

Case Report

A Rare Case of Uterine Primitive Neuroectodermal Tumor

Pattnaik SS*, Giri SK, Samantray S, Nayak BL, Mohapatra MR and Padhi AK

Mbbs at Scbmch Cuttack, (O&G) Vssmch Burla, Senior Resident Ahrcc Cuttack

***Corresponding author:** Smruti Sudha Pattnaik, Mbbs at Scbmch Cuttack, (O&G) Vssmch Burla, Senior Resident Ahrcc Cuttack

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Abstract

A 25 yrs female presented with mass abdomen. On imaging an abdomino-pelvic was detected, with an impression of a subserosal myoma, b/l ovaries appeared normal. She underwent myomectomy with left salpingo-oophorectomy. Her histopathology revealed to be a case of juvenile granulosa cell tumor, strongly positive for vimentin and focally reactive for calretinin. It was negative for pan-ck, ema, CD10. She presented two months later with mass and pain abdomen. She was planned for staging laparotomy in view of the CECT Findings large heterogenous solid cystic lesion 93x92x57, enhancement of solid component-pelvis and right adnexa fat plane between lesion and adnexa could not be delineated, ovaries not seen separately minimal ascites, no retroperitoneal lesion. On surgery there was extensive adhesions, with normal uterus and a uterine scar, the right ovary and tube buried. Biopsy from the ovary and tube taken. Hps of the deposits of ovary showed round cells, tubes were normal. Ihc of the specimen tissue inhibin-negative, cd99-: immunoreactive -4+in lesional cells nonspecific marker for ewings sarcoma. Associated with *ews- flil1* fusion transcript t(11:22)(q24;q12) FISH- positive 22q12 (*ewsr1*) gene rearrangement in 88% cells. The interpretation of the mass resected from the uterus in the first surgery was a pnet. The case was thus diagnosed as a pnet of the uterus.

Abbreviations

IOP: Intraoperative; POD: Pouch of Douglas; FISH: Fluorescence in Situ Hybridization

Introduction

Primitive neuroectodermal tumors, are thought to be derived from fetal neuroectodermal cells and that have a morphology of small round tumors with variable degrees of neural glial and ependymal differentiation.

This group includes rhabdomyosarcoma, small cell osteo sarcoma, neuroblastoma, and haematolymphoid tumors, and uterine tumors. Some have chromosomal translocation of the Ewing Sarcoma (EWS) gene on chromosome 22, which 90% of the time creates the EWSR1/FLI1 fusion product t(11;12)(q24;q12).

This demonstrates similarities in EWS/peripheral neural ectoderm central type pnets occur in children and young adults, (they are usually seen along the central axis particularly in the soft tissue and bone structures of chest and abdomen). However, neuroectodermal tumors have been reported in a variety of visceral sites and in older adults [1]. Small-cell carcinomas arising in the female genital tract are rare [2].

Case Report

A 25 yrs old female, with c/o- pain abdomen 15 days. Hpi- she had undergone a myomectomy outside our hospital. Her prior to myomectomy investigations done are USG17x14x14 cm abdominopelvic mass heteroechoic. b/l ovaries not seen separately. Minimal ascites. CECT-large sub serosal pedunculated

heterogeneously enhancing myoma 19x11x13 mm. predominantly solid no evidence of cystic and calcific degeneration, highly vascular with multiple tortuous collaterals along lesion capsule. b/l ovaries: normal sized morphology and separate from the uterus minimal ascites. No omental thickening.

Procedure

Left salpingo-oophorectomy and myomectomy, outside our institution intraoperative finding-Huge variegated mass connected to the left fundus and bladder. Hemorrhagic ascitic fluid.

Hpr- gross one side tube and one globular structure

Microscopic- neoplastic cells F/O jgct, large areas of haemorrhage with congested blood vessels capsular. Cellular neoplasm composed of round to moderately pleomorphic vesicular nuclei and moderate amount of clear cytoplasm arranged in diffuse solid sheets separated by fibrovascular septa. Many marofollicular areas seen.

Mitosis -3-10hpf.

Tube unremarkable

Left ovary-showed surface deposits

Imp- juvenile granulosa cell tumor

IHC -vimentin-strong and diffuse

Calretinin focal+

Pan ck- negative

CD 10 - negative

EMA - negative

Imp – juvenile granulosa cell tumor
 She presented to our hospital 2 months later
 O/e –P/A –uterus 16 wks size, p/s –cervix healthy
 P/v- uterus bulky (14 wks), left fornix a mass felt of variegated consistency
 Investigation – CA125 -258.2u/ml
 Inhibin -43PG/ml
 LDH – 290 U/ml

CECT: large heterogenous solid cystic lesion 93×92×57, enhancement of solid component-pelvis and right adnexa fat plane between lesion and adnexa could not be delineated, b/l ovaries not seen separately minimal ascites, no retroperitoneal lesion

PLAN-Staging laparotomy
 Top - extensive adhesions in pod
 Uterus normal size, myomectomy scar+
 Left tube absent
 Minimal ascites
 Right ovary moderately enlarged, right tube and ovary buried in pod
 Bowel adherent to uterus, POD, bladder and abdominal wall
 Biopsy of right ovary and tube taken.
 HPS – Section of ovary shows normal structure
 Section from surface deposits shows F/O neoplasm having round to ovoid cells with scanty cytoplasm (Figure 1). IHC PANEL

Analysis

Pan CK-negative
 Vimentin-positive
 EMA- negative
 CD10-NEGATIVE
 Inhibin-NEGATIVE
 Calretinin-Positive
 CD99-: immunoreactive -4+in lesional cells
 Nonspecific marker for ewings sarcoma. Associated with hews – FLI1 fusion transcript t (11:22) (q24;q12)
 FISH- positive 22q12 (EWSR1) gene rearrangement in 88% cells
DIAGNOSIS- the case is a PNET OF THE UTERUS
 Treatment- she was adviced for adjuvant chemotherapy (etoposide+cisplatin).

Discussion

The differential diagnosis of PNET usually includes other uterine tumors, small cell carcinomas, sarcoma, a lymphoma. IHC evidence of neuroectodermal differentiation with markers such as CD99, FLI-1,

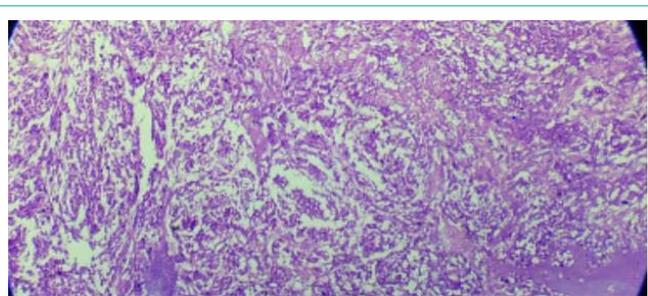


Figure 1: The hps showing ovoid to round cells with scanty cytoplasm.

vimentin and histology findings helps to distinguish. CD99 is highly specific marker of PNET. The majority of primary uterine PNETs lack the EWSR1 gene translocation, but in our case it is positive and therefore resemble a peripheral PNET [3].

PNETs belong to a group of small round cell tumors that are most commonly found in the central nervous system, soft tissues, or bones [2]. PNET has a mesodermal origin and is associated with of known muellerian origin [4,5,6]. 456 They can arise from any part of the female genital tract the ovary is the commonest [7] and next common site is the uterus.

64 cases of primary uterine neuroectodermal tumors have been reported [5,8]. 10 largest case series of seventeen patients case series by [6,9]. Various theories have been proposed for the origin of neuro ectodermal tissues in uterus. It has been suggested that benign glial tissue originated from the fetal central nervous system tissue implanted at the time of miscarriage.

However the presence of a glial tissue in young nulliparous patient has led to alternate theories, some proposed that is related to ectopically migrated neural crest cells at the time of foetal development.

PNET can present as in pure form or admixed with other components including endometrioid adenocarcinoma, adenosarcoma, carcinosarcoma and heterologous sarcoma.

Uterine tumors with neuroectodermal differentiation, similar to more common endometrial malignancies, tend to occur in postmenopausal women and frequently present with vaginal bleeding. An immunohistochemistry panel including cytokeratin, neurofilament, synaptophysin, and CD99 can highlight neuroectodermal differentiation and identify tumors for which molecular testing should be considered.

Risk factors of PNET, adolescent or postmenopausal age, Caucasian and Hispanic race. The most common presenting symptom is abnormal vaginal bleeding and a uterine mass.

Many uterine PNET ARE diagnosed in advanced stages highlighting their aggressiveness [12].

The two year survival rate of younger patients and postmenopausal patients has been reported as 75% and 32%, respectively [7]. Factors that portend poor prognosis for the PNET family of tumors include metastatic at primary presentation, primary osseous tumor central or pelvic disease, age at diagnoses 26 yrs older, tumor size greater than than 8 cm, poor response to chemotherapy, absence of EWS-FLI

FUSION GENE, and elevated pretreatment ldh [10].

Von Hippel–Lindau Disease (vHLD) has been associated with PNET tumors. The first description of the association of vHLD and a cerebellar PNET occurred in 1993 [11]. It was recently revealed that chromosomal translocation t(11;22)(q24;q12) occurs in most cases of Ewing’s sarcoma. Given this association, genetic testing should be considered if other risk factors are present.

When treated with local control measures only (surgery and/or radiation therapy), the disease has a high mortality rate and an 80-90% relapse rate. Although overt metastatic disease is found in fewer than 25% of patients at the time of diagnosis, subclinical metastatic disease, as in our case, is assumed to be present in nearly all patients due to this high relapse rate. Patients treated with surgery and radiation have a relapse rate approaching 90% [4]. Multimodal therapy improves disease free survival, but the optimal chemotherapeutic regimen has not yet been demonstrated.

Rather than cytotoxic treatment, in the case of PNET, surgery should be considered as the first step. Total hysterectomy with bilateral salpingo-oophorectomy with or without chemotherapy and/or radiotherapy is the usual course of treatment provided. Case reports have demonstrated long disease-free periods after treatment with platinum and etoposide therapy alone [12]. To the date there is only one case in the literature using the combination of cisplatin/etoposide/bevacizumab and favorable response to treatment (forty-eight months disease-free following intervention). The presence of endothelial proliferation and VEGF positivity within the tumor provides a rational explanation to the effectiveness of this novel chemotherapy modality against uterine cPNET [8].

Awareness of the occurrence of PNET in the uterus and its recognition is important to distinguish it from other tumors that may possess a different behavior and treatment. PNET is associated with advanced-stage disease and follows a potentially aggressive clinical course. Mortality can be high despite a combination therapy approach. While there is no consensus for the optimal chemotherapy treatment, carboplatin and etoposide should be considered as a viable option. Early diagnosis is essential as patients with non-metastatic disease respond relatively well to intense multi-modality treatment. Von Hippel-Lindau Disease (vHLD) has been associated with PNET tumors. The first description of the association of vHLD and a cerebellar PNET occurred in 1993 [11,13,14]. It was recently revealed that chromosomal translocation t(11;22)(q24;q12) occurs in most cases of Ewing’s sarcoma. Given this association, genetic testing should be considered if other risk factors are present. Awareness of the occurrence of PNET in the uterus and its recognition is important to distinguish it from other tumors that may possess a different behavior and treatment. PNET is associated with advanced-stage disease and follows a potentially aggressive clinical course. Mortality can be high despite a combination therapy approach. While there is no consensus for the optimal chemotherapy treatment, carboplatin and etoposide should be considered as a viable option. Early diagnosis is essential as patients with non-metastatic disease respond relatively well to intense multi-modality treatment.

Conclusion

She is a case uterine peripheral primitive neuroectodermal tumor. Due to the rare nature of uterine PNET and few case reports in the literature, it is difficult to determine the optimal course of treatment. Because cases of PNET are so rare, it is also problematic to accurately predict rates of survival or recurrence of this particular type of malignant neoplasm. Prospective clinical trials and studies of more cases with longer follow-up periods are required to estimate the clinical characteristics and evaluate the efficacy of this treatment schema in the management of advanced-stage uterine cPNET in the female genital tract. We should suspect this kind of tumor in healthy patients with a history of an aggressive and quick tumoral progression. For instance, our patient had an unremarkable previous gynecological examination.

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