

Extraosseous Ewing sarcoma of the vagina: a rare entity

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Ewing sarcoma, a highly malignant neoplasm of the bone, usually occurs during childhood. About 15% are extraosseous. The Ewing family of tumors (EFTs) are extremely rare in the vagina. A 40-year literature review from 1970 to 2010 revealed only nine cases. A 32-year-old woman presented with a painless vaginal mass. A wide excision was performed. Histopathology, immunohistochemistry and molecular studies confirmed extraosseous vaginal Ewing sarcoma. Despite aggressive chemotherapy with a good initial response, she developed local recurrence and metastasis to the spine and pelvis and succumbed 22 months later. A previous infiltrating ductal breast cancer, treated and in remission complicated the picture. We present the tenth case of vaginal Ewing sarcoma and the fourth to be confirmed by molecular studies. We stress the importance of molecular techniques in definitely diagnosing EFTs, especially those arising at unusual sites, particularly in the context of a previous diagnosis of breast cancer.

Ewing sarcoma, a highly malignant neoplasm of the bone, usually occurs during childhood. About 15% are extraosseous, involving the trunk, extremities, uterus, ovaries, cervix, vulva and vagina.¹ Ewing sarcoma and peripheral primitive neuroectodermal tumor (ES-pPNET) are two morphological ends of a spectrum of neoplasms, characterized by a t(11:22)(q24;q12) translocation involving fusion of the Ewing sarcoma gene on chromosome 22 to the FLI-1 gene on chromosome 11. The Ewing family of tumors (EFTs)² very rarely occur in the vagina. A 4-year literature review from 1970 to 2010 revealed only nine reported cases.¹⁻⁹

CASE

A 32-year-old Omani woman, para 5, presented with a painless vaginal mass and vaginal discharge of one-year duration. Local examination revealed an ulcerated, firm ovoid fleshy mass, 8×6 centimeters in size, arising from the upper third of the anterior vaginal wall, which bled on touch. CT imaging revealed a 6×4 centimeter contrast-enhancing upper vaginal mass infiltrating the left lateral wall (**Figure 1**), small local lymph node enlargement, no bladder or pelvic wall involvement, multiple bone metastasis in the pelvic

bones and sacrum. Tumor markers were normal.

Three years prior to the current presentation, she underwent a wide local excision and axillary clearance for a 7-centimeter, right-sided infiltrating ductal breast carcinoma (stage T4N1M0), ER/PR ++, 2/10 nodes positive. Adjuvant chemotherapy with 6 cycles of 5FU, epirubicin, cyclophosphamide, radiotherapy and tamoxifen resulted in remission.

Wide local excision of the vaginal mass was per-

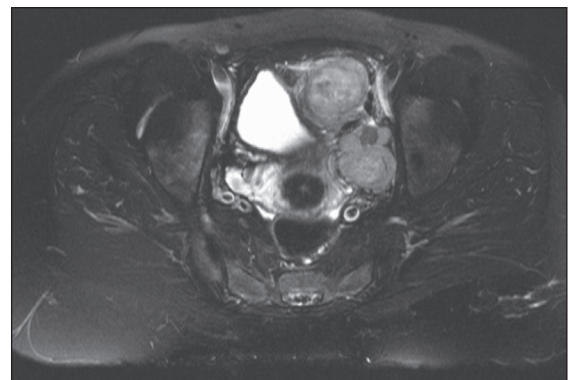


Figure 1. T2-weighted fat sparing axial images show a lobulated mixed signal intensity (solid and necrotic) mass lesion in the left side of pelvis.



Figure 2. Ovoid firm fleshy mass 8 x 6 centimeters arising from the upper third of the vagina near the anterior fornix with an ulcerated surface that bled on touch.

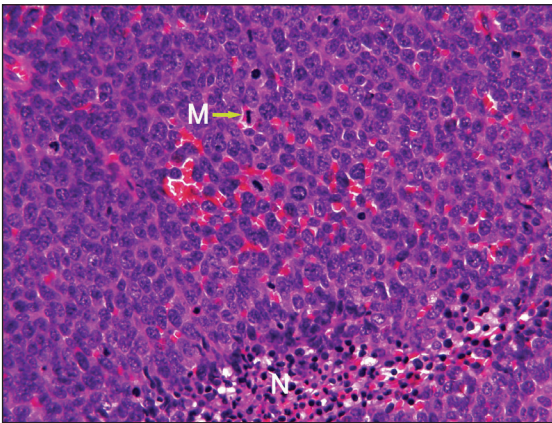


Figure 3. HE-stained slide from vaginal tumor $\times 40$ showing sheets of small round cells with hyperchromatic nuclei, mitotic figures (M) and areas of necrosis (N).

formed. Grossly, we found an ovoid firm mass, 8 \times 6 \times 4.5 centimeters, weighing 90 grams, with two areas of mucosal defects (**Figure 2**). The cut surface showed a lobulated greyish pink fleshy appearance. Microscopy revealed a lobulated neoplasm divided by fibrous septae into solid sheets of packed small round cells with hyperchromatic vesicular nuclei, small nucleoli and abundant eosinophilic cytoplasm (**Figure 3**). Central areas of necrosis and numerous mitotic figures were present. No rosettes were seen. The tumor was almost at the deep margin in one section. Overlying squamous epithelium was ulcerated, not dysplastic.

Immunohistochemistry showed strong membrane

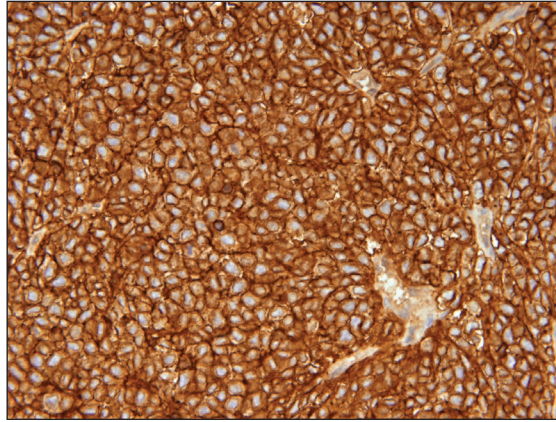


Figure 4. Immunohistochemistry stain for CD99 showing strong membrane positivity in the vaginal tumor.

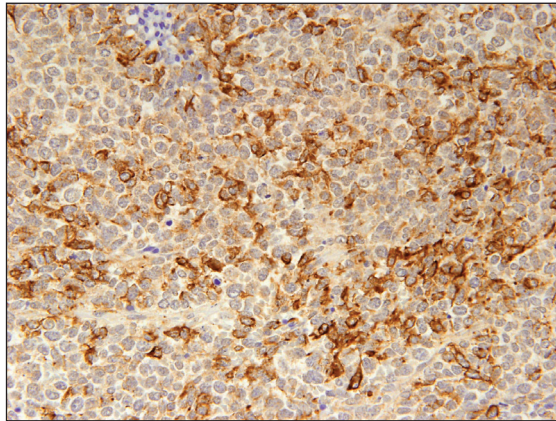


Figure 5. Immunohistochemistry stain showing focal positivity for cytokeratin.

positivity for CD99 (**Figure 4**) and vimentin, focal positivity for low-molecular weight cytokeratin and cytokeratin 20 (**Figure 5**) NSE and PGP9.5, nuclear positivity for FLI-1 and focal cytoplasmic PAS positivity. Staining for high-molecular weight cytokeratin, Epithelial membrane antigen, Cytokeratin 7, Estrogen receptor, S100, smooth muscle actin, desmin, Leukocyte Common Antigen, chromogranin, CD10, and sarcomeric actin were negative. A preliminary diagnosis of vaginal Ewing sarcoma was made, but the possibility of metastatic recurrence of the breast carcinoma to the vagina had to be eliminated.

Molecular genetic analysis of the tumor using RT-PCR demonstrated the (t11:22)(q24;q12) chromosomal translocation characteristic of the EFTs—irrefutable evidence of a primary vaginal Ewing sarcoma.

Initial treatment with one cycle of taxotere (75 mg/m²) and cisplatin (75 mg/m²) showed good response. On confirmation of primary vaginal Ewing sarcoma and

9 cycles of alternating VADA/IE were planned. There was good response following three cycles on re-evaluation CT/MRI scans. Since the maximum tolerated dose of anthracycline had been reached, a five-drug combination of etoposide, vincristine, dactinomycin, ifosfamide, and liposomal doxorubicin protocol was implemented with a plan to continue for 1 year. However, following the eleventh cycle, she showed rapid disease progression, confirmed on MRI (18 months post surgical excision). A vaginal mass entrapping the left ureter, causing left hydronephrosis was seen. She refused stenting, nephrostomy or any surgical resection, hence palliative topotecan and cyclophosphamide were used. She succumbed to metastatic disease 22 months after the initial presentation.

DISCUSSION

About 90% of EFTs exhibit the same t(11:22)(q24;q12) chromosomal translocation involving chromosome 22, giving credence to the idea of a common cell of origin, believed to be a mesenchymal cell reprogrammed to a neuro-ectodermal phenotype.^{1,2,10} EFTs predominantly occur in long bones, but can occur at extraskeletal sites like the chest wall, pelvis, paravertebral region, retroperitoneum and lower extremities.¹ Female genital tract involvement is rare and limited to a small number of mostly single case reports.^{1,7,11-14} On reviewing the published literature from 1970 to 2010 (using Pubmed, MEDLINE, Google and key search terms – ‘Ewing’s sarcoma’, primitive neuroectodermal tumors, vagina), we found vaginal Ewing’s sarcoma to be extremely rare

Table 1. A summary of the clinic-pathological profile of all reported cases of vaginal Ewing sarcoma over the last 40 years including the present case. Abbreviations used: HE: hematoxylin-eosin stained section, IHC: immunohistochemistry, EM: electron microscopy, RT-PCR: reverse transcription polymerase chain reaction.

Author (year)	Age (y)	Site	Symptoms	Gross appearance and size	Diagnostic modality HE/EM/IHC/RT-PCR
Vang et al ⁴ (2000)	35	Vagina	Mass	Solid/cystic, 3 cm	HE +EM+IHC +RT-PCR CD99+
Farley et al ⁵ (2000)	35	Vagina	Mass	Solid/cystic, 4x2 cm	HE +EM+IHC HBA-71+ve (antibody to MIC2 gene)
Petkovic et al ³ (2002)	45	Recto-vaginal septum	Mass, pain	Solid, 8.7x6.1 cm	HE +EM+IHC CD99+
Gaona-Luviano P et al ¹ (2003)	34	Vagina	Mass	Solid, 4x3 cm	HE +EM+IHC HW rosettes and pseudorosettes, CD99+, Chromogranin and NSE -
Liao X et al ⁶ (2004)	30	Vagina	Mass	Solid, 5x4 cm	HE +EM+IHC HW rosettes+, CD99+, FLI-1+ Vimentin, S100,NSE,Synaptophysin +
McCluggage G et al ² (2007)	30	Vagina	Mass	Solid, 8 cm	HE+EM+IHC+RT-PCR CD99+, FLI-1+, Vimentin+
Al-Tamimi et al ⁷ (2009)	47	Vagina	Mass	Solid/cystic, 3 cm	HE+EM+IHC Occasional rosettes, CD99+,Vimentin+ Focal + with S100, NSE, chromogranin
Yip CM et al ⁹ (2009)	28	Vagina	Mass, discharge	Solid/nodular, size	HE+EM+IHC Pseudorosettes,CD99+, Vimentin+ Focal + for synaptophysin,CD56,NSE
Rekhi B et al ⁸ (2010)	17	Vagina	Mass, discharge	Solid, 10x9.8 cm	HE +EM+IHC+RT-PCR Vimentin+, MIC2+, FLI-1+
Current report	32	Vagina	Mass, discharge	Solid, ulcerated.8x6 cm	HE +EM+IHC+RT-PCR No rosettes, CD99+, FLI-1+, PAS+, Vimentin+, focal + with NSE,PGP9-5, cytokeratin epithelial markers, AE1/3 and CAM5.2

Table 2. A summary of the treatment modalities and outcome of all reported cases of vaginal Ewing sarcoma including the present case.

Author	Treatment	Outcome	Follow-up in months
Vang et al4 (2000)	WSE + CMT + Xrt	NED	19 months
Farley et al5 (2000)	WSE + CMT + Xrt + IBT	NED	48 months
Petkovic et al3 (2002)	CMT + Xrt + IBT	AWD. Residual mass 3.5x2.5 cms	18 months
Gaona-Luviano P et al1 (2003)	SE + CMT + Re-resection + Xrt + IBT	NED	20 months
Liao X et al6 (2004)	WSE + Subsequent TAH + CMT + Xrt + IBT	NED	36 months
McCluggage G et al2 (2007)	NA	NA	NA
Al-Tamimi et al7 (2009)	SE + CMT + Xrt + IBT	NED	3 months
Yip CM et al9 (2009)	Partial resection + local Xrt	Residual mass 2 cms. Right fronto-parietal cranial metastasis 13 months later	18 months post craniectomy for metastatic tumor removal
Rekhi B et al8 (2010)	Biopsy + CMT + local Xrt	NED	7 months
Machado LSM et al (2010 – current case)	WSE + CMT	Died	22 months

Abbreviations used: SE- surgical excision, WSE- wide surgical excision, TAH – total abdominal hysterectomy, CMT- chemotherapy, Xrt – radiation therapy, IBT- intracavitary brachytherapy, NA – information not available, AWD – alive with disease, NED – no evidence of disease.

with only nine cases reported so far,¹⁻⁹ of which only three have had molecular confirmation (Table 1).^{2,5,8} The current case is the tenth case of EFTs involving the vagina and the fourth to have molecular confirmation studies.

As in our patient, light and electron microscopy shows solid sheets of undifferentiated primitive mesenchymal cells. Typically seen are small, round, blue cells with abundant glycogen, absent cytoplasmic filaments and variable degrees of neural, glial, ependymal and medulloepithelial differentiation. It has been proposed that if 20% or more of a tumor shows Homer-Wright rosettes, the lesion should be classified as PNET.^{1,2,4,6} Homer-Wright rosettes were not seen in our patient.

It is sometimes difficult to distinguish EFTs from other small round cell neoplasms.^{1,6} Immunohistochemical studies, as in the present patient, showing strong positivity for CD99 antigen and FLI-1 protein are valuable for diagnosis. Approximately 90% of EFTs harbor the t(11:22)(q24;q12) chromosomal translocation. The remaining 10% exhibit variant translocations involving the EWSR1 gene on chromosome region 22q12 such as t(21:22)(q22;q12), t(7:22)(p22;q12) or t(2:22)(q33;q12) resulting in different fusion proteins—EWSR1-ERG, EWSR1-ETV1 or EWSR1-FEV, respectively.² PCR or fluorescent in situ hybridization are confirmatory diagnostic techniques.³ RT-PCR clinched the diagnosis of primary extraosseous Ewing sarcoma in our patient.

The clinicopathological features of women with vaginal ES-PNET are summarized in Table 1.¹⁻⁹ The average age was 33.3 years. Of the nine previously reported cases, eight presented with painless vaginal masses, one involving the rectovaginal septum that was associated with dyspareunia. Grossly, all appeared solid with only three having a cystic component. The tumors showed characteristic sheets of monotonous undifferentiated small, round, hyperchromatic cells. Homer-Wright rosettes have only been reported by some authors. Strong positivity for CD99/MIC2 has been shown in all cases. Multiple immunohistochemical markers have been used in the current case and seven of the nine previous cases (Table 1). RT-PCR has been performed in only three cases.^{2,5,8}

In the current patient, her presentation with a vaginal mass and multiple bone metastasis in the context of the previous diagnosis of breast cancer posed a diagnostic dilemma. Were we dealing with metastatic carcinoma or was the vaginal tumor an entirely different entity? Histopathology and molecular studies irrefutably confirmed an extraosseous vaginal ES-PNET. Though extra-osseous ES-PNETs were classified and treated like rhabdomyosarcomas (Intergroup Rhabdomyosarcoma Study), they are now managed as osseous Ewing sarcoma¹⁵ with similar chemotherapy protocols, doxorubicin being preferred over actinomycin D. Current protocols combining doxorubicin, vincristine, cyclophosphamide, etoposide and ifosfamide improve 5-year overall survival.

al to 72% compared to 59% after surgery alone.¹⁶ Ewing sarcoma trials typically use neoadjuvant chemotherapy and delayed surgery.^{15,16} However, in vaginal Ewing sarcoma amenable to complete excision, wide surgical excision followed by chemotherapy or radiotherapy is recommended.^{1,10} Since these tumors are radiosensitive, those not amenable to resection or with positive margins on histology can be treated with radiation.

The treatment modalities and outcomes are outlined in **Table 2**. Surgical options have ranged from wide excision to total abdominal hysterectomy.¹⁻¹⁰ Vaginal or vulval ES-PNETs seem to have a less adverse prognosis than uterine, probably due to the younger age group, more uniform small, round cell tumors without other differentiation and the superficial location that makes complete surgical resection usually possible.⁶ The current patient is the only one who succumbed. Six others were alive with no evidence of the disease in follow-up periods ranging from 3-48 months. The case involving the rectovaginal septum had residual disease at 18

months and in one case, outcome details are not available.

Due to the paucity of cases reported in the literature, the prognosis for vaginal ES-PNET is difficult to determine and is related to the staging. The IRS staging system or staging based on size and metastasis may be used. The size cut-off for prognostic evaluation has been either 5 or 8 centimeters.¹ Metastasis are present at diagnosis in 9% to 20% of patients.¹ The 5-year disease-free survival is 24% to 80% for localized disease.¹ Smaller resectable lesions have a better prognosis.

Vaginal ES-PNETs occur in younger women with usually a relatively long disease-free period. ES-PNETs at unusual sites like the vagina warrant proper diagnosis based on clinical suspicion, history and physical examination, immunohistochemical and molecular analysis to optimize management. Wide local excision followed by adjuvant chemotherapy and/or radiotherapy is recommended. However, the rarity of these tumors preclude conclusions regarding treatment and prognosis.

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