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Case Report

Pathology Section

Primitive Neuroectodermal Tumour of Uterine Cervix: A Rare Case Report and Review of Literature

PALLAVI SRIVASTAVA[1], SAUMYA SHUKLA[2], NUZHAT HUSAIN[3]

ABSTRACT

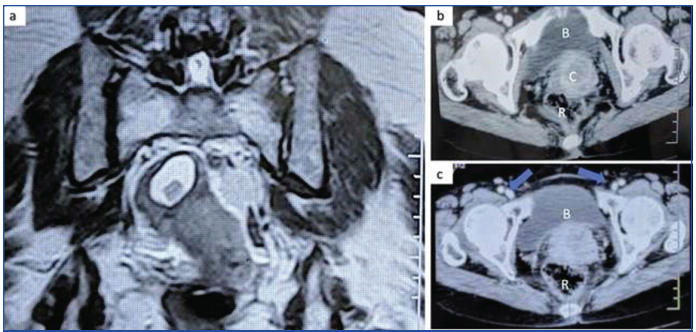
Primitive Neuroectodermal Tumour (PNET) of the uterine cervix is a rare entity. Till date, less than 25 cases have been reported from 1987-2021. Histopathologically, tumour is composed of small round blue cells, developing from neuroectodermal cells. Awareness of this rare entity is important from clinical, radiological and pathological aspect for prompt management. A 67-year-old female presented with abnormal vaginal bleeding and lower abdominal pain since two months. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) of the abdomen revealed the presence of a large mass measuring 71×63×47 mm in size along with, enlarged inguinal lymph nodes. Pathological examination of the tumour revealed a small round cell neoplasm, immunohistochemically positive for CD99 (Cluster of Differentiation) and Friend Leukaemia Intergration-1 (FLI-1). Diagnosis of PNET uterine cervix was rendered. Molecular testing for (Ewing Sarcoma breakpoint region 1) EWS/FLI-1 fusion transcripts could not be performed. Despite administration of the first cycle of adjuvant chemotherapy, the patient died from disease due to pulmonary metastasis. Due to unusual site and small round cell morphology, this entity may present as a diagnostic challenge to the pathologist.

Keywords: Inguinal lymph nodes, Metastasis, Neuroectodermal cells, Small round blue cell tumour, Uterine neoplasm

CASE REPORT

A 67-year-old postmenopausal woman presented in the oncology clinic with the chief complaints of lower abdomen pain along with vaginal bleeding for two months. Pain was dull aching and intermittent in nature. There was no significant past medical history, associated co-morbidity or family history. General physical examination and abdominal examination was unremarkable.

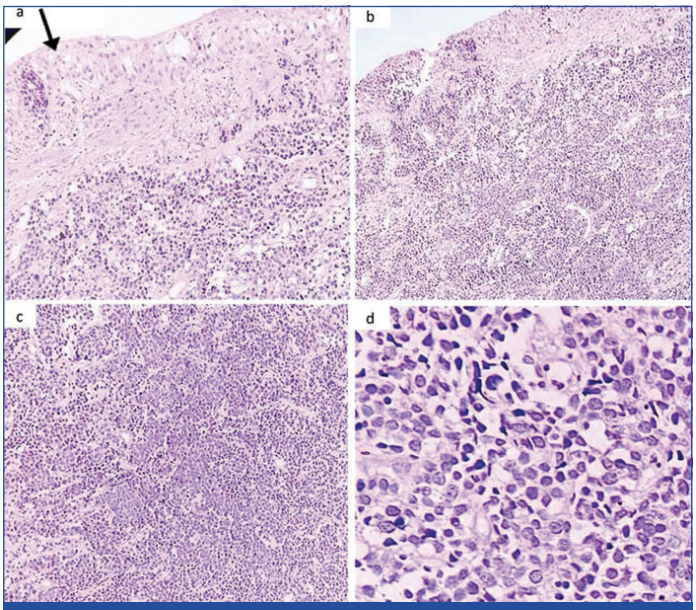
Per speculum examination revealed a friable mass seen arising from the cervix involving the anterior wall of vagina. Proctoscopic examination of the rectum revealed that the cervical mass was pushing the anterior wall, but the rectal mucosa appeared normal. Imaging including CT and MRI whole abdomen was performed which revealed bulky cervix with heterogenous irregular lesion measuring 71×63×47 mm in size extending into bilateral parametrium (Left>Right). Extension into pelvic wall was not seen. Anteriorly, the mass was seen abutting the posterior wall of urinary bladder, superiorly involving the lower half of uterus with collection in endometrial cavity and inferiorly infiltrating the proximal 1/3rd of vagina [Table/Fig-1 a-c].



[Table/Fig-1]: Imaging findings: Magnetic resonance imaging (a) and Computerised tomography axial view (b) showing mass in uterine cervix abutting the urinary bladder (B: bladder, C:cervix, R: rectum) with bilateral inguinal lymphadenopathy (c) marked by blue arrows.

Multiple bilateral inguinal lymph nodes measuring 30×24 mm in size were noted. The levels of tumour markers, including Carbohydrate Antigen (CA)-125, CA19-9, A-Fetoprotein (AFP), and β-Human Chorionic Gonadotrophin (β-HCG) were within the normal range.

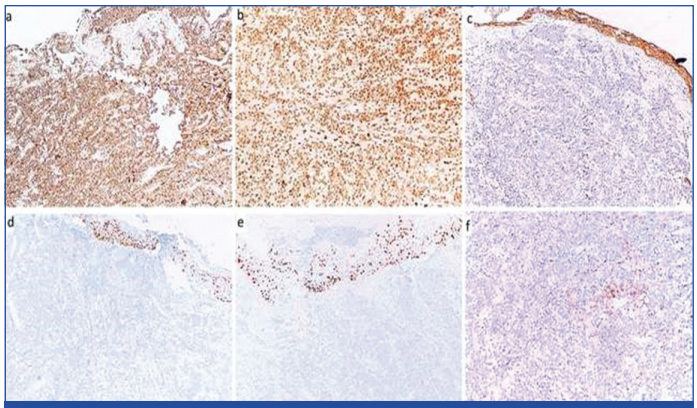
Biopsy was performed from the lesion measuring 2×2 cm in size and sent for histopathological evaluation. Histopathological evaluation revealed fragmented tissue bits lined by stratified squamous epithelium exhibiting focal full thickness dysplasia. The subepithelial tissue was infiltrated by tumour disposed in sheets and nests. Individual tumour cells appeared round to oval with scant to moderate amount of cytoplasm, high nucleo-cytoplasmic ratio, fine granular chromatin and inconspicuous nucleoli [Table/Fig-2a-d]. Brisk mitosis and areas of necrosis were also noted.



[Table/Fig-2]: Histopathology findings: Photomicropgraphs show partly ulcerated (arrow) dysplastic stratified squamous epithelium (a) Subepithelium showing tumour disposed in sheets of small round blue cells (100x) (b-d){Haematoxylin and eosin stain X40 (a-c), X400 (d)}.

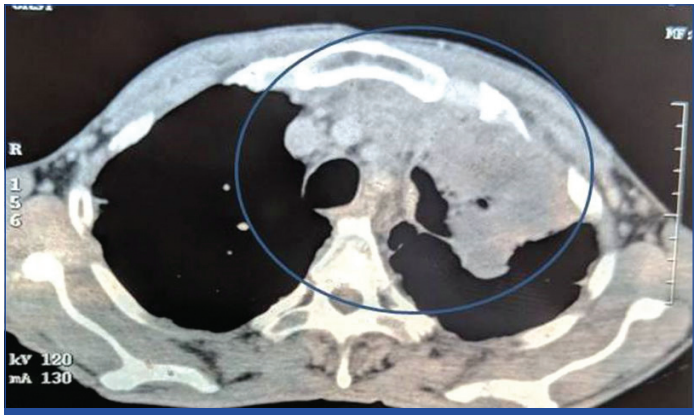
Immunohistochemistry (IHC) evaluation revealed CD99 (MIC2) strong positive [Table/Fig-3a], FLI-1 [Table/Fig-3b], Cytokeratin (CK) highlighting the dysplastic epithelium along with p63 and p40 [Table/Fig-3c-f], negative expression for synaptophysin, Chromogranin-A (CgA), CD56, S100, Melan-A, Leukocyte Common Antigen (LCA). Fluorescence In Situ Hybridization (FISH) for reciprocal translocation

t(11;22) (q24;12) could not be tested due to cost constraints, hence, a final diagnosis of PNET of the cervix (International Federation of Gynaecology and Obstetrics (FIGO) stage IIIB) [1] was rendered based on clinicoradiological correlation. The patient was planned for neoadjuvant chemotherapy comprising of Vincristine, Adriamycin, Cyclophosphamide (VAC) for three every 21 days followed by response assessment by Positron Emission-CT (PECT).



[Table/Fig-3]: Immunohistochemical findings: Tumour showing diffuse expression for CD99 (a) and FLI-1(b), Pan CK, p63, p40 highlighting the dysplastic epithelium (c-e), LCA highlighting scant stromal inflammatory cells.(f) {DAB X40 (a-f)}.

Patient presented with severe chest pain since two days, which was one month after the primary diagnosis. CT scan thorax was performed which revealed multiple mass lesions in apical and anterior segment of left upper lung lingual and anterior mediastinum largest measuring 56.5×55.8 mm in size [Table/Fig-4] suggestive of metastasis, however, patient had no evidence of metastasis at the time of primary presentation. Patient was started on VAC,



[Table/Fig-4]: Computerised tomography scan thorax showing multiple mass lesions in apical and anterior segment of left upper lung lingual and anterior mediastinum.

unfortunately patient died of disease after single dose with a survival of a month postdiagnosis.

DISCUSSION

The PNET of cervix is rare and aggressive malignancy, first described by Russin VL et al., with characteristic signature gene involving the EWS gene (EWSR1, Ewing sarcoma breakpoint region 1) at 22q12.2 and various Erythroblastic Transformation Specific (ETS)-family transcription factor genes, the most common of which is FLI-1 at chromosome 11q24, translocation (11;22) (q24;12) known as EWS-FLI-1 reported in 85-90% of cases [2]. These group of Ewing's Family Tumour (EFT) arise from mesenchymal progenitor cells, PNET showing neuronal differentiation distributed in central and peripheral location with most common involvement of skeleton, soft tissue and sympathetic nervous system [3]. PNET is also reported in female genital tract with ovaries and uterine corpus most commonly involved, cervix being a rare site of involvement, to best of our knowledge, less than 25 cases have been reported in English literature with only three case reports of PNET cervix in India [4-6]. Comparison of present case with contrast studies is summarised in [Table/Fig-5] [4-15].

PNET of uterine cervix is aggressive neoplasm, with ovaries being most common site of involvement in female genital tract followed by uterine corpus, cervix, vulva and vagina [9]. PNET uterine cervix presents with vague symptoms of vaginal bleeding, few with intermenstrual bleeding, lower abdominal pain, urinary frequency and dysuria with age range varying from 23-67 years. Two cases presented with pregnancy and one among them presented with obstructed labour. Association of origin of PNET cervix from pregnancy have been speculated, as one of the theories suggest that PNET may arise from implanted foetal tissue or displaced neural crest cells. However, due to sporadic cases presenting with pregnancy have been reported, hence, the theory of histogenesis and aetio-pathogenesis is not established [4,10]. Xiao C et al., have suggested a correlation of disease activity with increased levels of CA-125 and PNET of female genital tract [9].

Clinical and radiologically PNET cervix presents with non specific symptoms and signs, hence, histopathology along with IHC is the mainstay of diagnosis, however, due to small round cell morphology various differential diagnosis need to be ruled out including, non hodgkin lymphoma, neuroendocrine carcinoma, small cell malignant melanoma, neuroblastoma and rhabdomyosarcoma as histopathologically tumour cells are disposed in sheet with hyperchromatic, salt and pepper chromatin with nuclear moulding along with crush artefact. Panel of IHC markers are devised to rule out the differential which may include CD99, Non Specific Esterase (NSE), synaptophysin, chromogranin, LCA, Terminal

Clinical case	Age (years)	Place	FIGO stage	Symptoms	Diagnosis	IHC	Treatment	Distant metastasis/ recurrence	Follow-up
Khosla D et al., 2014 [4]	28	India	IB2	Pregnancy+vaginal bleeding and pelvic pain	HP+IHC	Vimentin, CD99	TAH+BSO and adjuvant CT	NED	33 months
Ahmed I et al., 2017 [5]	48	India	IIIB2	Vaginal discharge and lower abdominal pain	HP+IHC	CD99, synaptophysin	Neoadjuvant CT followed by RT and adjuvant CT	NA	NA
Gupta V et al., 2020 [6]	20	India	IB2	Vaginal bleeding, discharge	HP+IHC	CD99, FLI-1	Neoadjuvant CT	NED	44 months
Masoura S et al., 2012 [7]	23	Greece	IVB	Vaginal bleeding and abdominal pain	HP+IHC+RT-PCR	CD99, vimentin, c-kit	TAH+BSO, one cycle of cisplatin	Metastasis evident site not mentioned	DOD, 12 days after post surgery
Li B et al., 2013 [8]	27	China	IIIB	Vaginal bleeding and abdominal pain	HP+IHC	CD99, NSE, vimentin	RT followed by adjuvant CT	NED	6 months
Xiao C et al., 2014 [9]	52	China	IIA	Vaginal bleeding	HP+IHC	CD99	TAH +BSO cytoreductive surgery	Pelvic recurrence	DOD at 9 months
	59		IVB	Vaginal bleeding	HP+IHC	CD99, Synaptophysin, NSE	TAH+BSO partial small intestinal excision	Disseminated tumour in abdominopelvic cavity	DOD at 15 months

Al Nueimy WT and Mahmood SM 2014 [10]	26	Jordan	IB1	Obstructed labour	HP+IHC	CD99, NSE	TAH+BSO followed by adjuvant RT	NA	NA
Mashriqi N et al., 2015 [11]	49	USA	IIB	Vaginal bleeding	HP+IHC	NSE, CD56, synaptophysin	RT with concurrent CT followed by TAH+BSO and adjuvant CT	Metastases to lumbar spine, pelvis, bladder	DOD at 10 months
Benbrahim Z et al., 2015 [12]	25	Morocco	IIB	Vaginal bleeding	HP+IHC	Vimentin, CD99, synaptophysin, NSE	Neoadjuvant CT followed by conization and adjuvant brachytherapy	NED	8 years
Bilek O et al., 2015 [13]	57	Russia	IIB	NA	HP+IHC+RT-PCR for Ewing sarcoma breakpoint region 1-ETS related gene fusion gene	CD99	Intensive CT+ concomitant RT	Pulmonary metastasis	18 months
Wang X et al., 2017 [14]	48	China	IIb	Uterine bleeding	HP+IHC	Vimentin, CD99	Induction CT and internal radiation followed by radical hysterectomy+BSO	NED	27 months
	43		IIb	Urinary frequency	HP+IHC	CD99	Induction CT and internal radiation followed by radical hysterectomy+BSO	NED	12 months
Feng X et al., 2021 [15]	19	China	Ib1	Pregnancy with vaginal bleeding	H+IHC	CD99	TAH+BSO	NED	36 months
Present case	67	India	IIIB	Lower abdominal pain, vaginal bleeding	HP+IHC	CD99, FLI-1	Induction CT	Pulmonary metastasis	DOD within 1 month

[Table/Fig-5]: Review PNET cervix cases reported from 2012-21.
HP: Histopathology; IHC: Immunohistochemistry; TAH: Total abdominal hysterectomy; BSO: Bilateral salphingoophrectomy; NED: No evidence of disease; NA: Not available; DOD: Died of disease; CT: Chemotherapy; RT: Radiotherapy; CD: Cluster of differentiation; FLI: Friend leukaemia integration; NSE: Non specific esterase; RT-PCR: Reverse transcriptase polymerase chain reaction; Case of PNET cervix not published in 2016, 2018 and 2019

deoxynucleotidyl transferase (Tdt), Human Melanoma Black (HMB), melan-A, vimentin, desmin and Tdt to rule out small cell carcinoma lung. PNET shows positive membranous expression for CD99 (MIC2) in >97% of cases and bright nuclear expression of FLI-1 which is the target of a characteristic balanced chromosomal translocation t(11;22) (q24:q12) which results in the production of the EWS/FLI-1 fusion gene seen in 85-90% of cases as seen in index case, however CD99 and FLI-1 may be positive in lymphoblastic lymphoma hence additional markers including Tdt, Cd20, CD3 may be utilised to further rule out lymphoma. EWS-FLI-1 fusion can be detected by molecular cytogenetics (reverse transcription-Polymerase Chain Reaction (PCR)) and FISH which are costly methods, may not be applicable in every case of PNET in Indian scenario, however, two cases utilised RT-PCR and FISH for further confirmation of diagnosis, however, FLI-1 was not being used in any of the cases reported so far of PNET uterine cervix [7,16,17].

Standard management protocol has not being devised due to only sporadic case reports, various treatment options have been summarised in table which includes surgical resection along with radiotherapy and adjuvant chemotherapy which is based on trial with bone PNET [18]. Neoadjuvant chemotherapy was also being given in six cases which included VAC alternating with ifosfamide, etoposide (IE) showing favourable result, in the present case regimen was followed but unfortunately patient died after 1 cycle of chemotherapy. Ten patients received radiotherapy with one case radiotherapy was given by VMAT or incorporated PET registration which was utilised to maximise sparing of adjacent organ damage, hence the diagnosis of PNET cervix should be cautiously made only after ruling out possibility of bone lesion and thorough radiological investigation should be performed to rule out any metastatic disease as treatment options may vary considerably [12].

Distant metastasis has been reported as poor prognostic indicator of PNET cervix with Horn LC et al., reporting lung metastasis three years postdiagnosis [19], similar to the present case and Masoura S et al., reported multiorgan failure and cardiac arrest due to metastatic disease, however, site of metastatic involvement was not mentioned [7], while Xiao C et al., reported two cases presented with pelvic recurrence and disseminated tumour in abdominopelvic cavity and died due to widespread disease [9]. PNET cervix shows good response to the current therapeutic options, however, recurrence or metastatic disease proved to be fatal in all the cases reported till date, hence, in the era of molecular classification of sarcoma, IHC and genetic testing should ideally be performed to confirm the histopathological findings for early intervention to prevent local recurrence or metastatic disease.

CONCLUSION(S)

To conclude, this is an additional case of PNET of uterine cervix. Due to the small number of cases reported so far management modalities especially chemotherapy regimens and radiotherapy need to be devised along with surgery and more cases need to be reported for further understanding the phenotype and genotype of this rare entity.

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PARTICULARS OF CONTRIBUTORS:
1. Student (Senior Resident), Department of Pathology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
2. Professor, Department of Pathology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
3. Professor, Department of Pathology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Saumya Shukla,
Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
E-mail: saumyavarun@gmail.com

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