

Extraskelatal Ewing sarcoma arising from stomach and ovary: A case series of two rare sites

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ABSTRACT

Ewing sarcoma is the second most common tumor in children and young adults. Primitive neuroectodermal tumors/Ewing sarcoma family consist of small round cell of neuroectodermal origin. Ewing sarcoma commonly arises from long bones and pelvic region but extraskelatal Ewing sarcoma (EES) is a very rare tumor with highly malignant potential associated with poor outcome. We present a case series of two cases, one is from the ovary in a 24-year-old young, married, multiparous woman who presented with metastatic disease and was treated with palliative chemotherapy. The second is an Ewing sarcoma arising from the stomach in a 33-year-old male who underwent surgery followed by adjuvant chemotherapy. EES is usually an uncommon tumor and many times, the diagnosis becomes delayed and presents with metastatic disease. Immunohistochemical and molecular analysis is a must to diagnose the EES. There are no standard treatment guidelines. Surgery, various chemotherapy regimens, and radiotherapy are given for treatment. Early diagnosis and interventions are required for better outcomes.

Key words: Ewing sarcoma, Ovary, Rare sites, Stomach, Surgery

Primitive neuroectodermal tumors (PNET) are a group of small round-cell tumors originating from the neuroectodermal cells. They most commonly develop in young children and adolescents. These tumors commonly arise from the paravertebral region, extremities, and retroperitoneum [1]. It is very rare to present primarily from the stomach and ovary. Till now, only 13 cases of primary gastric Ewing sarcoma have been reported in the literature [2].

Here, we present the case of extraskelatal Ewing sarcoma (EES) of the ovary and stomach which are a rare and aggressive tumor having poor clinical outcomes.


CASE SERIES

Case 1

A 24-year-old married female with no comorbidity presented with complaints of abdominal distention, pain abdomen, vomiting, generalized weakness, and gross ascites. On examination, her performance status was 3, although her vitals were within normal

limits. She had a history of mature benign cystic teratoma of the right ovary for which she was operated on with exploratory laparotomy and right ovarian cystectomy 2 years back (in April 2021).

On investigations, serum tumor markers cancer antigen-125, alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen (CA19.9) were within normal limits. Radiologically, positron emission tomography-computed tomography (PET-CT) showed a large solid cystic mass (10×11.6×10 cm SUVmax14.4) arising from the right adnexa and a few internal septations with no internal calcification. Gross Ascites is causing clumping of bowel loops. FDG avid (suv 9.7) omental haziness and caking noted predominantly in supraumbilical region. There is FDG avid peritoneal thickening along the pelvic reflection (max thickness 2.1cm and suv 10.0) (Fig. 1). Pre-aortic, left paraaortic, right retrocrural (2.2×1.2 cm SUV7.2), right common iliac, external iliac, inguinal, and left internal mammary (1.2×1.5 cm suv4) lymph nodes were noted. Ascitic fluid cytology was negative for malignant cells. Biopsy from the adnexal mass shows an infiltrating tumor made up of round cells arranged in sheets, focal microfollicular structures separated by fibro collagenous structures, irregular nuclear contour, and vacuolated cytoplasm in favor of Ewing sarcoma (Fig. 2a and b). Further, immunohistochemical (IHC) examination done for

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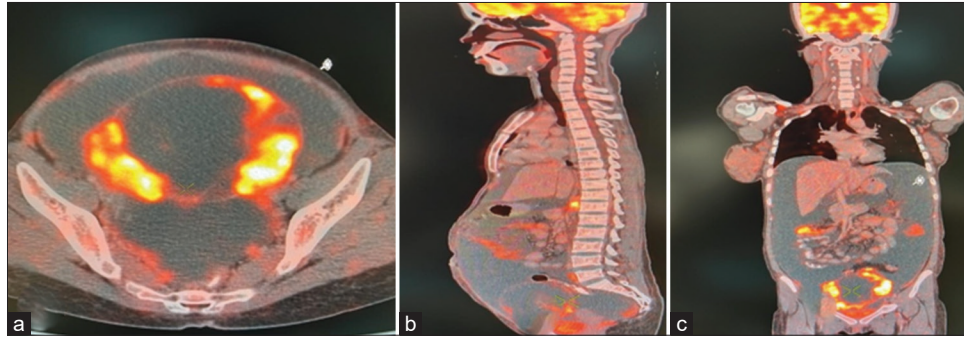


Figure 1: Positron emission tomography-contrast-enhanced computed tomography scan Ewing sarcoma ovary (a) Axial images (b) Coronal (c) Sagittal view showing large pelvic mass with gross ascites (Case 1)

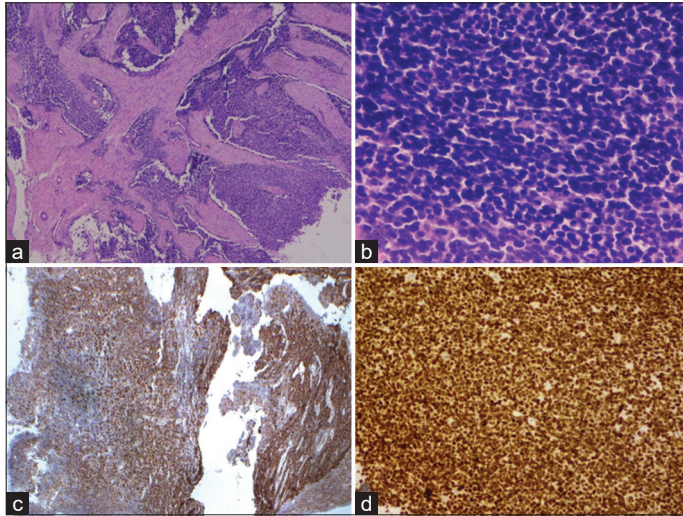


Figure 2: (a) Hematoxylin and Eosin stain. Tumor cells infiltrating the ovarian stroma; (b) The tumor cells were characterized by small uniform, compact, round-to-oval nuclei, a modest amount of pale eosinophilic cytoplasm and pseudorosette formation (c) with immunohistochemical diffuse immunopositivity for CD 99, and (d) NKX2 positivity (Case 1)

characterization of the tumor revealed CD 99 and NKX2.2, and inhibin (rare cells) was positive and negative for CD10, WT, ER, CK, and Ki 67–35%. IHC confirms the EES (Fig. 2c and d).

The patient was started on palliative chemotherapy with a VAC/IE regimen (vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide). As the patient's general condition was not good, she could not tolerate chemotherapy. After two cycles of chemotherapy, the patient did not survive.

Case 2

A 32-year-old young male without any comorbidity complained of melena and weakness for the past 3–4 months. His performance status was one and his vitals were within normal limits. Upper gastrointestinal endoscopy showed a polypoidal mass arising from the fundus and the proximal body of the stomach. Biopsy from the stomach was suggestive of poorly differentiated adenocarcinoma. PET-contrast-enhanced CT (CECT) scan shows FDG-avid mass arising from fundus and proximal body of the stomach protruding into the lumen (Fig. 3).

He underwent proximal radical gastrectomy surgery with Roux-en-Y jejunal interposition. Post-surgery, histopathological examination revealed a polypoidal ulcerated tumor close to the GE junction involving the cardia and part of the body. Tumor was 5.5×5×3.2 cm in size, presenting predominantly in the submucosa with extensive infiltration and ulceration of the overlying mucosa. Histologically, a poorly differentiated tumor with negative lymphovascular and perineural invasion was noted. There were 28 lymph nodes dissected and no lymph node was involved. The omentum was free of tumor with a pathological staging of pT3N0M0. Immunohistochemistry (IHC) was positive for CD 99 (membranous), vimentin, NKX2 (nuclear), and FL11 (nuclear) and negative for DOG1, CD117, S100, SOX10, synaptophysin, EMA, TLE1, BCL2, CD34, desmin, caldesmon CK (AE1/AE3) CD 45. IHC was in favor of EES. Cytogenetic analysis by fluorescence *in situ* hybridization was positive for translocation EWSR1 (22q12.2) score 85.

The patient was on adjuvant chemotherapy with VAC alternating with IE-based regimen and he completed 14 cycles of chemotherapy without any significant drug toxicity. At present, he is on adjuvant chemotherapy as per the planned schedule (for 1 year). Post 12 cycles of chemotherapy, PET-CECT was normal.

DISCUSSION

In children and adolescents, Ewing sarcoma is the second most common malignancy arising from the bones after osteosarcoma. Although the tumor responded to chemotherapy and radiotherapy, it is an aggressive tumor that metastasizes very rapidly. EES accounts for 15–20% of all ES/PNET family tumors [3]. EES arising from visceral organs such as the stomach and ovary is extremely rare. Very few cases have been reported till now.

Clinical symptoms are not so obvious to diagnose and morphologic features are not very specific so to characterize the tumor. There are monotonous sheets of small round cells with hyperchromatic nuclei containing fine chromatin. Sometimes, a higher degree of pseudorosettes is present [4] and the cytoplasm contains glycogen and diastase-type granules. IHC and cytogenetic analysis are usually required to confirm the EES. In Ewing sarcoma and PNET, the most common chromosomal rearrangement is translocation between chromosome 11 and 22,

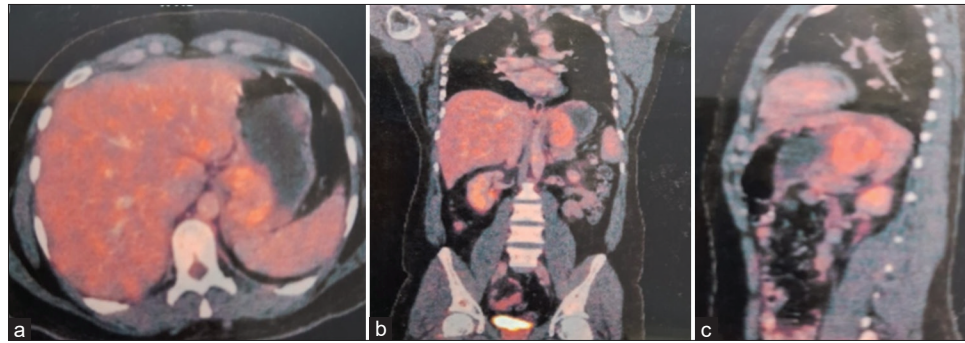


Figure 3: Pre-operative positron emission tomography-contrast-enhanced computed tomography (a) Axial (b) Sagittal and (c) Coronal view showing polypoidal mass in fundus and body of the stomach (Case 2)

t(22:11) (q24q12) which can lead to EWSR1-ETS fusion protein as transcription factors that regulate target genes and lead to cell transformation resulting in tumors with morphology and gene expression characteristic of ES [5].

The most useful diagnostic on IHC is CD99 positivity for the ES/PNET family of tumors. This cell surface protein (CD99) is the product of MIC-2 which is located on the pseudoautosomal region of the X and Y chromosomes [6].

Although Ewing sarcoma can involve any site, it may also arise from the gastrointestinal tract and female genital tract. The ovary is the most common site followed by the uterus for EES in the genital tract [7]. Most ovarian tumors present in the advanced metastatic stage due to delays in diagnosis as their non-specific clinical presentation and imaging are always a dilemma with common ovarian tumors. Ovarian PNET is divided into two categories – cPNET and pPNET. cPNET is further subdivided into three variants: Differentiated, anaplastic, and primitive. pPNETs are rarer than cPNETs and they are composed of a diffuse proliferation of small blue cells, without resembling any specific tumor and on IHC diffusely positive for CD99, CD 56, synaptophysin, and NKX2.2.[8,9].

Chao *et al.* [10] reviewed 19 cases of PNET ovary having a median age of 25 years (range 13–79) and a median diameter of 13.4 cm (range 5–30). The main clinical manifestations were abdominal pain, abdominal distension, and pelvic/abdominal mass. Czekalla *et al.* reported a case of gastric Ewing sarcoma in 2004 [11], and a few cases have been reported in the literature so far. The treatment of EES is not specified. A combination of surgery with chemotherapy is the main treatment modality and radiotherapy can be given as per site and for palliation for metastatic sites [12].

CONCLUSION

Due to the rarity of this entity, the clinical, histopathological, and prognostic implications of ovarian PNETs are still unclear. There are no standard therapeutic guidelines, and an individualized strategy is currently the best practice.

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