

Case Report:**Primary vaginal ewing's sarcoma/primitive neuroectodermal tumour :
diagnostic and treatment challenges****Pranabandhu Das,¹ K. Gunaseelan,² Debdatta Basu,³ Ramesh Ananthkrishnan,⁴ K.S Reddy²***Department of ¹Radiation Oncology, Sri Venkateswara Institute of Medical Sciences, Tirupati and Departments of ²Radiation Oncology, ³Pathology, ⁴Radiodiagnosis, JIPMER, Puducherry***ABSTRACT**

Extra osseous Ewing's sarcoma/primitive neuroectodermal tumour (PNET) of the genital tract of women is scarcely described in the literature and involvement of the vagina is even rarer with a very few cases reported so far. We present 50-year-old-woman who presented with a vaginal mass that was diagnosed to be a malignant round cell tumour which later was confirmed to be primary vaginal Ewing's sarcoma/PNET on light microscopy and immunohistochemical staining. She was then treated with induction chemotherapy followed by local radiotherapy and further maintenance chemotherapy. This rare case of primary vaginal Ewing's sarcoma/PNET emphasizes the need for combining morphological features with immunohistochemistry with a panel of antibodies in establishing the diagnosis of Ewing's sarcoma/PNET at an uncommon site. Further, the case also highlights the use of induction chemotherapy followed by radiation therapy and subsequent maintenance chemotherapy as a treatment modality.

Das P, Gunaseelan K, Basu D, Ananthkrishnan R, Reddy KS. A rare case of primary vaginal ewing's sarcoma/primitive neuroectodermal tumour : diagnostic and treatment challenges. J Clin Sci Res 2014;3:145-9. DOI: <http://dx.doi.org/10.15380/2277-5706.JCSR.13.033>.

INTRODUCTION

Primitive neuroectodermal tumour (PNET) and Ewing's sarcoma suggest a single group of bone and soft-tissue neoplasms in which typical undifferentiated Ewing's sarcoma and PNET with clear evidence of neuroectodermal differentiation morphologically represents both ends of the spectrum.¹ PNET of the female genital tract is very unusual, but has been reported to involve the ovary, uterine corpus, uterine cervix, and vulva.²⁻⁵ PNET and Ewing's sarcoma were considered as distinctive entities in the past. However some recent studies have shown that the small round-cell tumours seen in both tumour types share common phenotypic and molecular features supporting the likelihood of a common progenitorship. Hence the term Ewing sarcoma /PNET family of tumours is very often employed in the literature.¹ Ewing's sarcoma /

Received: 01 June, 2013.

PNET are now defined as a group of small round-cell sarcomas that show varying degrees of neuroectodermal differentiation. Ewing's sarcomas refer to those neoplasms that lack evidence of neuroectodermal differentiation when assessed by light microscopy, immunohistochemistry, and electron microscopy where as PNET tumours show neuroectodermal features when assessed by one or more of the above investigation modalities.^{2,3} This condition has rarely been described in the literature and Ewing's sarcoma/PNET of the vagina is even rarer.

CASE REPORT

We present the case of a 50-year-old post-menopausal lady with complaints of irregular vaginal bleeding for the last two years. She also had the history of difficulty in passing urine at initiation of micturition of two months duration. Clinical examination of vagina showed a hard,

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Online access

http://svimstpt.ap.nic.in/jcsr/apr-jun_14_files/3cr214.pdf
DOI: <http://dx.doi.org/10.15380/2277-5706.JCSR.13.033>



Figure 1: Contrast enhanced computed tomography of pelvis (axial view) showing large heterogenous mass lesion in anterior vaginal wall displacing urinary bladder anteriorly

smooth indurated mass lesion in anterior vaginal wall extending upto lower-third of the vagina. All fornices were free and the uterus and cervix appeared to be normal. Rectal mucosa and bilateral parametria appears free on digital rectal examination. Routine haemogram, renal and liver function tests were within normal limits. Chest radiograph revealed no abnormality and contrast-enhanced computed tomography (CECT) thorax revealed sub-centimeter sized nodule in subpleural location. Bilateral lung parenchyma, pleural spaces, heart, great vessels, bilateral bronchi were normal. CECT abdomen revealed both right and left kidneys with pressure changes and minimally dilated ureters, other organs and biliary tree were normal; no abdominal lymphadenopathy was evident. Pelvic CECT scan showed a moderately defined heterogeneously enhanced mass lesion measuring $7.0 \times 3.4 \times 6.3$ cm that involved anterior vaginal wall showing mass effect on urethra. Fat planes were not clearly maintained with urethra and bladder. Endometrial fluid collection and evidence of right fundal fibroid were evident. The mass was seen extending up to the introitus along anterior vaginal wall thereby the urinary bladder was pushed anteriorly towards the right side. Bilateral adnexae were normal with no ascites or lymphadenopathy (Figure 1). Punch biopsy of the vaginal mass was then performed

which showed multiple polypoidal bits of tissue lined by stratified squamous epithelium. Sub-epithelium showed dilated blood vessels with sheets of malignant round cells, often in a perivascular location (Figure 2A). No definite rosette formation was visible. These cells were seen to encroach right upto the epidermis however epidermotropism was not seen. Mitotic rate was high. Focal necrosis was seen. A diagnosis of malignant round cell tumour was made with the following differential diagnoses such as embryonal rhabdomyosarcoma, non-Hodgkin's lymphoma and PNET/Ewing's sarcoma. The cells showed intracytoplasmic periodic acid-schiff (PAS) positivity suggestive of presence of glycogen. Immunohistochemistry was done with a panel of antibodies, which revealed strong positivity for CD99 (Figure 2B) and vimentin and negativity for cytokeratin (Figure 2C), epithelial membrane antigen, desmin, leucocyte common antigen, chromogranin. S-100 protein and neuron specific enolase, suggestive of PNET / Ewing's sarcoma / PNET of anterior vaginal wall. Bone marrow trephine biopsy showed normocellular marrow with no evidence of tumour infiltration. She was subjected to 3 cycles combination chemotherapy with vincristine (1.5 mg/m^2), doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) given 3 weekly alternate with ifosfamide (1800 mg/m^2) with mesna and etoposide (100 mg/m^2) (VAC/IE). The induction phase was followed by local treatment with external beam radiotherapy (EBRT) to a total dose of 50 Gray in 25 fractions over a period of 5 weeks after which she was found to be clinico-radiologically free of the disease. Following this she received three cycles of maintenance chemotherapy using the above mentioned drugs. She is presently free of disease and asymptomatic at 24 months after diagnosis of disease. Details of earlier published cases on this subject are shown in Table 1.¹⁻¹⁰

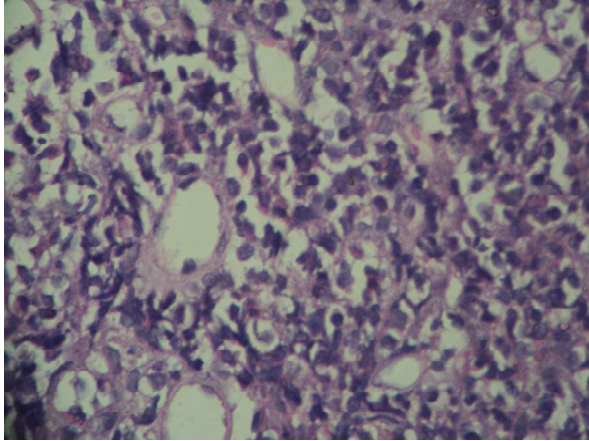


Figure 2A: Photomicrograph showing perivascular location of round tumour cells with hyperchromatic nuclei and scant cytoplasm (Haematoxylin and eosin, × 400)

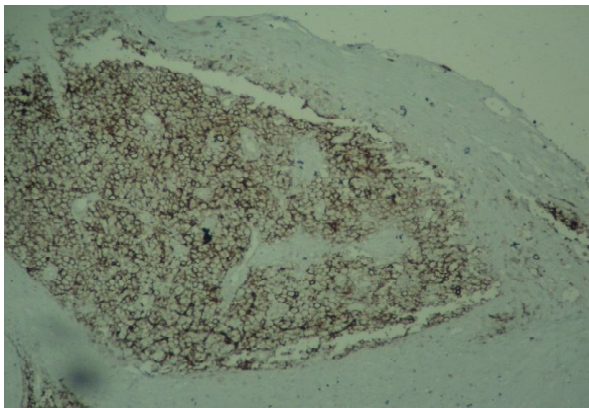


Figure 2B: microphotograph exhibiting strong cytoplasmic positivity of tumour cell for MIC 2 (CD99) on immunohistochemistry (× 200)

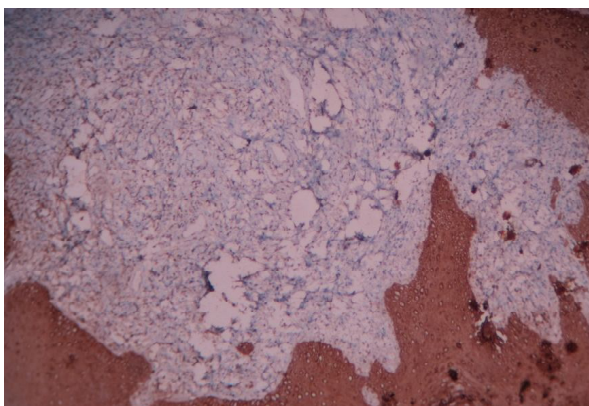


Figure 2C: Photomicrography exhibiting cytokeratin negativity in tumour cells on immunohistochemistry (× 200)

DISCUSSION

A *Medline* search using key word (tumour, primitive neuroectodermal, Ewing's sarcoma, vaginal neoplasm) revealed that only ten

cases¹⁻¹⁰ of PNET of vagina have previously been reported in English language in journals indexed in *Medline*.

Extrasosseous Ewing sarcomas can arise in the soft tissues of the chest wall, extremities, paravertebral and retroperitoneal regions, abdomen and pelvis, visceral organs, skin, head and neck,^{4,5} but infrequently occur in the female genital tract (Table 1). The diagnosis of Ewing's sarcoma Vs PNET is based on histologic, immunohistochemical and molecular cytogenetic features. Uniform small round cells with round nuclei containing fine chromatin, clear or scanty eosinophilic cytoplasm with glycogen content, and indistinct cytoplasmic membranes are common microscopic features of Ewing's sarcomas. In cases of PNET, the tumours comprise small to medium sized cells with moderate amounts of cytoplasm, variable glycogen content, and variable degrees of neuroectodermal differentiation.¹ Immunohistochemical markers currently employed in the diagnosis of Ewing's sarcoma /PNET family of tumours include MIC2 (also designated CD99), synaptophysin, S-100, neuron-specific enolase, vimentin, and HBA-71.^{1,6,7} CD99 is mainly expressed in the membranes of almost all Ewing's sarcoma /PNET tumours. MIC2 expression is a highly sensitive and reliable marker for the diagnosis of Ewing's sarcoma /PNET when used as part of a panel of immunohistochemical marker antibodies, in spite of the lack of complete specificity.^{1,8,9} The diagnosis in our patient was revised from undifferentiated malignant round cell tumour to Ewing's sarcoma/PNET based on the results of immunohistochemical staining. Management of Ewing's sarcoma/PNET of vagina remains controversial due to its rarity of presentation. On literature review¹⁻¹⁰ only one of ten reported cases of primary vaginal Ewing's sarcoma/

Table 1: 10 cases of primary vaginal Ewing's sarcoma/PNET reported earlier.

Study	Age	T-size (cm)	IHC profile	Treatment	Follow-up (Months)	Outcome
Liao et al ²	30	5	VIM+, MIC2+, FLI1+, synaptophysin+, NSE+, S-100+	TAH+BSO+CT	36	FOD
Farley et al ³	35	4	MIC2+	CT+EBRT+ICBT	48	FOD
Vang et al ⁴	35	3	VIM+, MIC2+	WE +CT+RT	19	FOD
Gaona-Luviano et al ⁵	34	4	MIC2+	WE + CT + RT + ICBT	20	FOD
Rekhi et al ⁶	17	10	VIM+, MIC2+	CT+EBRT	FU	
Al-Tamimi et al ⁷	47	ND	FLI1+, BCL2+	ND	ND	ND
Yip et al ¹	27	6	MIC2+	WE+RT	18	FOD
Pang et al ⁸	54	4	MIC2+	EBRT+, ICBT	18	DOD
Petkovic et al ⁹	45	9	MIC2+	CT+EBRT+ICBT	18	AWD
McCluggage et al ¹⁰	40	8	VIM+, MIC2+, FLI1-	ND	ND	

PNET = primitive neuroectodermal tumour; T-size = tumour size in largest dimension; IHC = immunohistochemistry; VIM = vimentin; + = positive; -, negative; WE Wide excision; CT = chemotherapy; EBRT = external beam radiotherapy; ICBT = intracavitary brachytherapy; TAH+BSO = total abdominal hysterectomy + bilateral salpingoophorectomy; MIC2 = Microneme protein 2; FLI1 = FOD = free of disease; AWD = alive with disease; DOD = died of disease; FU = follow-up; ND=not described

PNET presented with cranial metastasis 13 months after initial treatment of vaginal PNET, multiple modalities of treatment like surgery in the form of wide excision or hysterectomy with bilateral salpingo-oophorectomy, chemotherapy and local radiotherapy have been employed.¹⁻¹⁰ Out of ten documented cases so far,¹⁻¹⁰ three cases were offered chemotherapy and EBRT with intracavitary brachytherapy had favorable outcome whereas one case using both induction and maintenance chemotherapy with local radiotherapy reported good clinical response to treatment (Table 1). The 5-year disease-free survival is 24%-80% for localized disease³ with smaller resectable lesions i.e, the reported cases with vaginal location had a better prognosis than other relatively common sites of genital tract PNETs, namely, uterus, ovary, cervix and vulva.

This case is being reported for its rarity of presentation, emphasizing the utility of immunohistochemical staining in establishing the diagnosis of tumours at unusual sites. Further the case also highlights the utility of induction chemotherapy followed by radiation treatment and subsequent maintenance chemotherapy as a treatment modality.

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