Primitive neuroectodermal tumour of the Cervix: A rare entity
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Citation

Abstract
A 19-year-old female presented with discharge per vaginum and was found to have a heterogenous pelvic mass involving the uterine cervix, vagina and the adnexal region on CT scan. Histopathological examination revealed a small round cell tumour and immunohistochemical studies with CD-99 showed strong positivity. Based on Morphologic and Immunohistochemical profile a diagnosis of extraosseous Ewing's sarcoma/ primitive neuroectodermal tumour was made (EES/PNET). The patient is now being treated under the high risk protocol followed for Ewings family of tumours. This case represents one of the rare entities of a primary EES/PNET arising in the female genital tract presenting as a cervico-vaginal mass.

BACKGROUND
Ewings sarcoma (ES) and primitive neuroectodermal tumour (PNET) are regarded as two ends of a morphologic spectrum of the same tumor entity based on similar natural history, prognosis, immunohistochemical, and cytogenetic profiles. Extra osseous tumors resembling Ewing sarcoma was first described by Teft in 1969.[1] Ewings sarcoma-Primitive neuroectodermal tumour (ES–PNET) is a small round cell tumor with variable degree of neural, glial, ependymal, and medulloepithelial differentiation containing well formed rosettes or pseudorosettes. PNETs of female genital tract are a rare entity, commonly occurring in the ovaries.[2] These tumours are occasionally observed in the uterine corpus,[3, 4], cervix,[5, 6], and vulva.[7] A few cases of ES–PNET have been previously described in the vagina and recto vaginal septum[8-10] and an exceptional case of PNET in the broad ligament has also been observed.[11] Conventionally, the diagnosis of ES–PNET can be made based on histologic examinations. However, immunohistochemical studies further substantiate the morphological findings Recognizing the existence of these rare entities in cervix is of paramount importance as some primary tumors of the gynecological tract and of other systems may resemble it. Histologically ES–PNET of the vagina may be confused with primary or metastatic small cell (neuroendocrine) carcinoma, non-Hodgkin's lymphoma, alveolar rhabdomyosarcoma, poorly differentiated squamous cell carcinoma of small cell type, and malignant melanoma which have round cell morphology. In addition to the evidence of neuroectodermal differentiation (Homer–Wright rosettes), immunohistochemical studies assist in diagnosing and differentiating ES–PNET from other round cell pathologies. The index case showed strong positivity for CD-99(MIC-2) antigen. However, it was negative for other immunohistochemical markers (CK, CEA, and Desmin).

Generally, PNETs arising from extra osseous sites have an aggressive natural history and portends poorer prognosis as compared to Osseous PNETs.[12] Though not much has been commented about the prognosis of ES-PNET occurring in the female genital tract, nevertheless, literature review has shown ES–PNET’s occurring in the vagina or vulva to have less adverse prognosis than those in the uterus.[13,14] The better outcome of vaginal ES–PNETs strongly suggests that these cases, being mucosa associated, may be similar to the vulvar and non-gynecological cutaneous ES–PNET.

One of the commonly used protocols for such tumours in the pelvis is the Ewings family of tumours IESS-II protocol.[15] This multimodality approach consisted of high-dose intermittent multiagent chemotherapy (vincristine, cyclophosphamide, Adriamycin [doxorubicin] and dactinomycin) for 6 weeks before and for 70 weeks following local therapy with surgery or radiotherapy (in inoperable cases).Patients in whom only tumor biopsy or incomplete resection was performed, radiotherapy dose of 55 Gy was given to the tumor bed.

In summary, the poor prognosis of ES-PNETs, the variety in
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anatomical locations and the rarity of the tumour precludes any recommendation for optimal treatment but there is definitely a role of multimodality treatment as in cases of Osseous PNETs. Hence, in order to achieve cure managing these tumours require aggressive multimodality approach consisting of combination chemotherapy and radiotherapy over a prolonged period of time.

CASE HISTORY

A nineteen year old premenopausal nulliparous female with no significant past medical history presented with watery and foul smelling discharge per vaginum and dull aching lower abdomen pain for the past three months. Additionally she had complaints of tenesmus and difficulty in passing urine for the past two and half months. There was no history of any bleeding per vaginum. Menstrual history suggested an irregular pattern of cycles. Physical examination did not reveal any mass or hepatosplenomegaly or paraaortic lymphadenopathy. Local examination revealed an irregular non tender mass involving the cervix and the upper vagina projecting into the vaginal cavity. Per rectal examination revealed an extra luminal growth with moderate degree of luminal compromise.

Investigative work up with USG pelvis showed a well defined mixed echogenic mass, predominantly hypoechoic in nature situated posterior to the bladder with increased vascularity. [Figure-1]

Figure 1
Figure 1: Ultrasound of the pelvis showing a mixed echogenic mass, predominantly hypoechoic in nature situated posterior to the bladder. Mass shows increased vascularity.

CT scan showed a heterogeneously enhancing soft tissue mass of 94.9mm x 89.2 mm in the region of cervix extending into the vagina, left adnexal region, left pelvic wall and ischorectal fossa with loss of fat planes between the mass and rectum and involvement of anterior rectal wall and Peri rectal fat stranding. The enormity of the lesion precluded any definite diagnosis of the exact organ of origin. Nonetheless as the bulk of the lesion occupied the cervico vaginal region, an opinion of the lesion arising from the cervix was given by the reporting radiologist. [Figures-2, 3, 4]

Figure 2
Figure 2: Axial sections of the contrast enhanced CT scan of pelvis showing a heterogeneously enhancing soft tissue mass with extension to the left pelvic wall and ischorectal fossa with loss of fat planes between the mass and rectum and involvement of anterior rectal wall and Peri rectal fat stranding.

Figure 3
Figure 3: Coronal sections of the contrast enhanced CT scan of pelvis
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**Figure 4**
Figure 4: Sagittal section of the contrast enhanced CT scan of pelvis showing a heterogeneously enhancing soft tissue mass of 94.9mm x 89.2 mm in the region of cervix and vagina extending into the left adnexal region.

Bone Scan did not show any evidence of skeletal metastasis while bone marrow biopsy showed mild hypocellular uninvolved bone marrow. A Cervical biopsy was taken for confirmation of malignancy and the histopathology revealed proliferation of round tumour cells in solid sheets separated by fibrous septae. The tumour cells were small and uniform with rounded nuclei bearing small nucleoli. The surrounding cytoplasm was illdefined. [Figure-5A & 5B]

**Figure 5**
Figure 5a: Low power photomicrograph showing Nests and sheets of medium sized tumor cells with scant amount of cytoplasm (10X, Haematoxylin & Eosin)

The morphological findings were confirmed by Immunohistochemistry which showed a strong positivity for membrane antigen CD-99(Monoclonal, Mouse, Anti-human CD-99 Ewing's sarcoma marker, MIC-2 gene product, Clone: 12E7, Dako, Denmark) [Figure- 6] and was negative for cytokeratin (CK: Clone: AE1/AE3, Dako, Denmark), Carcinoembryonic antigen (CEA: Clone: II-7, Dako, Denmark,) and Desmin (Clone: D33, Dako, Denmark). Based on the morphological and immunohistochemical findings a final diagnosis of extra osseous primitive neuroectodermal tumour arising from the female genital tract was made.

**Figure 5b**
Figure 5b: High power photomicrograph showing proliferation of round tumour cells in solid sheets separated by fibrous septae. The Individual tumour cells are small and uniform with rounded vesicular nuclei bearing small nucleoli. The surrounding cytoplasm is scanty and illdefined. N/C ratio is high and there is brisk mitotic activity (45X, Haematoxylin & Eosin)

**Figure 6**
Figure 6: High power photomicrograph showing proliferation of round tumour cells in solid sheets separated by fibrous septae. The Individual tumour cells are small and uniform with rounded vesicular nuclei bearing small nucleoli. The surrounding cytoplasm is scanty and illdefined. N/C ratio is high and there is brisk mitotic activity (45X, Haematoxylin & Eosin)
Figure 7
Figure 6: The tumor cells show diffuse membranous positivity for CD-99 (MIC-2) counter stained by haemotoxylin.

The Patient has been planned for multimodality treatment consisting of combination chemotherapy sandwiched with radiotherapy based on high risk protocol for Ewings family of tumours. [13] Presently the patient is undergoing combination chemotherapy with Vincristine, Cyclophosphamide, and Adriamycin and will be planned for further consolidation chemotherapy after radiation therapy. She has completed six weeks of chemotherapy and has been started on Local treatment with radiotherapy to the pelvis from week fifteen by four field box technique with 6 MV X rays to a dose of 55.80 Gy in 31 fractions (50.40Gy/ 28 fractions to whole pelvis + boost to tumour alone 5.40 Gy / 3 fractions) over 6.5 weeks. Presently she has a subjective improvement in her symptoms and on examination the mass has markedly reduced in size.

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References
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