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Case Report

High grade primitive neuroectodermal tumor of the uterus: A case report☆

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Introduction

Primitive neuroectodermal tumors (PNETs) were first described in 1973 as a group of small round cell tumors that appeared to have developed from neuroectodermal cells (Hart and Earle, 1973). This group of tumors also includes Ewing sarcoma, rhabdomyosarcoma, small-cell osteosarcoma, neuroblastoma, and hematolymphoid tumors (Dehner, 1993). PNETs are usually seen along the central axis, particularly in the soft tissue and bone structures of the chest and abdomen of young adults and adolescents; predominately affecting Caucasians and Hispanics. Small-cell carcinomas arising in the female genital tract are rare (Kim et al., 2004). Early diagnosis is essential as patients with non-metastatic disease respond relatively well to intense multi-modality treatment (Grier et al., 2003).

Case

The patient is a 50 year old para 2 with a history of breast cancer eight years prior to admission. She was treated with lumpectomy and axillary lymph node dissection, adjuvant chemotherapy and radiation, followed by five years of Tamoxifen. She was thought to be with no evidence of disease from her breast cancer. The patient presented to her primary care physician complaining of abdominopelvic pain and soreness. An abdominal and pelvic ultrasound revealed a 15 cm complex right lower quadrant mass. Follow-up CT scan revealed a markedly enlarged uterus with an ill defined right adnexal/lower quadrant mass contiguous with the uterine fundus suggestive of possible sarcoma (Fig. 1). CA-125 was noted to be 407. She was referred to Gynecologic Oncology for definitive surgical management. The patient underwent a diagnostic laparoscopy, exploratory laparotomy, radical hysterectomy, bilateral salpingo-oophorectomy, debulking, omentectomy, and extensive lysis of adhesions. A 15 cm necrotic mass was found arising from the fundus. Frozen section returned poorly differentiated carcinoma of unknown etiology. The uterine mass demonstrated multiple friable tan-pink and hemorrhagic portions of tissue. The uterus contained myometrium with diffusely infiltrative tumor without involvement of the endometrium or serosal surface. The omentum was negative for malignancy. Histologic sections of the debulked uterine mass and myometrium involved by tumor demonstrated a poorly circumscribed tumor with infiltrative borders containing poorly differentiated epithelioid and spindle cells with a high nuclear/cytoplasm ratio and scant cytoplasm (Fig. 2). The tumor also contained many areas of geographic necrosis on examined sections. Several areas revealed tumor in an angiocentric pattern giving the appearance of pseudorosettes. CD 99, Fli-1, and Vimentin were positive on immunohistochemical stains (Fig. 3). Final pathology revealed high-grade primitive neuroectodermal tumor. The patient received 6 cycles of adjuvant carboplatin and etoposide. Follow up CT scan showed no abnormalities and she remains with no evidence of disease 16 months following completion of treatment.

Discussion

Primitive neuroectodermal tumors (PNETs) belong to a group of small round cell tumors that are most commonly found in the central nervous system, soft tissues, or bones (Kim et al., 2004). The most common site of PNET in the female genital tract is the ovary (Odunsi et al., 2004). PNET of the uterus, however, is rare, and has been reported in less than 50 cases in the English literature (Bhardwaj et al., 2010). The keywords "uterine" or "uterus" and "primitive neuroectodermal tumor" were used in the PubMed search engine to find a list articles reporting

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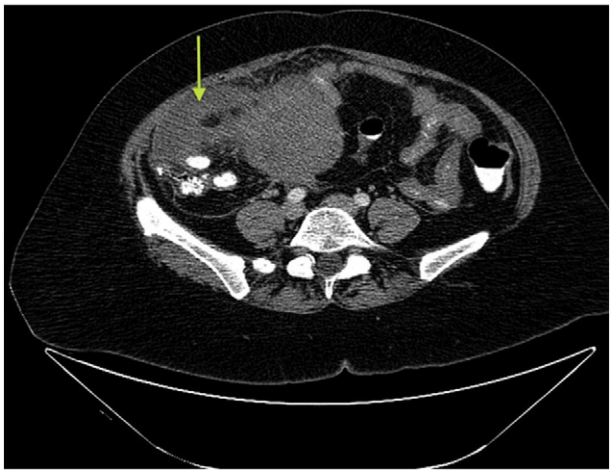

Fig. 1. CT scan. Mass contiguous with the uterine fundus.

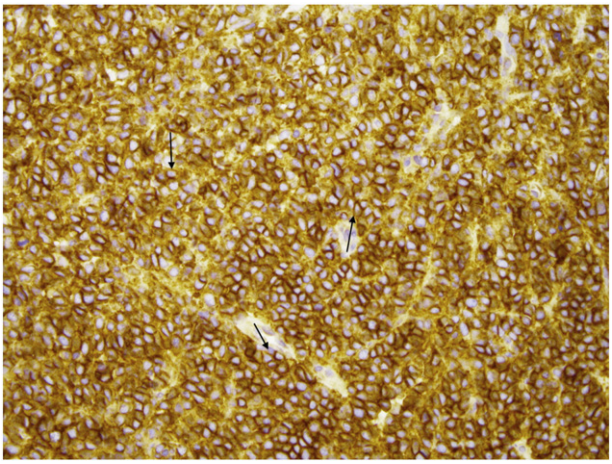

Fig. 3. CD99 immunostain. Strong reactivity of neoplastic cells for this marker (400×).

less than 50 cases of uterine PNET tumors in the English literature. Most notably, Bhardwaj et al.'s article summarizes this list in their discussion.

Risk factors for uterine PNET are few, but include adolescent or postmenopausal age, and Caucasian or Hispanic race. The most common presenting symptom is abnormal vaginal bleeding, similar to endometrial adenocarcinoma. However, in contrast to endometrial cancer, which is typically detected in early stages, many uterine PNET cases are diagnosed at advanced stages (Park et al., 2007). Interestingly, this patient was premenopausal and presented with abdominopelvic pain. She denied abnormal uterine bleeding.

The differential diagnosis of uterine PNETs include tumors exhibiting neuroectodermal elements found in the central nervous system, including mature glial tissue of the endocervix or endometrium, immature teratoma with glial tissue, pure uterine gliomas, carcinosarcoma with neuroectodermal differentiation, and retinal anlage tumor. The diagnosis is based on light microscopic and immunohistochemical evidence of neuroectodermal differentiation, with markers such as CD99, FLi-1, and Vimentin (Park et al., 2007). CD99 is a highly specific marker for PNET.

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 (Becker et al., 1993). It was recently revealed that chromosomal translocation t(11;22)(q24;q12), which fuses the *EWS* gene on chromosome 22 and the *FLI-1* gene on chromosome 11 and encodes a chimeric *EWS/FLI-1* protein, occurs in most cases of Ewing's sarcoma (Bernstein et al., 2006; Shulman et al., 2012). The *EWS* gene can accidentally form fusion gene products with *ERG*, or ETS-related gene, found in Ewing's sarcoma, which is similar in morphology to PNET and other neuroendocrine tumors found in vHLD. In fact, Shibanski et al. reported a rare case of mandibular ES with chromosomal translocation t(21;22)(q22;q12) in which the *EWS* gene is fused with the *ERG* gene on chromosome 21 (Shibanski et al., 2013), while Dagher et al. found that 58 (76.3%) of 76 patients had translocations (53 with the *EWS/FLI-1* fusion transcript and 5 with the *EWS/ERG* fusion transcript) (Dagher et al., 2001). Given this association of vHLD and neuroendocrine tumors, genetic testing should be considered if other risk factors are present.

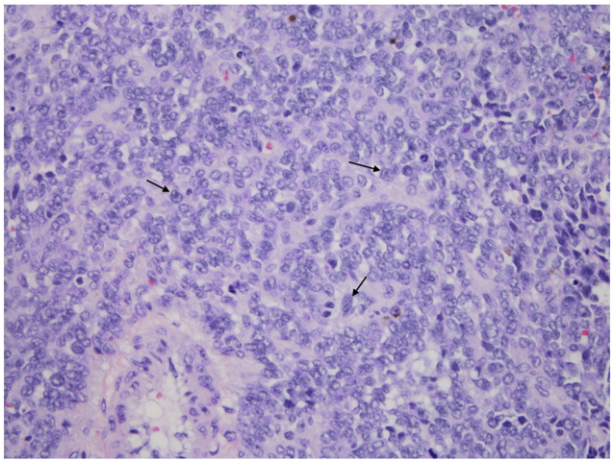

Fig. 2. H&E photo. High-power view of diffusely infiltrative epithelioid tumor cells with few mitotic figures (400×).

Optimal treatment methods have not yet been established due to of the rarity of these tumors. Treatment for PNETs has included surgery, radiation, and chemotherapy alone, and multimodal therapy with surgery, adjuvant chemotherapy, and radiation. The prognosis varies depending on the age of the patient. Younger patients have a better prognosis with 75% surviving at least 2 years compared with 32% in the postmenopausal age group (Odunsi et al., 2004). 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 is assumed to be present in nearly all patients due to this high relapse rate (Peres et al., 2005). The utility of lymphadenectomy is unclear. Systemic chemotherapy has evolved as an important component of treatment. The use of adjuvant chemotherapy began in the early 1970s and has resulted in a marked improvement in outcome. Grier et al. published data from a randomized trial showing improved five-year event-free survival (69%) after the addition of etoposide and ifex to a standard regimen in patients with nonmetastatic Ewing sarcoma, primitive neuroectodermal tumor of bone, and primitive sarcoma of bone. The standard regimen of vincristine, doxorubicin, and cyclophosphamide produced a five-year survival of 54%. Overall survival was also significantly better among patients in the group with etoposide and ifex (72%) versus those without (61%). The most significant side effects with the addition of etoposide and ifex were infection, hemorrhage, and anemia requiring more red-cell transfusions.

Morphologically, Ewing's sarcoma appears similar in appearance to PNET. Published case series or reports of intracranial or spinal Ewing's sarcomas have documented treatment using carboplatin and etoposide. As such, platinum-based chemotherapy has been investigated for the

treatment for PNETs. Platinum based chemotherapy for PNET has shown to have similar rates of survival to the much more toxic regimens. Case reports have demonstrated long disease-free periods after treatment with platinum and etoposide therapy alone (Tsai et al., 2012). Also of note, treatment considerations for small cell and large cell neuroendocrine carcinoma variants of the cervix take into account the treatment options for cervical cancer, and draw on the data for treating small cell lung cancer. Recent data supports the use of platinum with or without etoposide in small cell and large cell neuroendocrine carcinomas to improve survival (McCusker et al., 2003; Embry et al., 2011).

Conclusion

Primary PNET of the uterus is rare and requires early diagnosis and treatment due to aggressive behavior of the tumor. 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.

Disclaimer

No author has direct or indirect commercial financial incentive associated with publishing this article.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

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