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Rare case of primary extraosseous Ewing's sarcoma of the cervix: A rare case report

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Abstract
Ewings sarcoma (ES) is an uncommon malignancy belonging to small round cell tumour family. It is an aggressive tumor with a 5-year survival rate of 60 percent. Majority of cases occur in the long bones, followed by the pelvis or ribs, and only less than 20% occur at extraosseous sites. Extraosseous ES is a rare diagnosis and is more likely to be seen in adolescents. Cervical EES is extremely uncommon, with only 28 cases reported in literature so far. Depending on the stage at diagnosis, survival in literature varies from 12 days - 4.2 years. Diagnosis is challenging and is predominantly based on immunophenotyping, along with presence of chromosomal translocations. There are no specific consensus for management, with most reported cases being treated in lines with osseus ES. We had a 75-year-old female, presenting to our hospital with complaints of scanty bleeding per vagina. Gynaecological examination and imaging revealed a localized tumor in cervix with parametrial invasion and no regional nodal involvement. Biopsy was suggestive of small round cell tumor. As the patient had a poorly differentiated malignancy, suspicious of high-grade sarcoma and a panel of immunohistochemistry (IHC) was performed, and it was finally concluded as Ewings sarcoma of the cervix. This case report highlights our experience in the diagnosis and management of this rare condition and challenges we encountered, along with detailed review of available literature.

Keywords: Extraosseous ewings sarcoma, ewings sarcoma of the cervix, ESFT/PNET, small round cell tumor, pseudorosettes, immunohistochemistry, neoadjuvant chemotherapy, radiotherapy

Introduction
Ewings sarcoma (ES) is a rare and aggressive malignancy belonging to small round cell tumour family. With a 5-year survival rate of 60 percent, it is a tumor with an adverse prognosis and a short overall survival rate [1]. The majority of cases (about 45%) occur in the long bones, followed by the pelvis or ribs, and only approximately 20% occur in extraosseous sites [2]. In teenagers aged 10 to 20 years, ES primarily affects the pelvic area or the proximal long bones. Children and teenagers are more likely to have Extraosseous ES, and older people rarely are diagnosed with it [3].

Primary Extraosseous Ewing's sarcoma (EES) has been reported with less frequency: sites reported being ileum (Li *et al*. 2017), breast (Papi *et al*. 2022), thyroid (Seipel *et al*. 2022), pancreas (Patel *et al*. 2020), as well as vagina (Tintila *et al*. 2021). Cervical EES is extremely uncommon, with only 28 cases reported in literature so far. Depending on the stage at time of diagnosis, survival in literature varied from 12 days - 4.2 years [2]. Diagnosis is based on morphology as well as immunophenotyping, along with presence of chromosomal translocations. Diagnosis of ES could be challenging, particularly when they occur in unusual locations.

Surgery (hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection) has been main modality of treatment in most cases reported in literature, many of them were also treated with chemotherapy regimen based on Adriamycin, vincristine, along with cyclophosphamide. There is an increasing consensus to treat these patients akin to osseous ES with neoadjuvant chemotherapy followed by surgery, followed by adjuvant chemotherapy, as ES has been considered a systemic disease to begin with. Radiation therapy can be administered as a postoperative adjuvant or as a substitute for surgery in locally advanced disease. According to earlier research, the survival rate of EES can be considerably increased by local treatment, such

as surgery and/or radiotherapy (Rud *et al*. 1989). Overall survival (OS) as well as Event Free Survival (EFS) are impacted by the initial tumor size, which is the most crucial prognostic factor for this tumor, along with presence of metastases and margin of surgical resection (Foulon *et al*. 2016).

Case history

A 75-year-old female with no comorbidities and in relatively good general condition, presented to our hospital with complaints of scanty bleeding per vagina for past two months, accompanied by white discharge per vagina. Gynaecological examination and imaging revealed a localized tumor in cervix with parametrial invasion, no regional nodal involvement. Biopsy was suggestive of small round cell tumor. As the patient had a poorly differentiated malignancy, suspicious of high-grade sarcoma, immunohistochemistry (IHC) was performed. IHC demonstrated positivity for CD99 and FLI-1 (Friend leukaemia integration-1); however, pancytokeratin, desmin, leucocyte common antigen (LCA), as well as terminal deoxynucleotidyl transferase (TdT) were negative, favouring ESFT (Ewing's sarcoma family of tumour) or PNET (peripheral neuroectodermal) group of tumours. As per decision of our multidisciplinary tumour board, in view of inoperability, she was planned for definitive radiotherapy (RT) followed by adjuvant chemotherapy as per Vincristine, Adriamycin, Cyclophosphamide alternating with Ifosphamide, as well as etoposide every three weeks for total 6 cycles and to reassess.

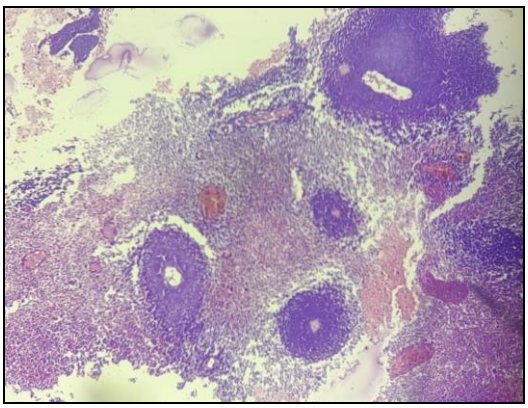

Fig 1: Light microscopy showing peritheliomatous pattern of viable tumor cells around central blood vessels. (H&E, x100)

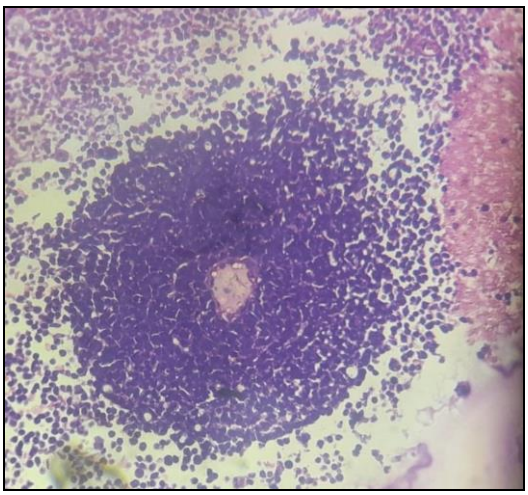

Fig 2: Uniform small round cells with round nuclei and stippled chromatin. Scanty eosinophilic cytoplasm, few showing cytoplasmic vacuolisation. Homer-Wright like pseudorosettes, with central fibrin surrounded by sheet like growth of round blue cells. (H&E, x400)

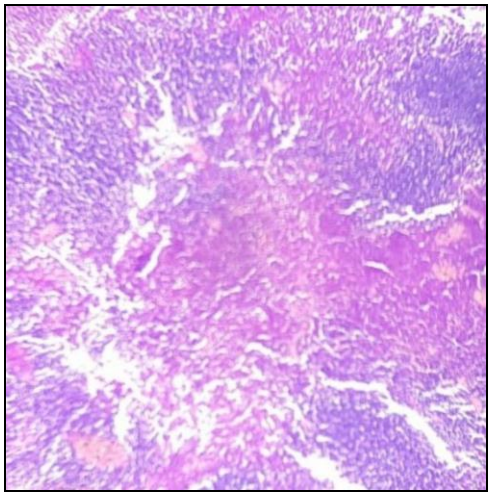

Fig 3: Tumor cells showing necrosis. (H&E, x100)

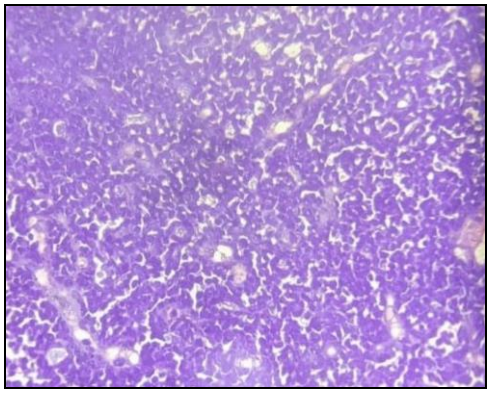

Fig 4: Few small rosettes with few Homer-Wright appearance.

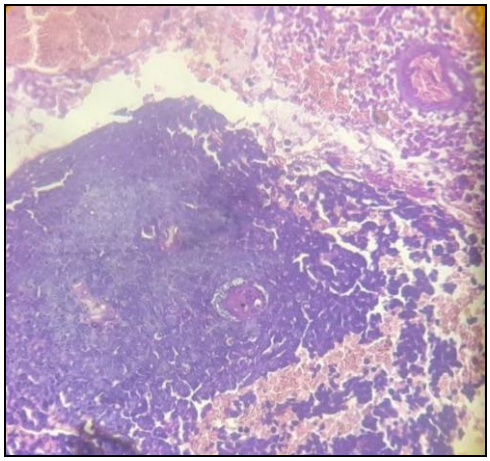

Fig 5: Few rosettes show perivascular pseudorosette type.

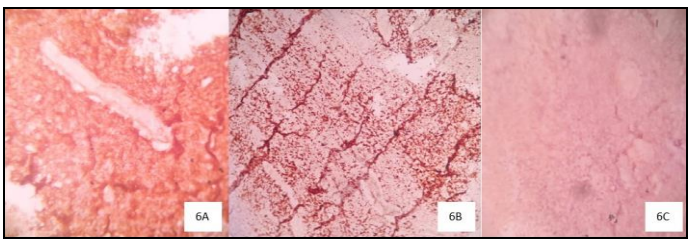

Fig 6: Immunohistochemistry demonstrating strong positivity for CD99 [6A], high Ki67 expression [6B], focal positivity for Synaptophysin [6C].

The patient received a total dose of 50.4 Gy in 28 fractions of External beam radiotherapy from 30th August 2023 to 9th

October 2023, followed by 3 sittings of Intracavitary brachytherapy. Following RT, there was a good tumour response clinically. She has been started on adjuvant chemotherapy of Vincristine, Adriamycin, Cyclophosphamide alternating with Ifosphamide, along with Etoposide every three weeks for total 6 cycles. After she received 1st cycle of adjuvant VAC-IE regimen, the patient defaulted further chemotherapy and was lost to follow-up. She could not be contacted despite repeated phone calls.

She presented back after 14 months, having complaints of bleeding per vagina and white discharge. Examination revealed a large nodular, hard, and fixed growth replacing the cervix and filling entire vagina with bilateral parametrial invasion up to pelvic sidewall. She had a local disease recurrence with upstaging. CT Abdomen and Pelvis was done, which revealed a large lesion replacing the cervix with parametrial invasion. CT thorax showed suspicious lung metastases. In order to palliate the symptoms and arrest bleeding, she was given 30 Gy in 10 fractions reirradiation to pelvis from 10th February 2025 to 22nd February 2025. She was shown to Medical oncologist and planned for palliative systemic therapy with VAC + IE regimen in view of limited options for Ewing's sarcoma group. After receiving one cycle of VAC + IE, the patient developed grade 3 neutropenia (CTCAE version 5), and further chemotherapy was withheld, and she was treated with growth factors. After her counts recovered, she was planned for continuation of chemotherapy, however with a 25% dose reduction and a VAC-only regimen with no further IE. She is currently on dose-reduced chemotherapy and has completed 4 cycles of adjuvant chemotherapy. Response assessment imaging is planned after 2 more cycles (6 cycles).

This patient had an initial good response to RT, which could have been consolidated with adjuvant chemotherapy. However, she defaulted and the disease recurred with a locally advanced stage and lung metastases. Considering her age, tolerance to further chemotherapy is questionable.

Discussion

Ewing's sarcoma is a rare and aggressive malignant tumour belonging to malignant small round cell tumour family. It is a bone and soft tissue tumour with the usual sites being pelvis, ribs, as well as proximal long bones, and only approximately 20 percent cases occur in extraosseous sites (Riggi *et al*. 2021). PNET and Ewing's sarcoma are both classified as small round cell tumors. Even though Ewing's and PNET were once thought to be distinct diseases, research has revealed that they have shared phenotypic and molecular characteristics, leading to their grouping in same class. They differ primarily in that Ewing's sarcoma does not exhibit neuroectodermal differentiation, while the PNET/Ewings sarcoma group of tumors (ESFT) has neuroectodermal characteristics on light, IHC, and electron microscopy [4].

ES of bone, Askin's tumor (Ewing's sarcoma of chest wall), PNET (primitive neuroectodermal tumor), and EES are all members of ESFT (Grünewald *et al*. 2018). Although cervical EES is highly rare, primary extraosseous Ewings sarcoma EES has been observed to occur less frequently in the ileum (Li *et al*. 2017), breast (Papi *et al*. 2022), thyroid (Seipel *et al*. 2022), pancreas (Patel *et al*. 2020), as well as vagina (Tintila *et al*. 2021).

Diagnosis of these tumours could be challenging, particularly when they present at such uncommon locations. Diagnosis is based on morphological as well as immunophenotyping, and presence of chromosomal translocations. Small round cells with fine chromatin, eosinophilic cytoplasm or scanty clear cytoplasm that contains glycogen, along with unclear cytoplasm, are common histological traits; however, they are not always the only ones seen [5]. The combination of CD99 and FLI1p is the most sensitive and specific test panel for ESFT/PNET diagnosis. A highly sensitive marker for ESFT/PNET diagnosis is MIC 2 (also known as CD99). However, it lacks specificity because it is also expressed in a wide range of different tumors, including mesenchymal chondrosarcoma, synovial sarcoma, small-cell carcinoma, Merkel cell carcinoma, rhabdomyosarcoma, and lymphoblastic lymphoma. FLI1 is considered a more precise indicator of tumors in the ES family [6]. However, additionallylymphomas, rhabdomyosarcomas, and synovial sarcomas are reported to be FLI-1 positive.

LCA negative ruled out a lymphoma diagnosis in this case, while the absence of desmin ruled out rhabdomyosarcoma. Additionally, other forms of tiny, blue, round cell tumors that entered differential diagnosis were ruled out by negative staining for other markers such as TdT, desmin, as well as cytokeratin. Fluorescent in situ hybridization, or FISH, exhibited a moderate sensitivity of 50% but a very high specificity of 100% [7].

The symptoms of intermittent vaginal bleeding and white discharge are common in patients with ESFT/PNET. This mimics those who have cervical squamous cell carcinoma (SCC). However, to note, PNET is more prevalent in younger women, while SCC of cervix is more prevalent in middle-aged to older women[8]. Additionally, the ESFT/PNET category of tumors is typically larger. Regional node involvement has been more commonly reported in Extraosseous Ewings sarcoma than those occurring in typical bony locations (12.4% for extraosseus ES compared to 3.2% for skeletal ES). Five-year overall survival was also inferior for these patients (45.9% vs. 60.3%; $P < 0.001$) [6]. Our patient also had regional node involvement.

These tumors can be difficult to diagnose, particularly when they appear in such unusual places. As computed tomography (CT) and ultrasonography are less sensitive, identifying EES is difficult (Papi *et al*. 2022). Since ES/PNET tumors are sensitive to fludeoxyglucose, PET might be more effective for diagnosis, staging, as well as tracking treatment response [8]. However, the histology, IHC and other ancillary tests are most crucial for the definitive diagnosis of ESFT/PNET.

RT-PCR (Reverse transcription-polymerase chain reaction) as well as fluorescence in situ hybridization (FISH) could be employed to look for genetic translocations (Abboud *et al*. 2021). It is noted that 85% of people with ES have fusion gene EWS or FLI (FLI, ETS family member of transcription factors), which is a molecular diagnostic feature of ESFT and is brought on by the characteristic chromosomal translocation t(11;22)(q24;q12) (Balamuth and Womer 2010). Other gene fusions between EWS as well as ETS families, including ERG, ETV1, or E1AF, may also occur in the remaining 15% of cases (Riggi and Stamenkovic 2007). Magnetic resonance imaging as well as Fluorodeoxyglucose-Positron Emission Tomography (FDG PET) are diagnostic imaging techniques utilized for local staging as well as metastatic exclusion (Meyer *et al*. 2008).

Xiao *et al*. [9] (2024) summarized total 28 cervical ES cases. The median age of the patients was 35.5 yrs, with a range 13 - 59 yrs. Majority of individuals have lower stomach pain and abnormal vaginal bleeding. With minimum diameter 3cm and maximum diameter 10cm, ES frequently presented with cervical expansion. Seven patients lacked clinical staging data. The disease's high rate of metastasis needs our attention, as shown by the 9 patients (43%) who were stage IV at diagnosis. Nine patients (43%) had stage IB1 or IB2, two patients (10%) had

stage II, and one patient (5%) had stage III. Seventy-nine percent of patients underwent surgery. Eleven patients (50%) underwent pelvic lymphadenectomy (PL), bilateral salpingo-oophorectomy (BSO), and extensive total hysterectomy (ETH).

Twenty four patients (86%) underwent postoperative chemotherapy (smallest tumor size was three cm), except for one case for which there was insufficient evidence. However, the chemotherapy regimen varied and only 12 patients had details of chemotherapy regimen. Eight of these 12 cases (66%) had VAC in their chemotherapy regimen. Three cases (25%) had VAC alone, and VAC + IE in the remaining five cases. The duration of follow-up varied from one month to over ten years. Eight patients passed away in less than a year. Interestingly, all patients who passed out within six months had systemic metastases or tumors with a size of> 7 cm[9]. As a result, significant prognostic markers may include tumor size and metastasis upon diagnosis. Just three (11%) of the 28 cervical ES cases that were studied did not get chemotherapy, alongside one of them experienced paraplegia and vertebral metastases before chemotherapy (Jia *et al*. 2022)

Regarding treatment of EES, treatment is primarily multimodal that includes local therapy (radiotherapy and/or surgery) and induction chemotherapy (Cidre-Aranaz *et al*. 2022). ESMO (European Society of Medical Oncology) (Casali *et al*. 2018) and the NCCN (National Comprehensive Cancer Network) (Biermann 2013) have both suggested that EES should get same course of treatment as other ES family members. Furthermore, Weshi *et al*. demonstrated that adult EES are usually identical to those of bone with regard to prognostic variables influencing the outcome and response to therapy (El Weshi *et al*. 2010). Hence, strong chemotherapy, local adjuvant radiotherapy, and appropriate surgical resection are necessary for ultimate therapeutic benefit of EES.

It is yet unknown how best to manage and treat ES that occurs in the cervix due to rarity. There is no consensus for effective diagnosis as well as treatment for cervical ES, and local treatment and radiotherapy approaches, primarily follow those of classical bone ES (Gerrand *et al*. 2020). Many of these patients in literature underwent chemotherapy as Adriamycin, vincristine, along with cyclophasphamide, generally after surgery.

Since Ewing's sarcoma has been historically seen as a systemic disease, there has been increasing consensus recently to treat these patients similarly to osseous Ewing's sarcoma using neoadjuvant chemotherapy, followed by surgery, as well as adjuvant chemotherapy. Radiation therapy can be administered as a postoperative adjuvant or as a substitute for surgery in cases of locally advanced disease. Depending on the stage at diagnosis, survival varied from 12 days - 4.2 years[8]. Our patient responded well to RT and was diagnosed at stage IIB

Conclusion

In conclusion, our case report of an aggressive extraosseous Ewings sarcoma of cervix highlights that a high index of suspicion is necessary for diagnosis and early initiation of appropriate treatment which might affect prognosis. In recent times an increasing number of sarcomas are being classified into the PNET/Ewing's sarcoma family of tumors due to expanding availability of IHC markers. Both the pathologist and the surgeon still face difficulties in diagnosing and treating these tumors, particularly when they appear in such unusual places. The most effective method of diagnosis is high index of suspicion, alongside judicious use of imaging as well as IHC tests. Radiation and chemotherapy are effective adjuncts to surgery, which is still the mainstay of treatment. Establishing international databases for these uncommon tumors could aid in data collection and treatment strategy improvement.

Conflict of Interest
Not available

Financial Support
Not available

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