



Primitive Neuroectodermal Tumors of the Vulva in a Pregnant Woman: Case Report and Review of the Literature

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Abstract

Ewing's sarcoma and peripheral primitive neuroectodermal tumour (pPNET) are now regarded as two morphological ends of a spectrum of neoplasms, characterised by a t(11;22) or other related chromosomal translocation involving the EWS gene on chromosome 22 and referred to as Ewing family of tumours (EFTs). They usually originate in bone or soft tissue but rarely arise in the vulva. Extra-skeletal Ewing sarcoma in pregnancy is rare. The current case report presents a case of PNET originating in the vulva in a 35-year-old pregnant woman. The patient benefited from a large excision of the tumor after giving birth to a healthy baby girl. She was treated for her pulmonary metastasis with conventional chemotherapy. She has had a stable disease with 6 months' review. From this, physicians should give more attention to any vulva mass, especially in case of pregnancy that may accelerate the growth of Ewing's sarcoma of the vulva, which can improve the prognosis of these pregnant women and their pregnancy.

Subject Areas

Gynecology & Obstetrics

Keywords

CD99, Extraskelatal Ewing's Sarcoma, Immunohistochemical, Vulva, Pregnancy

1. Introduction

The Ewing sarcoma family of tumors (ESFT/PNETs) is a group of highly aggres-

sive and often metastatic small round cell tumors characterized by specific t(11;22)(q24;q12) chromosomal rearrangements, which create the EWS/FLI1 gene fusion and thereby a chimeric, oncogenic transcription factor [1].

ESFT most commonly arise in young patients (the peak incidence is in the 20s) with a slight male predilection and occur at a variety of bone and soft tissue sites [2] [3].

Most extrasosseous neoplasms involve the soft tissues of the chest wall, pelvis, paravertebral region and lower extremities. ESFT have rarely been described in the vulva. We report this case not only because of the rarity of this tumor and its location but because of the patient's unusual concomitant pregnancy.

The prognosis is poor, as ESFT/PNETs are considered to be rare aggressive tumors. ESFT/PNETs often recur locally after resection and metastasize to the lungs and liver. A 3-year survival rate is estimated to be 30% [4].

To our knowledge, only few cases of primary vulvar Ewing's sarcoma/PNET have previously been reported in the literature. We present the case of a primary vulvar Ewing's sarcoma and the first case in pregnant woman.

2. Case Report

A 35-year-old woman, gravida 3, para 2 with non-significant past medical history referred to our hospital in the third trimester of her pregnancy (39 weeks gestation) due to a tumor mass in her vulva. She reported a 10 months history of 8 cm vulvar mass, painless and mobile (**Figure 1**). She had no other symptoms or lesions. The lesion increased progressively in size but it doubles in size during pregnancy. The clinical impression was a cyst or lipoma without any other symptoms. Pelvic computed tomography, chest radiograph, and bone scan showed no evidence of metastasis. Routine clinical laboratory tests remained within normal limits. A tumor resection was planned after delivery. The obstetrical examination was normal. The ultrasound examination showed a normal female fetus. Three days after the first consultation, patient gave birth to a healthy baby girl. It was a vaginal delivery, without any complication. Then,



Figure 1. 8 cm vulvar mass, painless and mobile.

complete resection conducted successfully. Grossly, the tumor was a well-delineated unencapsulated friable mass measuring 8cm/8cm/8cm. Its cut surface had a gray-tan fleshy appearance with focal areas of necrosis and hemorrhage (**Figure 2**, **Figure 3**).

Microscopically, the tumor was composed of solid sheets of undifferentiated small round cells with numerous Homer-Wright rosettes. Necrosis and hemorrhage were present, accounting for approximately 5% of the total tumor area. Focal areas showed geographic necrosis with perivascular preservation of viable tumor cells. The tumor cells were characterized by scanty cytoplasm, round to oval hyperchromatic nuclei, finely stippled chromatin, and conspicuous single nucleoli. The mitotic index was low with 2 - 3 mitotic figures/10 high power fields. The elongated hair like cytoplasmic extensions coalesced to form prominent central solid fibrillary Homer-Wright rosettes (**Figure 4**). Scattered apoptotic nuclei were seen. There was no evidence of lymph-vascular space invasion. Immunohistochemistry showed, the neoplastic cells stained strongly and diffusely positive for CD99 in a membranous staining pattern. FLI-1 protein was expressed in nearly all tumor cells, as demonstrated using a polyclonal antibody (**Figure 5**).

The patient was thereby diagnosed with pPNET.

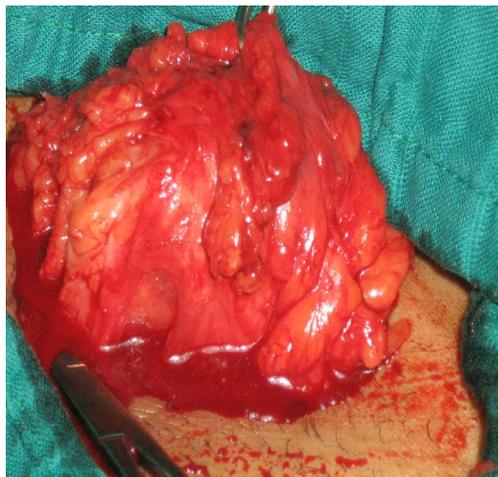


Figure 2. Per-operative look.

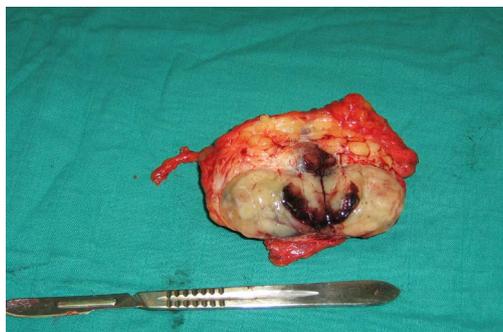


Figure 3. Macroscopic view.

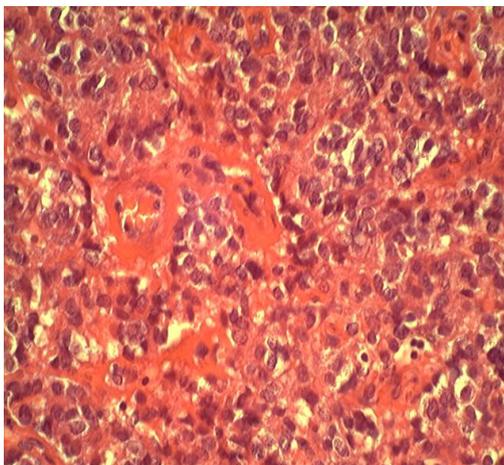


Figure 4. Numerous small overlapping pleomorphic cells, frequent mitoses and areas of hemorrhage and necrosis consistent with a small round blue cell malignant neoplasm.

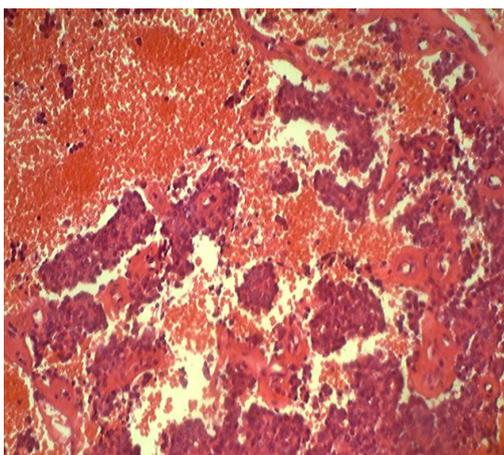


Figure 5. Immunohistochemistry showing membranous staining for CD99.

Two months after a surgery of wide excision, she was found to have pulmonary metastasis and received six cycles of cyclophosphamide, adriamycin and vincristine chemotherapy.

Her baby was in good health. Since then she has had no more metastasis with 6 months' follow up.

3. Discussion

Ewing's sarcoma is a primitive malignant tumor of bone and soft tissues preferentially arising in children and young adults. It shows an extremely aggressive behavior and rapidly disseminates to bones, bone marrow, and lungs.

In 1921, James Ewing described a small round cell tumor arising in bone [5]. His accurate description of the clinical features of the disease that carries his name has now been expanded to include extraosseous (EOE) and peripheral

primitive neuroectodermal tumors (pPNET), which are histologically similar to Ewing's sarcoma of bone and demonstrate the same rearrangement of chromosome 22 in more than 95% of tumors, most commonly as t(11;22). Because they share many clinical and pathological features, these tumors are classified as the Ewing's family of tumors (EFT). The EFT can develop in almost any bone or soft tissue, but the most common site is in a flat or long bone, and patients typically present with localized pain and swelling. The cells that make up EFT are very similar. They tend to have the same gene abnormalities and share similar proteins, which are rarely found in other types of tumors.

The majority of these neoplasms are composed of solid sheets of primitive undifferentiated "small round blue cells", corresponding histologically to Ewing's sarcoma, although rosettes are seen in more differentiated tumours, which histologically correspond to pPNETs.

Ewing's sarcoma-peripheral primitive neuroectodermal tumor (ES-pPNET) of the female genital tract is rare. Most of the cases occur in the ovary [6] [7]. Similar tumors were occasionally observed in the uterine corpus [8] [9], cervix [10], vulva [11] [12], vagina and rectovaginal septum. EFTs involving the vulva are extremely rare with only few previously reported possible cases, the largest series of four cases, three cases involving in the vulva and one case in the vagina is reported by Gleen McCluggage *et al.* The rarity of EFTs at this site can be seen from a series of 66 cases from a single institution, in which only tumours with molecular confirmation were included. In that series, none of the neoplasms involved the vulva, underscoring the rarity of this tumour at this site [13].

The incidence of pPNET in the adult population is difficult to ascertain due to diagnostic difficulties, especially differentiation from lymphomas and neuroendocrine carcinomas. PNETs occur more commonly in the second decade of life, predominantly affecting Caucasians and Hispanics and rarely occurring in individuals of African or Asian descent [14] [15].

The cause of ESFT is unknown. It does not appear to be inherited, radiation exposure and other environmental factors do not appear to be associated with the disease [16]. The family of tumors is not commonly associated with congenital diseases [17]. The tumors may occur as secondary malignancies but the incidence is low. The diagnosis of pPNET remains dependent on tissue biopsy.

Cell-surface staining for the protein product of the pseudo-autosomal gene MIC2 (CD99) has been very helpful in identifying ESFT from other small round-cell tumors. The MIC2 protein product is expressed by normal tissue and by other tumors such as rhabdomyosarcoma, neuroblastoma, some lymphomas and leukaemias, Merkel cell carcinoma, mesenchymal chondrosarcoma, small cell neuroendocrine carcinoma and synovial sarcoma, but the degree and level of expression are considerably less than in ESFT. The introduction of monoclonal antibodies that recognize this protein product has been very useful in confirming the diagnosis of ESFT [17].

FLI-1 is a DNA-binding transcription factor which is involved in cellular pro-

liferation and tumorigenesis, as well as in endothelial differentiation and blood vessel development. Besides being positive in normal endothelial cells and vascular neoplasms, FLI-1 is expressed (nuclear staining) in a large majority of neoplasms in the EFTs. Other neoplasms that may enter into the differential of EFTs, including Merkel cell carcinoma, neuroblastoma, synovial sarcoma, malignant peripheral nerve sheath tumour and malignant melanoma, may occasionally be positive with FLI-1 [13].

Cytogenetic and molecular genetic identification of the ES-pPNET-associated translocation is the “gold standard” as approximately 90% of ES-PNET are characterized by the translocation t(11;22)(q24;q12) that results in the fusion of the EWS gene on chromosome 22 to the FLI-1 gene on chromosome 11.

The treatment for ESFT consists of a multimodal approach chemotherapy, radiation therapy, and surgery. Systemic chemotherapy is for eradication of microscopic disease, and radiation therapy and surgery are for control of the primary lesion. The ultimate goal of treatment is cure while preserving function and reducing late effects.

The prognosis of ESFT varies with site of the primary tumor, presence of metastases, and tumor size.

Neoplasms in the EFTs are aggressive with a poor prognosis. It is difficult to ascertain whether the behaviour of vulval tumour is similar to those neoplasms that arise at more usual sites, as too few cases have been reported and many of them have limited or no follow-up.

The association between EFTs of the vulva and pregnancy, to our knowledge, has never been reported in the literature. In our case, the tumor increased during pregnancy, it doubled in size. The patient presented to our department at the third trimester of her pregnancy, fortunately she was able to end her pregnancy without complication. The management of her care did not affect her baby's health.

Cancer during pregnancy is a rare event, occurring approximately once per 1,000 pregnancies annually, corresponding to 0.07% to 0.1% of all malignant tumors [18]. Hormonal changes occurring during pregnancy may give the tumor a boost. The mechanism by which pregnancy might be connected with Ewing sarcoma is still unclear, but so far limited epidemiological data are available.

The patient presented to our department at the third trimester of her pregnancy, fortunately she was able to end her pregnancy without complication. The management of her care did not affect her baby's health.

The diagnosis of EFTs at earlier stage of pregnancy may cause a real diagnostic and therapeutic dilemma.

4. Conclusion

Extra-skeletal Ewing sarcoma of the vulva in pregnancy is rare. This case highlights the importance that physicians must give to vulva mass especially in pregnancy. Taking care of these patients earlier makes her prognosis better, and a

missed diagnosis at earlier stage may cost high to patient and her baby.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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