

Case Report

Primitive Neuroectodermal Tumor of Cervix: Report of a Rare Case and Review of Literature

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Abstract: Background – Primitive neuroectodermal tumor / Ewing’s sarcoma (PNET/ES) of uterine cervix is extremely rare tumor and only 27 cases have so far been reported in the literature. We hereby present one case report diagnosed by histopathology and IHC and review of literature. Objective – A young girl aged 20 years was admitted. Her routine investigations and CT and MRI scan of chest, abdomen and pelvis were performed. Biopsy was taken from vaginal mass and histopathologist reported as round cell tumor. The slides were reviewed by another pathologist and found to be rhabdomyosarcoma. Thus immunohistopathology was done and a diagnosis of PNET/ES was established. Methods – The patient presented with complains of vaginal bleeding, generalized body ache, poor nutritional intake, found extensive loco regional disease with metastases to liver, lung and multiple bones, stage FIGO IV, performance score ECOG -4. Owing to her low general condition, we could not plan any anti-cancer treatment like chemotherapy or radiation therapy. She was discharged on symptomatic treatment. Results – Her biopsy and immunohistopathology turn out to be PNET/ES of uterine cervix. Conclusion - The rarity of this entity poses a challenge to pathologists and oncologists. The PNET/ES of uterine cervix can be potentially curable if presented at an early stage and found operable. IHC plays an important role in establishing this rare diagnosis.

Keywords: PNET, PNET Cervix Uteri, Immunohistochemistry, Peripheral, Neuroepithelioma, Uterine Cervix

1. Introduction

PNET of the cervix is an extremely rare entity and to the best of our knowledge, only 27 cases have been reported in the literature (Table 1 and 2). [1-23] The PNET/ES is an aggressive tumor primarily affecting children and adolescents between 10-20 years of age and commonly involving long

bones or deep soft tissues. Ewing’s sarcoma and PNET family of tumors were classified differently in the past, but now due to their common molecules of origin and clinical features they are considered as single tumor category known as Ewing’s family of tumors (EFTs). More than 90% of these tumors contain ES RNA binding protein – 1 (EWSR-1) – FLI 1 fusion protein due to t (11; 22) (q 24; q 12) chromosomal

translocation. These tumors are derived from primordial mesenchymal stem cells which originate from bone marrow. PNET have been classified according to WHO as central PNET (involving brain and spinal cord) or peripheral PNET (involving sympathetic nervous system, skeletal and soft tissues). The incidence of EFT is 1 per million and extra-osseous presentation is even rarer. [24] The most common site of PNET of the female genital tract is ovary, followed by uterine corpus. Cervix and vulva are extremely rare. [22] The diagnosis is made by histopathology and IHC plays an important role in confirming the diagnosis of Ewing's sarcoma by excluding other common type of sarcomas which occur in the cervix uteri. The treatment is challenging because of the absence of optimal therapeutic strategy.

Poor prognostic factors are the presence of metastases at presentation; site of metastases, (worst with bone marrow infiltration); systemic symptoms like fever and weight loss; tumor size more than 8 cm and tumor volume >200 cc.

2. Case Report

Nineteen year old unmarried girl presented with pain in abdominopelvic region and blood stained vaginal discharge for one month associated with generalized weakness and loss of appetite. Per abdominal examination revealed tender abdominopelvic mass. On gynecologic examination, the external genitalia were normal with no inguinal lymphadenopathy. On separation of labia, a soft tissue friable growth was seen occupying whole of vaginal lumen, the growth was found arising from anterior wall of vagina and uterine cervix could not be felt separately. Both parametria were found to be involved up to the lateral pelvic wall. Her routine hematological, serum hepatic and renal functions were normal. Ultrasonography of the abdomen and pelvis revealed a large hypo echoic mass measuring 10.8 X 9.1 cm. in region of the uterine cervix, along with mild hydronephrotic changes seen in right kidney. MRI of abdomen and pelvis (Figure 1) exhibited 11.3 X 8 X 7.5 cm. sized heterogeneously appearing lesion on T1 and T2 images infiltrating anterior cervix pushing urinary bladder anteriorly and rectum posteriorly with intervening fat planes. Multiple solid and necrotic areas were seen within the mass lesion. Both ovaries were normal. Liver was 17 cm in size and showed multiple varying sized (largest 21x15 mm) cystic lesions in its entire parenchyma suggestive of cystic metastasis. Visualized left thorax showed 10x8 mm sized multiple pleural deposits in posterior inferior costal pleura. Right kidney showed mild dilatation of entire visualized right ureter. Multiple varying sized metastasis seen in vertebra, bilateral pelvic bones and visualized bilateral femurs. Punch biopsy was taken from the vaginal mass. Microscopy showed a cellular tumor composed of sheets of round to oval cells with prominent necrosis. The tumor cells have fine nuclear chromatin, nucleoli and scant cytoplasm. The histopathology slides were reviewed by another pathologist and he suggested a diagnosis of rhabdomyosarcoma (Figures 2, 3). On immunohistochemistry,

the tumor cells expressed Mic-2 (Figure 4). There is focal expression of NKX 2.2 (Figure 5) and weak expression of EMA (Figure 6). The tumor does not express Cytokeratin, Desmin, Myogenin, Myo D1, Synaptophysin, LCA, CD 43, CD 30, SOX-10, Calretinin and Inhibin. Thus the diagnosis arrived is primitive neuroectodermal tumor of cervix. Her ECOG score was 4, nutritional intake was poor, owing to her low general condition and widely disseminated disease, we could not plan for any chemotherapy or radiotherapy.

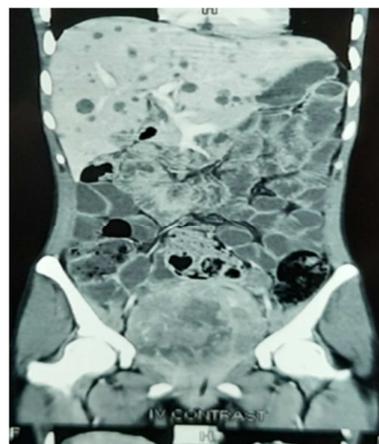
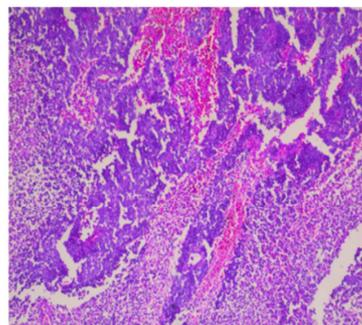
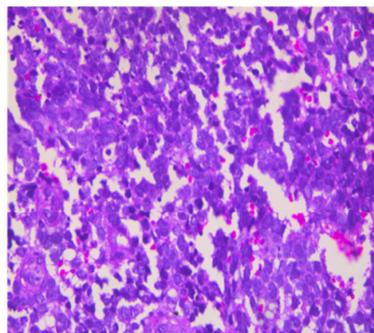


Figure 1. MRI Scan; Coronal section shows pelvic mass with multiple cystic hepatic metastases.



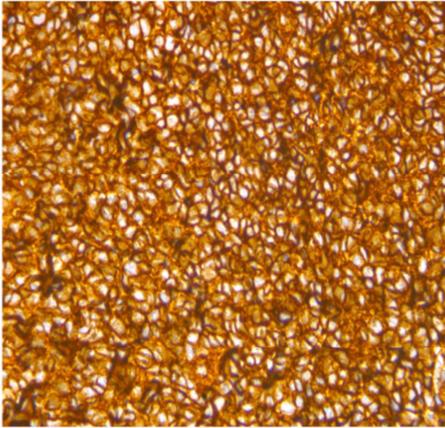
HE 10X

Figure 2. H & E Stain 10X showing cellular tumor composed of sheets of round to oval cells.



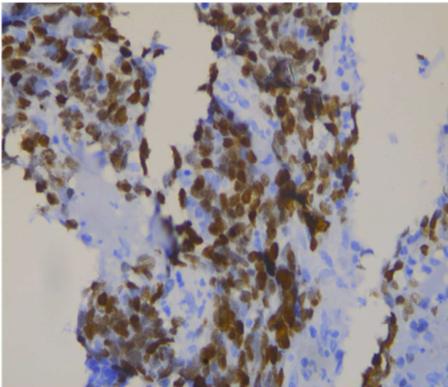
HE 40X

Figure 3. H & E Stain 40X showing a cellular tumor composed of sheets of round to oval cells.



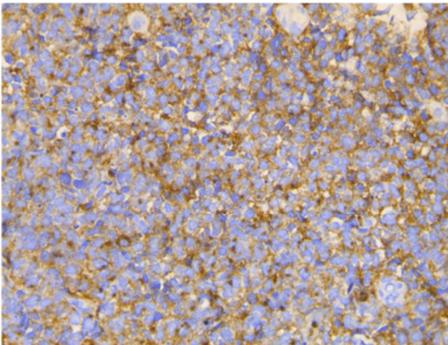
IHC MIC2 40X

Figure 4. IHC tumor cells express MIC2 40X.



IHC NKX2.2 40X

Figure 5. Tumor cells shows focal expression of NKX2.2 40X.



IHC EMA 40X

Figure 6. Tumor cells shows weak expression of EMA 40X.

3. Discussion

The ES/PNET was first described by James in the year 1921.[25] The extra skeletal ES/PNET usually occurs in the soft tissue of lower extremities, paravertebral tissue, chest wall (askin tumor), retro peritoneum, skin, visceral organs,

head and neck. The age at presentation ranges between 14-59years with the mean age being 35 years (Table 1 and 2). The most common symptoms are irregular vaginal discharge/bleeding, dysuria and lower abdominal pain. The most common physical findings are nodular lesion of uterine cervix extending into the anterior vaginal wall and enlarged uterus. The diagnosis of EFTs is difficult by routine microscopy since they have small blue cell morphology. EFTs has two different spectrums – undifferentiated ES at one end and features of neuroectodermal differentiation by PNET at the other end of the spectrum. The differential diagnosis includes a wide variety of rare malignancies which can be remembered by mnemonic “LEMON” (lymphoblastic lymphoma, ES, medulloblastoma, oat cell carcinoma / small cell neuroendocrine tumor, and neuroblastoma); other soft tissue sarcomas like liposarcoma, leiomyosarcoma, alveolar soft-part sarcoma, rhabdomyosarcoma, undifferentiated endocervical sarcoma, osteosarcoma; malignant melanoma; malignant peripheral nerve sheath tumor and metastatic tumors. ESMO and NCCN guidelines recommend treating these tumors like uterine sarcomas. [26]

The best outcome was noted in patients who underwent trimodality therapy with surgery, chemotherapy and radiotherapy. Ideally the patient should undergo Wertheim hysterectomy if feasible. The palliative radiation therapy is used for inoperable tumor or adjuvant radiation therapy in post-operative case or with positive resection margins to prevent local recurrence. The disease is supposed to be systemic or disseminated therefore systemic chemotherapy plays an important role in preventing metastases and prolonging survival. Although abundant newer drugs, targeted therapy and immunotherapy have been tested in the past 15 years, the irinotecan based cytotoxic chemotherapy has shown promising response. [27] The commonly used chemotherapeutic agents are cisplatin, vincristine, doxorubicin, ifosfamide, cyclophosphamide, actinomycin-D, gemcitabine, irinotecan and etoposide. The common chemotherapeutic regimens are VIDE and VAC/IE alternatively every 3 weekly for 17 cycles. Targeted therapy viz: Temozolamide, Nab-Rapamycin [28], ganitumab, regorafenib, pazopanib, cabozantinib, apatinib are under trial and results are anticipated as a single agent or in combination with chemotherapeutic regimens. Thalidomide is found to be a potent antiangiogenic agent and immunomodulator which inhibits PNET growth. [29] Similar to skeletal ES, the most unfavorable prognostic factors are inadequate surgical resection, large tumor size, poor response to chemotherapy and presence of distant metastases; stage IV disease being universal fatal. [18]

The FIGO stages encountered in the 28 cases reviewed are; Stage I in 11, stage II in 5, stage III in 3, stage IV in 5 patients, whereas staging status was not known in 4 patients. Sixteen patients underwent TAH +BSO+ lymph node dissection, only TAH BSO was done in 2, TAH was done in 3 patients, local excision was done in 2, four were found to be inoperable where as in 1 patients status of surgery was not known. One patient underwent ovariopexy (transposition of ovaries) [5].

Associated pregnancy was reported in 3 patients [14, 16 and 23]. In one patient only biopsy report is available, no other clinical or treatment records found. [17] In this review series, three or less than 3 cycles of chemotherapy was given in 8 patients, 4 or more than 4 cycles were administered in 12, in 7 patients chemotherapy was not given where as in 1 patient status of chemotherapy administration is not known. Adjuvant post-operative radiation therapy was given in 14 patients only. Out of 28 patients including one of the present studies 20 were

NED on follow-up, 1 was alive with disease, 6 died and status of follow is not known in 1 patient.

Fertility is an important but often ignored issue. Many strategies have been undertaken to minimize or counter the gonadotoxic effects of cancer treatment especially with chemotherapy and radiotherapy. Sperm cryopreservation, embryo cryopreservation of mature and immature oocytes is a viable option. Cryopreservation of ovarian tissue or ovariopexy is another alternative.

Table 1. Reported cases of cervical Ewing sarcomas with clinical data, treatment and outcome.

Patient No.	Author (Year)	Age (Year)	Stage	Surgery
1	sato et al 1996	44	IB2	TAH+BSO+LND
2	Horn et al 1997	26	IB1	TAH+BSO+LND
3	Cenacchi et al 1998	36	IB2	TAH without BSO
4	Pauwels et al 2000	45	IB2	TAH
5	Tsao et al 2001	24	N/A	TAH+transposition of the ovaries+LND
6	Malpica et al 2002	35	IB1	TAH+BSO+LND
7	Malpica et al 2002	35	IB2	TAH+BSO+LND
8	Snijders-Keilholz et al 2005	21	IB2	TAH
9	Goda et al 2006	19	IVA	NO
10	Farzaneh et al 2011	45	IB2	Radical Hysterectomy
11	Arora et al 2012	23	N/A	TAH+BSO+LND
12	Masoura et al 2012	23	IV	TAH+BSO
13	Benbrahim et al 2012	25	IIB	Cervical Conization
14	Li et al 2013	27	IIIB	NO
15	Khosla et al, 2014	28	IB2	MTP +TAH+BSO+LND
16	Xiao et al 2014	52	IIA	TAH+BSO+LND
17	Xiao et al 2014	59	IVB	TAH+BSO+LND
18	Al-Nueimy 2014	27	IB	CS for obstructed labor, Wertheim's Hysterectomy
19	Weissferdt A 2015	35	Details not available	-
20	Mashriqi et al 2015	49	IIB	TAH+BSO
21	Bilek O et al 2015	57	IV	NO
22	Ahmed I et al 2017	48	IIIB	Local Excision
23	Hu X et al 2017	39	Details not known	TAH+BSO+LND
24	Hu X et al 2017	14	IIIC2	TAH+USO+LND
25	Wang X 2017	48	IIB	TAH+BSO+LND
26	Wang X 2017	43	IIB	TAH+BSO+LND
27	Kyriazoglou A et al 2019	38	IB2	MTP + TAH+BSO+LND
28	Present case 2020	19	IVB	NO

Table 2. Reported cases of cervical Ewing sarcomas with clinical data, treatment and outcome.

Patient No.	RT	Chemotherapy	No. of cycles	Follow Up (Months)
1	YES	Cisplatin, VP-16, Doxorubicin, Cyclophosphamide	not known	Alive with disease 6 months
2	YES	Cisplatin and 5FU	6	Died 50 months
3	NO	NO	-	Alive 18 months
4	YES	NO	-	Alive 42 months
5	YES	VAC + IE	2	Alive 24 months
6	NO	NO	-	Alive 5 months
7	NO	NO	-	Alive 18 months
8	NO	DIME X 6 + VIA X 5	6+5	Alive 27 months
9	YES	VAC	6	Alive, on treatment
10	NO	VAC + IE	2	Alive 48 months
11	YES	VAC X 1 + VP-16+cisplatin X 2	3	Alive 48 months
12	NO	Cisplatin	1	Died 12 days
13	Tele +brachytherapy	CHOP X 1 + AC X 4	5	NED 96 months
14	YES	VAC with IE	1	Alive 6 months
15	NO	VAC	6	Alive 33 months
16	NO	PVB 2 cycles	2	Died 9 months
17	NO	NO	-	Died
18	NO	No	-	NED, FU not reported
19	-	-	-	-
20	YES	VAC with IE	4	Died 10 months
21	YES	VIDE with VIA	6	Alive 18 months
22	YES	VAC with IE	6	NED 2 months

Patient No.	RT	Chemotherapy	No. of cycles	Follow Up (Months)
23	NO	Ifos+ CDDP+Doxo	6	NED 60months
24	NO	Ifos + Epirubicin	4	NED 6 months.
25	Brachy+Tele	Pirarubicin +CDDP+Ifos	6	NED 27 months
26	Brachy	Pirarubicin +CDDP+Ifos	2	NED 12 months
27	YES	VIDE	6	Alive 42 months
28	NO	NO	-	died

TAH- total abdominal hysterectomy; BSO- bilateral salpingo oophorectomy; USO - unilateral salpingo oophorectomy; LND - pelvic lymphadenectomy; RT- radiation therapy; DIME- Doxorubicin, Ifosfamide, Mesna, Etoposide; VIDE- Vincristine, Ifosfamide, Doxorubicin, Etoposide; IE- Ifosfamide, Etoposide; PVB- Cisplatin, Vincristine, Bleomycin; VAC - Vincristine, Dactinomycin, Cyclophosphamide; CHOP – Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone; VIA– Vincristine, Ifosfamide, Dactinomycin; VP16 - Etoposide; 5-FU - 5-fluorouracil; CDDP –Cisplatin; N/A - not applicable. NO – chemotherapy not given, CS – Caesarian section.

4. Conclusion

PNET/ES with multiple disseminated metastases has a dismal prognosis and no significant advantages have been made to these patients to improve outcome in last four decades. Hence early diagnosis and initiation of treatment helps improve survival / relapse/ recurrence rates. Integrating conventional therapy with novel therapeutic agents holds a promise for high risk patients with ES. Poor prognosis is partially due to insufficiently chemotherapeutic doses and prolonged dose intervals. No potential biomarker has been identified so far to predict therapeutic efficacy of treatment. These cases are reported for its rarity of presentation, emphasizing the utility of IHC staining in establishing the diagnosis of tumors of unusual sites. Overall the PNET of cervix is a rare finding and requires early detection, correct diagnosis and multimodality therapy including total excision, adjuvant chemotherapy and/or radiation therapy. Once the diagnosis is made, referral to a tertiary care center with dedicated multispecialty tumor board and special expertise in sarcoma management is recommended.

Conflict of Interest

The authors declare that they have no competing interests.

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