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, uterus 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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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 58x44x50 mm 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\text{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.
| No  | Reported by (study type)                  | Site and nature                  | Clinical presentation                                                                 | Radiologic diagnosis                                                                 | Pathological                                                                 | Immunohistochemistry                                                                 | Diagnostic procedure                  | Cytogenetics                                                                 |
|-----|----------------------------------------|----------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------|--------------------------------------------------------------------------------|
| 1.  | Schutte and Knight (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 - AE1/AE3, Moderate – EMA, Strong - Strong - SOM, Chromogranin A, S-100, VIM, CD99, ER, PR, and INB | Distal pancreatectomy               | N R                                                                               |
| 2.  | Movahedi-Lankarani et al. (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. (case report)                | Tumor grown superiorly to the infrahepatic space, postero-lateral aspect of the duodenum, and in front 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       | Positive - SOM, 111-MIBI                                                      | Surgical resection                  | N R                                                                               |
| 4.  | Kim et al. (case series)                | Body of the pancreas             | Incidentally detected                                                                | Pancreatic cancer/metastatic tumour/neuroendocrine tumour                              | INR                                                                            | INR                                                                                   | Biopsy/chemotherapy                 | INR                                                                               |
| 5.  | Rao et al. (case report)                | Body and tail of the pancreas    | Abdominal pain                                                                       | Exophytic pancreatic mass or exophytic gastrointestinal stromal tumour (GIST) from the postero-lateral wall of the stomach was proposed | Peripherally compressed pancreatic tissue was seen and no tumour infiltration was discerned | Positive - CD99, Negative - AE1/AE3, DES, SVP, and CHR                             | Distal pancreatectomy               | N R                                                                               |
| 6.  | Teixeira et al. (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, β-catenin, automated RP (ribosomal protein), and LCA | GDPx                                 | N R                                                                               |
| 7.  | Welch et al. (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 locally, Homer-Wright rosettes were observed | Positive – CD99, VIM, cytokeratin (K1-1, 18), cytokeratin 18, EMA, SYN, CD56, and CD117. Negative – Cytokeratin 7, 8 and 19, CEA, AFP, BIACT, protein S100, melan A, and HMB-45. | Left pancreatectomy                 | Tumour cell nuclei showed one fused signal and one dislocated hybridization signal on chromosome 22q12, indicative of a chromosomal translocation involving the EWS gene |
PNETs comprise nearly 1% of all sarcomas with an estimated five-year survival rate of 50%. 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. In organs that contain neuroendocrine cells such as the pancreas, PNETs are extremely rare and account for only 0.3% of all primary tumours. To the best of our knowledge, there are only a few pancreatic ES/PNET cases reported in the literature. 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.

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-renal neuroblastoma, pancreatic endocrine tumour (PET), visceral small cell neuroendocrine carcinoma (SCNC), extra-renal Wilm’s tumour, and pancreatoblastoma.

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. 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).

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. 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. The second most common translocation is t (21; 22) (q22; q12) which is observed in nearly 5%–10% of cases.

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

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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REFERENCES

1. Ewing J. Diffuse Endothelioma of Bone. CA Cancer J Clin. 1972; 22(2): 95-8.
2. Crist WM, Raney AB, Tefft M, Heyn R, Hayes DM, Newton W, et al. Soft tissue sarcomas arising in the retroperitoneal space in children a report from the intergroup rhabdomyosarcoma study (IRS) committee. Cancer. 1985; 56(8): 2125-32.
3. Aurias A, Rimbaud C, Buffe D, Zucker JM, Mazabraud A. Translocation involving chromosome 22 in Ewing’s sarcoma. A cytogenetic study of four fresh tumors. Cancer Genet Cytogenet. 1984; 12(1): 21-5.
4. Schutte WP, Knight PJ. Precocious puberty because of a pancreatic neuroendocrine tumor. J Pediatr Surg. 2006; 41(11): 1916-8.
5. Hashimoto H, Enjoji M, Kiryu H, Daimaru Y. Malignant neuroepithelioma (peripheral neuroblastoma): A clinicopathologic study of 15 cases. Am J Surg Pathol. 1983; 7(4): 309-18.
6. 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): 1040-7.
7. De Alava E, Gerald WL. Molecular biology of the Ewing’s sarcoma/primitive neuroectodermal tumor family. J Clin Oncol. 2000; 18(1): 204-13.
8. Mao Y, Sang X, Liang N, 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.
9. Kim JY, Song JS, Park H, Byun JH, Song KB, Kim KP, et al. Primary mesenchymal tumors of the pancreas: single-center experience over 16 years. Pancreas. 2014; 43(6): 959-68.
10. Kumar V, Singh A, Sharma V, Kumar M. Primary intracranial dural-based Ewing sarcoma/peripheral primitive neuroectodermal tumor mimicking a meningioma: A rare tumor with review of literature. Asian J Neurosurg. 2017; 12(3): 351.
11. Jin SG, Jiang XP, Zhong L. Congenital Ewing’s Sarcoma/Peripheral Primitive Neuroectodermal Tumor: A Case Report and Review of the Literature. Pediatr Neonatol. 2016; 57(5): 436-9.
12. Welsch T, Mchtersheimer G, Aulmann S, Mueller SA, Buechler MW, Schmidt J, et al. Huge primitive neuroectodermal tumor of the pancreas: Report of a case and review of the literature. World J Gastroenterol. 2006; 12(7): 6070-3.
13. Lee ES, Lee JM. Imaging diagnosis of pancreatic cancer: A state-of-the-art review. World J Gastroenterol. 2006; 20(24): 7864-77.
14. 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; 27(1): 91-4.
15. Plis A, Zygulska A, Piskuliwko M, Szczepański W, Bialas M, Krupiński M, et al. Synchronous extraskeletal Ewing’s sarcoma/PNET and gallbladder carcinoma: a case report and literature review. Contemp Oncol (Pozn). 2016; 20(6): 496-500.
16. Tural D, Molinas Mandel N, Dervisoglu S, Dinchs FO, Koca S, Colpan Okus D, et al. Extraskeletal Ewing’s sarcoma family of tumors in adults: prognostic factors and clinical outcome. Jpn J Clin Oncol. 2012; 42(5): 420-6.
17. Teixeira U, Galdoni M, Unterleider M, Diedrich J, Balbinot D, Rodrigues P, et al. Primitive neuroectodermal tumor of the pancreas: a case report and review of the literature. Case Rep Surg. 2015; 2015: 42596.
18. Khuri S, Gilshtein H, Sayidaa S, Bishara B, Kluger Y. Primary Ewing Sarcoma/primitive neuroectodermal tumor of the stomach. Case Rep Oncol. 2016; 9(3): 666-71.
19. Nishizawa N, Kumamoto Y, Igarashi K, Nishiyama R, Tajima H, Kawamata M, et al. Primitive neuroectodermal tumors of the pancreas: A report of 14 cases. Hepatobiliary Surg Nutr. 2013; 2(1): 51-60.
20. Pereck S, Pereck A, Sarman K, Tuzun H, Buyukunal E. Primitive neuroectodermal tumor of the pancreas: A case report of an extremely rare tumor. Pancreatology. 2003; 3(4): 352-6.