Case Report

**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, ES/PNET of the pancreas is an extremely unusual finding. Although there are a handful of pancreatic ES/PNET, 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.

Key words: Pancreas, Ewing sarcoma, synchronously, carcinoma, cervix.

Introduction

Ewing's sarcoma/Primitive neuroectodermal tumor (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 of four sub-types: peripheral primitive neuroectodermal tumor (pPNET), Ewing's sarcoma of bone (ESB), Askin's tumor, and extraosseous Ewing's sarcoma (EES). ES/PNET has been reported in several case reports and series with unusual sites such as 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 are reporting a rare case of ES/PNET in the pancreas of a 51-year old woman with synchronous carcinoma cervix. Reporting of such rare

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form will help us in improving the characterization of the pathology, while contributing to the cancer treatment advancement. In future, it will also serve as a guidance in such rare cases treatment.

Case presentation

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

Per speculum examination showed an ulceroproliferative growth over cervix which bled on touch. A computed tomography (CT) revealed a large 7x6.8x6.6cm 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 tumor cells show 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.

A magnetic resonance imaging (MRI) was performed on routine follow-up after two months. A regression in previously visualized cervical lesion was noted. There was a resolution of previously mentioned pelvic nodes. A well-defined altered signal intensity heterogeneously enhancing tissue lesion measuring 58x44x50mm 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.

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A whole body PET-CT scan showed a large FDG avid mass involving tail of pancreas with metabolically active left para-aortic nodes just below the level of left renal hilum (SUV Max 12.7).

Tumor 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 pancreaticosplenectomy. 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, tumor showed diffuse sheets of round cells (figure 2A). Tumor cells were showing small round cells with large central nucleus and scanty cytoplasm. (figure 2B). Tumor cells showed minimal nuclear pleomorphism. Brisk mitosis was noted.

On immunohistochemistry, these tumor 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

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planned for three cycles of VAC and three cycles of IE followed by radiation therapy with vincristine. The patient is currently doing well.

Discussion

PNETs comprise of 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 which is rare. In some cases, PNETs have been found arising from the pelvis, thoracopulmonary region, 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 0.3% of all primary tumors (8,9). To the best of our knowledge, there are only few pancreatic ES/PNET cases rarely with the synchronous tumors being reported in the literature (1–18). Herein we are presenting the first synchronous case of PNET with a squamous cell carcinoma of cervix.

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

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

In context to imaging tests, abdominal MRI and CT are the most useful in the detection of such tumors. However, the diagnosis is not easy as there are no specific patterns in radiological

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findings as shown in table 1 (13). A histopathological test with immunohistochemistry 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 differential diagnosis of 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 tumor 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 tumor cells. The diagnosis of pancreatic ES/PNET is made by the 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 has been a recognized and dominant adjunct for sarcoma diagnosis and classification. As per 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).

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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 tumor dissemination as compared to 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 of carcinoma cervix. Round cell tumors 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 tumors of the pancreas. We think that our case may contribute to the literature for this rare and unusual entity.

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Conflicts of interest: None

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Figure legends:

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.

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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.

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Table 1 - Present and previous reported reports of Ewing sarcoma/peripheral primitive neuroectodermal tumors

S. N. o.	Reported by (study type)	Site and nature	Clinical presentation	Radiologic diagnosis	Pathological	Immunohistochemistry	Diagnostic procedure	Cytogenetics
1.	Schutte WP and Knigght PJ(cases)	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,	Distal pancreatectomy	NR

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	report) (4)					CD99, ER, PR, and INB		
2.	Lankarani SM and Westra WH (case series)) (6)	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 Y et al., (case report)) (8)	Tumor grown superiorly to the	Mild abdominal pain, anorexia, polyuria, polydipsia, weight loss, and	A large mass was seen between the liver, the pancreas	a thin and flat neoplasm which was seen in the uncinate	Negative – SOM, ¹³¹ I-MIBI	Surgical resection	NR

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		infra hepa tic spac e, poste ro- later al aspe ct of the duod enu m, and infer iorly	immobile firm mass that was tender to deep palpation	and the right kidney with focal irregular intensific ation in the arterial period	process of pancreas			
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		to the hepa tic flexu re of colo n						
4.	Kim JY et al (case series) (9)	Bod y of the panc reas	Incidenta lly detected	Pancreati c cancer/m etastatic tumor/ne uroendoc rine tumor	INR	INR	Biops y/che mothe rapy	INR
5.	Rao L et	Bod y and	Abdomin al pain	Exophyti c pancreati	Peripher ally	Positive - CD99,	Distal pancr	NR

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	al (14)	tail of the panc reas		c mass or exophyti c gastroint estinal stromal tumor (GIST) from the posterola teral wall of the stomach was proposed	compres sed pancreati c tissue was seen and no tumor infiltrati on was discerne d	Negative - AE1/AE3, DES, SYP, and CHR	eatect omy	
6.	Teixe ira U et al (case	Panc reati c	Epigastri c pain, cutaneou s	A volumino us expansiv	Neoplas m of small	Positive - CD99, VIM, automated	GDP Sx	NR

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	report) (17)	head and body	pruritus, jaundice, choluria, and acholia	e lesion in pancreatic head and body, with well delimited borders was observed	round blue cells with scant cytoplasm arranged in nests with fibrovascular stroma was seen	CKM, and CD56. Negative - CHR, SYN, NBL, MYG, automated CD10, β - catenin, automated RP (ribosomal protein), and LCA		
7.	Welsch T et al (case	Pancreatic tail	Acute abdominal pain	A mass arising from the pancreatic tail	Nests of medium-sized round or oval	Positive – CD99, VIM, cytokeratin (KL-1,18),	Left pancreatic resection	Tumour cell nuclei showed one

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	report (12)			compress ing the stomach and spleen	tumor cells with enlarged round or oval nuclei and scant cytoplas m surround ed by fibrovas cular septae and focally, Homer-	cytokeratin 18, EMA, SYN, CD56, and CD117. Negative - Cytokeratins (7, 8 and 19), CEA, AFP, α 1ACT, protein S100, melan A, and HMB-45.		fused signal and one dislocat ed hybridi zation signal on on chromo some 22q12, indicati ve of a chromo somal transloc ation involvi
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					Wright rosettes were observed			ng the EWS gene
8.	Khuri S et al (case report) (19)	Panc reati c tail	Upper abdomin al pain and coffee ground vomiting	Mass at lesser curvature of the stomach, with compress ion on the splenic vein was observed	Mass invading the gastric wall, pancreas , and splenic hilum was observed	Positive – CD99, FLI1, VIM, and Ki67. Negative - Cytokeratin, S100, CD20, CD3, CD79A, PAX5, CD30, CD43, DOG-1, CD68, CD163, CD33, MPOX, and DES	Distal pancr eatect omy	Positive for EWSR1 gene rearran gement (11:22 transloc ation)

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9.	Nishi zawa N et al (case report) (20)	Panc reati c head	Upper abdomin al discomfo rt and nausea	Giant tumor with mild enhance ment occupied the pancreati c head	Atypical small round cells with scant cytoplas m, and each had a round nucleus with a distinct nuclear membra ne	Positive - CD99, NSE, NEAM, VIM, SYN, and CAM5.2. Negative - CHR A, AE1/AE3, cytokeratin (7 and 20), carbohydrate antigen 19-9, and CD10	PD	Breakp oint region 1 gene, 22q12 rearran gement was proven
10	Perek S et al	Head and the	Malaise and fever	Subhepat ic, hypodens	Irregular nuclear membra	Positive – CD99, and β2- microglobulin	Surgi cal	Inconcl usive

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	(case report) (21)	body of the panc reas		e, solid mass with hyperden se borders and focal necrotic areas	nes with occasion al cleaving. round or oval nuclei without any distincti ve cytoplas m; coarser chromati n pattern and more promine		resect ion	
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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 - α 1-fetoprotein; α 1ACT - α 1-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; ¹³¹I-MIBI - Methoxyisobutyl isonitrile; GDPSx – Gastroduodenopancreatectomy; PD – Pancreaticoduodenectomy; CT- Computed tomography; USG - Ultrasonography; NR – Not reported; INR – Individually not reported.

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