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Case Report

PRIMITIVE NEUROECODERMAL TUMOUR OF CERVIX-A RARITY

***Mandal S., Pramanik S., Mondal S., Paul S., Joycerani D. and Banerjee S.**
Department of Obstetrics and Gynecology, I.P.G.M.E & R, Kolkata
**Author for Correspondence*

ABSTRACT
Primitive neuroectodermal tumor is not a very common tumor and pnet of cervix is extremely rare. Pnet commonly occur in children and young adult. Ewing's sarcoma and pnet represents a family of tumor showing varying degree of neuronal differentiation. Herein we present a case of pnet involve cervix uteri in a 16 years old women. This tumor shows characteristic histopathological features of pnet and on immuno histochemical staining the tumor cells express mic-2 and synaptophysin. Treatment plan of this stage 1b2 tumor is neoadjuvent chemotherapy with alternate cycle vac & i.e. followed by surgery.

Key Words: *Primitive Neuroectodermal Tumor, PNET, Immunohistochemistry, IHC*

INTRODUCTION
Primitive neuroectodermal tumors (pnets) are a group of high grade malignant invasive tumor histologically characterized by small round cells of primitive neuroectodermal origin. It was first described by Arthur Purdy scout in 1918 in relation to lunar nerve. Most common sites of origin are chest wall and par spinal region but may occur in other organ like brain, lung, and kidney. Female genital tract is a rare site and sporadically can involve uterus, vulva and also uterine cervix. Peripheral primitive neuroectodermal tumor (pnet) of the cervix is extremely rare and as per our knowledge, till now only twelve cases have been reported. There is no universal treatment protocol because of rareity of the tumor and different time period of diagnosis. Herein we present a case of primary cervical pnet to increase awareness about this tumor.

CASES
A 16 years old nulliparous Indian female presented to our outpatient department with irregular vaginal bleeding for 5 months with a histopathological report of small round cell tumour of cervix with extensive necrosis.

Our patient before presenting to our institution initially presented to a local regional facility with inters menstrual bleeding per vagina for two months. Upon examination by gynecologist she was taken for laparotomy with provisional diagnosis of cervical fibroid but following which only biopsy was taken from cervical lesion and a diagnosis of small round cell tumour with extensive necrosis was made and then this patient was referred to our hospital.

On admission she was normotensive with mild pallor. Abdominal examination revealed a 10 -12 weeks size of abdominopelvic mass. Other systemic examination was normal. Per speculum and bimanual examination under anesthesia revealed a 8x6 cm hard, friable, highly vascular mass arising from the cervix without any extension of the lesion into the vagina, parametria, and other adjacent organs including bladder and rectum. The size of the uterus was around the size of a 12 weeks pregnancy. Clinical staging was assigned as stage IB. A repeat cervical biopsy was taken and sent for histopathological and Immunohistochemistry confirmation.

Her haemoglobin was 10gm/dl with normal total and differential count. Blood sugar, renal and liver parameters were normal. Ultrasonography (USG) showed to have a SOL of homogenous echogenecity measuring 7.4x6.2cm involving uterine cervix. Pelvic MRI showed a fairly large heterogenous predominantly solid, altered signal intensity abdomino-pelvic space occupying lesion (SOL) measuring 13.8x12.3x9.6cm size with intense contrast enhancement and mass effect in the form of inferior displacement of bladder and superior displacement of body of uterus and compression over rectum with

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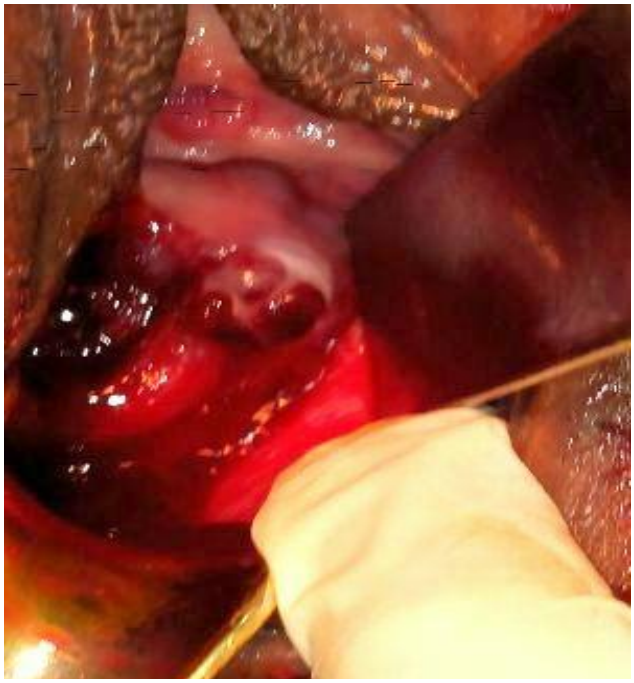

Figure 1: On speculum examination-highly vascular mass arising from the cervix

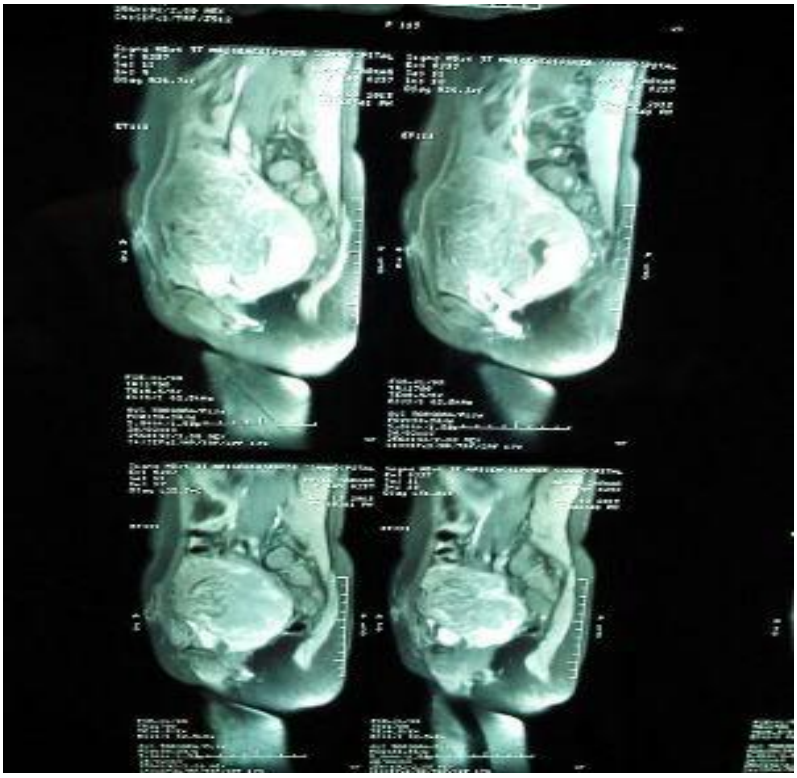

Figure 2: Pelvic MRI showing fairly large heterogenous predominantly solid altered signal intensity abdomino-pelvic space occupying lesion (SOL)

encasement of iliac vessels and with multiple enlarged lymph nodes in common iliac regions on both sides.

After discussion in our radiotherapy department regarding further treatment it was decided to treat our patient in the following manner: initially our patient would received neoadjuvent chemotherapy regimen consisting of vincristine 2g, adriamycin75mg/m^2, cyclophosphamide 1200mg/m^2 (VAC) followed three weeks after with ifosphamide 2g and etoposide 100mg/m^2. Patient was discharged after one week following first cycle of chemotherapy in favorable condition with all the blood reports within normal limit. Patient was in good general condition for one month following first therapy.

Pathologic Findings

Section shows a tumor composed of sheets and nests of round or oval cells with vesicular nuclei, inconspicuous nucleoli and scanty cytoplasm. The tumor exhibits brisk mitotic activity. The nest of the tumor cells are surrounded by fibrocollagenous septa.

IHC shows that the tumor cells express Mic-2 and synaptophysin (focal) and are immunonegative for Chromogranin A, Cytokeratin, EMA, Desmin, Myogenin, S-100 protein, TdT and LCA.

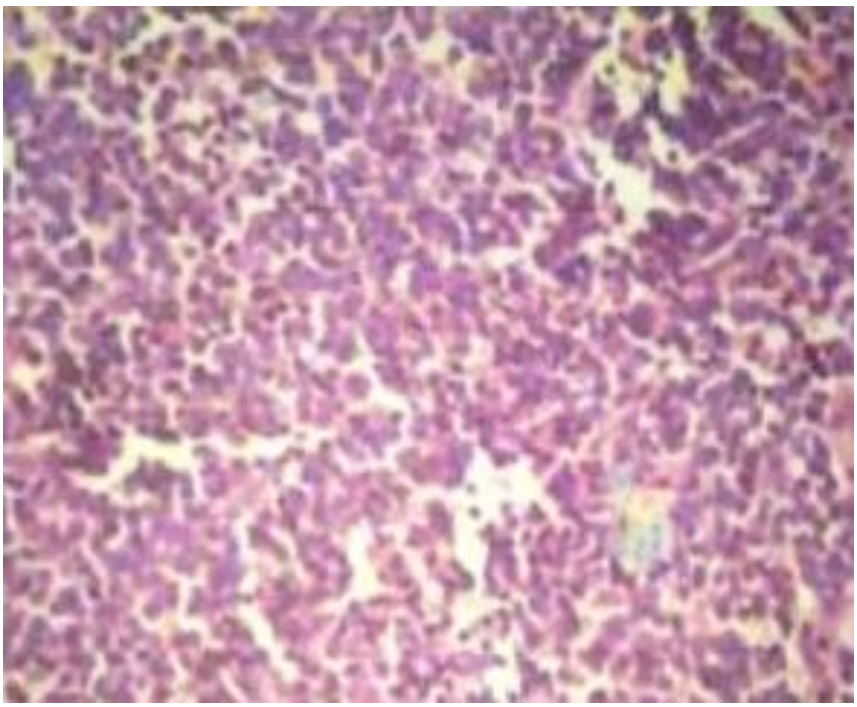

Figure 3: HPE Of cervical mass shows sheets and nests of round or oval cells with vesicular nuclei, inconspicuous nucleoli and scanty cytoplasm with brisk mitotic activity.

DISCUSSION

Primitive neuroectodermal tumor (PNET), a subgroup of small round cell tumor first described in 1918 in relation to lunar nerve. Ewings sarcoma and PNET represents a family of tumor showing varying degree of neuronal differentiation and consistent with Ewings sarcoma gene rearrangement (Delatree *et al.,* 1994). Uterine PNETS have been suspected to develop from the migration of embryonal cells of neural crest or neural tube from implanted neuroectodermal fetal tissue or from a mullerian origin (Fukunaga *et al.,* 1996)

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Table 1: Clinical presentation, management and outcome of women with primitive neuroectodermal tumour

Author year	Age	parity	Clinical presentation	Stage	Metastasis	Treatment	Follow-up
Russin 1987	60	2/2		IB2	Not mentioned	Internal and external RT f/b TAH+BSO+Staging laparotomy for residual tumour in end cervical curette f/b CT (VAC 6 cycles) for cul-de-sac deposits	Alive 16m after diagnosis
Sato 1996	44	4/2	Irregular vaginal bleeding and cervical growth	IB2	Nil on whole body X-ray and bone scan	TAH+LSO+pelvic lymph node dissection f/b unknown no. of courses of cisplatin, etoposide, adriamycin, cyclophosphamide. Second-look surgery after 6 months	Alive 6m after first operation
Horn 1997	26	3/2	Cervical growth	IB2	Not found after hysterec-tomy	TAH+BSO+pelvic lymphadenectomy f/b RT of the pelvis, 3 years later, pulmonary mets: CHT (5FU/cisplatin) + thorax RT	Died 4.2 yr after surgery
Cenacchi 1998	36		Irregular vaginal bleeding and cervical mass	IB2	Not found after whole body CT Scan	TAH	Alive , 18m after surgery
Pauwels 2000	45		Irregular vaginal bleeding and cervical mass	IB2	Not mentioned	TAH f/b pelvic RT	Alive 42m after surgery
Tsao 2001	24	3/2 gravid	Abnormal vaginal bleeding, urinary frequency and cervical mass		No bone or lymph node metastasis	Neoadjuvent CT(2 alt. cycles of VAC & IE), f/b TAH+transposition of the ovaries and para-aorticLN sampling, f/b 2 alt. cycles of VAC & IE, f/b pelvic RT.	Not reported

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Author / year	Age	Parity	Clinical presentation	Stage	Metastasis	Treatment	Follow-up
Malpica 2002	51		Same as before	IB2	Not mentioned	Same as before	Alive 18m after diagnosis
Snijders-Keilholz, 2005	21	Nulli-para	Intermenstrual vaginal bleeding and cervical mass		Nil at diagnosis	6 cycles DIME f/b hysterectomy f/b 5 cycles of VIA	Alive 27m after diagnosis
Goda, 2007	19	Nulli-para	Vaginal discharge, irregular vaginal bleeding and cervical mass		Nil	CT with VAC, planned for consolidation CT after RT	Alive
Farzaneh, 2011	45	multipara	Purulent vaginal discharge	IB2	Nil at the time of diagnosis	Neoadjuvent CT (alt. cycles of VAC & IE for 12 wks) f/b radical hysterectomy f/b adjuvant CT (same regime for 12wks)	Alive after 4yrs
Arora, 2013	23	1/1	Irregular vaginal bleeding, dysuria and cervical mass		Not mentioned	Neoadjuvent CT f/b Radical hysterectomy + BSO+ pelvic lymphadenectomy and postoperative RT	Alive 4 yr after diagnosis
Li, 2013	27		Vaginal bleeding with yellow vaginal discharge and lower abdominal pain	IIIB	Not mentioned	Partial RT f/b CT (alt cycles of VAC & IE)	Alive 6m after treatment
Present case 2013	16		Intermenstrual bleeding and cervical mass	IB2	Nil	Planned as adjuvant CT with alt. cycles of VAC and IE f/b surgery	Alive 1m after 1st cycle of CT

As far as we are aware only 12 cases have been reported till now. Though PNET is a rare tumor, it mainly occurs in trunk, limbs and retro peritoneum (Shimada *et al.*, 1988) and primary cervical PNETS are extremely rare. This tumor mostly occurs in adolescents and young adults but significant number of cases

was reported above 40 years of age (Weiss and Goldblum, 2004). Among the reported cases of cervical PNET (table1) the age of the patient varied from 12yrs to 72yrs (Tsao *et al.,* 2001). The age of our patient at the time of presentation is 16yrs. It seems that PNET of cervix is not limited to certain age group.

In most of the reported cases, initial clinical presentation was abnormal vaginal bleeding and cervical mass and same is for our case. The clinical presentation of our case was misinterpreted as due to cervical fibroid for which patient underwent laparotomy. Similar kind of misdiagnosis has been reported previously in two instances (Tsao *et al.,* 2001; Arora *et al.,* 2013)

Diagnosis of PNETs is problematic for both clinicians and pathologists. The exact histopathological diagnosis of these tumors by routine microscopy is not possible and immuno histochemical and cytogenetic studies are needed to differentiate it from other round cell tumors like lymphoblastic lymphoma, desmoplastic small cell tumor & embryonal alveolar rhabdomyosarcoma (Rosai, 2004)

PNETs stain for two or more of the following neural markers - neuron specific enolase, s-100 protein, Leu-7(HNK-1), synaptophysin, neurofilament protein, vimentin, CD99. Sometimes cytokeratin. actin, Desmin will also stain positively. Small cell neuroendocrine carcinoma is differentiated from PNETs by the lack of rosettes and more positive staining with cytokeratin. In our case the tumor cells expressed synaptophysin and MIC2 and was immunonegative for s-100 protein, Chromogranin-A, cytokeratin, EMA, TdT, LCA, cytokeratin, Desmin, Myogenin.

Due to extreme rarity of this tumour till now standard management protocol has not been formulated. However, being the same member of family of Ewings sarcoma, management protocol may be extrapolated to these tumors as they share similar cytogenetic and immnohistochemical characteristics.

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