creatine kinase muscle, VIM: vimentin, DES: desmin, MYG: myogenin, LCA: leucocyte common antigen, AFP: α1-fetoprotein, α1ACT: α1-antichymotrypsin, NBL: neuroblastoma, ACT: actin, INS: insulin, GLU: glucagon, MPOX: myeloperoxidase, FLI1: friend leukemia integration 1, SOM: somatostatin, NSE: neuron-specific enolase, NEAM: neural cell adhesion molecule, ER: estrogen receptors, PR: progesterone receptors, INB: inhibin, $^{131}$I-MIBI: Methoxyisobutyl isonitrile, GDPSx: gastroduodenopancreatectomy, PD: pancreaticoduodenectomy, CT: computed tomography, USG: ultrasonography, NR: nor reported, INR: individually not reported.

## DISCUSSION

PNETs comprise nearly 1% of all sarcomas with an estimated five-year survival rate of 50%.[4-7] PNETs have been reported to develop in solid organs, although this is rare. In some cases, PNETs have been found arising from the pelvis, thoracopulmonary region, and the lower limbs of children and young adults.[6] In organs that contain neuroendocrine cells such as the pancreas, PNETs are extremely rare and account for only 0.3% of all primary tumours.[8,9] To the best of our knowledge, there are only a few pancreatic ES/PNET cases seen with synchronous tumours reported in the literature.[1-20] Herein, we present the first synchronous case of PNET with a squamous cell carcinoma of the cervix.

Patients with such neoplasms are often asymptomatic or have a poorly symptomatic course even in advanced stages, as observed in our case.[8,9]

ES/PNET is comprised of small round cell tumours, morphologically. They are poorly differentiated tumours. There are several entities that have small round cell morphology such as desmoplastic small round cell tumour (DSRCT), lymphoma, extra-adrenal neuroblastoma, pancreatic endocrine tumour (PET), visceral small cell neuroendocrine carcinoma (SCNC), extra-renal Wilm's tumour, and pancreatoblastoma.[14-17]

In terms of imaging tests, abdominal MRI and CT are the most useful in the detection of such tumours. However, their diagnosis is not easy as there are no specific patterns in the radiological findings as shown in Table 1.[13] A histopathological test with immunohisotchemistry is required to confirm the diagnosis of ES/PNET as in our case, but it varies from case to case (Table 1).[13]

Although pancreatic ES/PNETs are an extremely rare disease, they should be considered in the differential diagnosis of the pancreatic mass panel. We also suggest that cases with pancreatoblastoma, undifferentiated small cell carcinoma, and neuroendocrine carcinomas should be investigated for ES/PNET.[17] The clinical presentation of the tumour is diffuse while its histological findings are not exclusive.

In our case, the pathologic diagnosis was based on the positive immunoreactivity for CD99, Fli-1, and PAN-CK in many of the tumour cells. The diagnosis of pancreatic ES/PNET is made by a combination of clinical, pathological, immunohistochemical, and cytogenetic features. However, in our case, cytogenetic features were not taken into account due to limited resources.

Molecular analysis of translocation and cytogenetic evaluation have been a recognized and dominant adjunct for sarcoma diagnosis and classification. As per the evidence, ES/PNET demonstrate chromosomal translocations including the EWS gene on chromosome 22 and a member of the ETS family of genes. The most common translocation include t (11; 22) (q24; q12) that results in the fusion product EWS-FLI1 which is observed in 85%–95% of cases.[7] The second most common translocation is t (21; 22) (q22; q12) which is observed in nearly 5%–10% of cases.[7]

The standard treatment of PNET involves the use of systemic multi-agent chemotherapy along with surgery and/or radiotherapy.[12] Poor outcomes are associated with tumour dissemination in comparison to a localized disease at the time of diagnosis.[12]

In conclusion, Ewing's sarcoma/PNET of the pancreas is a rare pancreatic malignancy. To the best of our knowledge, this is the first case of Ewing's sarcoma synchronously diagnosed in a patient with carcinoma cervix.

Round cell tumours of the pancreas can be diagnosed as lymphomas, neuroendocrine carcinomas or PNET. Thus, a combination of histology and immunohistochemistry is required to differentiate PNET from other round cell tumours of the pancreas. We think that our case may contribute to the literature for this rare and unusual entity.

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## MAIN POINTS

- Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET) is an unusual malignant neoplasm.
- ES/PNET synchronous with carcinoma cervix is extremely rare and reporting it can help in improving the characterization of the pathology, while contributing to the cancer treatment advancement.

## ETHICS

**Informed Consent:** There is informed consent of patient for this case report.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: R.P., S.G., R.N., Design: R.P., S.G., Y.V.R., R.N., Supervision: S.G., R.N., Data Collection and/or Processing: R.P., S.G., Y.V.R., R.N., Analysis and/or Interpretation: R.P., S.G., Y.V.R., R.N., Literature Search: Y.V.R., Writing: Y.V.R., Critical Review: R.P., S.G., R.N.

## DISCLOSURES

**Conflict of Interest:** No conflict of interest was declared by the authors.

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