Case report

Primitive neuroectodermal tumor of the uterus: Excellent clinical response following a multimodal treatment approach

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ABSTRACT

We present a case report of a patient with uterine primitive neuroectodermal tumor (PNET). The patient underwent surgical management followed by pelvic radiation and intravaginal brachytherapy. Following a stable interval, the patient was found to have new onset spinal, pulmonary, and adrenal metastatic disease. She was subsequently started on high dose carboplatin and etoposide. An interval reduction of her metastatic disease was observed after three cycles. We conclude that a multimodal approach, including platinum-based adjuvant chemotherapy with etoposide, can be effective in patients who present with residual or recurrent disease after surgical and radiation therapy. However, more robust studies with longer follow-up periods will be needed to establish a consensus regarding effective treatment options.

1. Introduction

Primitive neuroectodermal tumors (PNETs) belong to a spectrum of diseases known as Ewing family of tumors (EFTs). (Akazawa et al, 2018) PNETs are highly malignant neoplasms characterized by small round blue cell tumors of neuroectodermal origin. These tumors have a bimodal distribution, most commonly diagnosed during adolescence and the post-menopausal period. (Novo et al, 2015) PNETs of the genital tract are rare. Cases of uterine involvement typically present with abnormal uterine bleeding and a pelvic mass. Many uterine PNET cases are diagnosed at advanced stages highlighting their aggressive nature. (Novo et al, 2015) Due to its rarity, universally accepted treatment guidelines for PNETs are not available. Current treatment involves surgery followed by chemotherapy and/or radiotherapy. (Eskiyörük et al, 2015) While there is no standard chemotherapy for PNET, the combination of carboplatin with etoposide is an accepted treatment approach. In this report, we present a case of an advanced uterine PNET and its clinical course.

2. Case

A 66 year old female, gravida 2, para 0, initially presented to her gynecologist with a one month history of vaginal bleeding. Her last menstrual period was ten years prior. She also reported an unintentional weight loss of ten pounds over the last six months. However, she denied any pelvic pain or appetite changes. The patient’s past medical history was otherwise non-contributory.

Physical exam revealed a large pelvic mass spanning the entire pelvis. Pelvic ultrasound partially visualized a 17.4 cm heterogeneous right adnexal mass. A computed tomography (CT) scan of the chest, abdomen, and pelvis showed a large heterogeneous uterine mass concerning for malignancy. (Fig. 1) No metastases were identified. Pre-surgical labs were notable for anemia, as well as a normal CA-125. An endometrial curettage was obtained, which showed a high grade uterine neoplasm with neuroendocrine features.

Patient was taken to the operating room for an exam under anesthesia, exploratory laparotomy, total abdominal hysterectomy, bilateral pelvic and para-aortic lymphadenectomy and infracolic omentectomy. (Fig. 2) The mass involved the endometrium and nearly the entire myometrium. No serosal involvement was seen.

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Histologic evaluation showed a nodular low-power pattern of invasion into the myometrium and myometrial vessels. The tumor cells form interanastomosing cords and trabeculae with areas of rosette formation. (Fig. 2) No discrete areas of carcinoma, carcinosarcoma, endometrial stromal or smooth muscle neoplasia were identified. The tumor cells display a primitive appearance with cytologic atypia and brisk mitotic activity. Immunohistochemical stains were diffusely positive for CD56, CD57, and desmin, multifocally positive for NEU, WT-1 with multifocal nuclear positivity for beta-catenin, and negative for chromogranin, NSE, SMA, inhibin, calretinin, CD99, EMA, myoD1, and myogenin. The final diagnosis was primitive malignant neoplasm, most consistent with primitive neuroectodermal tumor.

Our institutional Gynecologic Oncology tumor board reviewed the final diagnosis and recommended systemic therapy with Etoposide/Carboplatin followed by intravaginal brachytherapy. The patient refused systemic therapy and was treated with external radiation therapy to the pelvis followed by intravaginal brachytherapy. She completed 45 Gy in 25 fractions to her whole pelvis followed by intravaginal brachytherapy 15 Gy in three weekly applications.

The patient was asymptomatic for eight months following radiotherapy. However, she then developed severe back pain, requiring hospitalization. Magnetic resonance imaging (MRI) showed multiple lesions at the L3 and L4 vertebral bodies. CT of the chest, abdomen, and pelvis also showed interval development of multiple bilateral pulmonary nodules and a heterogeneous mass superior to the left kidney. (Fig. 3) The patient also reported right shoulder pain and was found to

Fig. 1. CT scan (a) showed large heterogeneous uterine mass measuring 14.5 × 15.4 × 13 cm compressing the bladder, adjacent bowel loops, and distal ureter. MRI (b) showed the uterus is significantly enlarged with a mass lesion measuring approximately 16 × 11 cm presumed to be in the uterine myometrium.

Fig. 2. Photomicrograph of the tumor at 20× (a) showing formation of interanastomosing cords and trabeculae. Photomicrograph of the tumor at 100× (b) showing cytologic atypia, mitotic figures, and rosette formation. Cross section of the uterus (c) showing a lobulated tan mass involving the entire myometrium with central necrosis and calcification.
have sclerosis, suggestive of metastatic disease. The patient then underwent five fractions of stereotactic body radiation therapy (SBRT) to the L3 and L4 vertebral bodies and adjacent nerve roots and the right shoulder.

At this point, the patient agreed to chemotherapy and was started on weekly carboplatin and etoposide. After three cycles of chemotherapy, CT scan demonstrated marked interval improvement of the bilateral pulmonary nodules and left adrenal lesion. (Fig. 3) The patient tolerated therapy well. Given her excellent response to treatment after the third cycle, her regimen was switched from once weekly to two weeks on, one week off. Currently, the patient continues to be treated with carboplatin, etoposide. The tumor was checked for targetable driver mutations which were not present. Her most recent CT scan showed a new 7 mm nodule which the patient is scheduled to receive four fractions of SBRT. Despite residual disease on imaging, she remains symptom free two years after her initial diagnosis.

3. Discussion

PNETs belong to a group of small round cell tumors that are most commonly found in the CNS, soft tissues, or bones. PNETs of the genital tract are quite rare. They tend to occur in postmenopausal women and frequently present with vaginal bleeding and uterine enlargement. Many uterine PNET cases are unfortunately diagnosed at advanced stages. (Novo et al, 2015)

The diagnosis of PNETs requires both light microscopic and immunohistochemical (IHC) evidence of neuroectodermal differentiation to distinguish from other tumors with small round cells. On light microscopy, they are characterized by small, uniform round malignant cells with rounded vesicular nuclei bearing small nucleoli, with a high mitotic activity. IHC typically shows diffuse membranous CD99, a highly specific marker for PNET. Vimentin, FLi-1, and sometimes CAM 5.2, AE1/AE3 may also be seen. (De Nola et al, 2018) In our case, the tumor cells were undifferentiated, round, and small with a tendency to form interanastomosing cords. IHC showed focal positivity for CAM 5.2 and AE1/AE3, but negative for CD99.

When treated with surgery and/or radiation therapy, the disease has a high mortality rate with a high relapse rate. Multimodal therapy improves disease free survival, but the optimal chemotherapeutic regimen is not known. (Elizalde et al, 2016) Tsai et al in 2012 demonstrated that adjuvant chemotherapy consisting of platinum and etoposide therapy was effective in a patient with advanced stage (IIIB) uterine PNET. Additional case reports have also demonstrated extended disease free periods after treatment with platinum and etoposide therapy alone.

A number of biologically targeted therapies are currently being investigated, but not yet approved for treatment. One promising drug target is the insulin-like growth factor-I receptor (IGF-1R), which is involved in PNET growth. Other potential biological therapies being studied include mTOR inhibitors, Anti-GD2 monoclonal antibody, multi-targeted tyrosine kinase, CDK4/6, and PARP inhibitors. (Bailey et al, 2019)

Younger patients have a better prognosis with 75% survival at two years compared with 32% in the post-menopausal age group. (Dizon et al, 2014) Prognosis of uterine PNETs also varies depending on surgical stage. The two-year survival rate is 68% for stage 1, but only 58% for stage 3, and 0% for stage 4. (Eskiyörük et al, 2015)

While PNETs are typically quite aggressive and portend a poor
prognosis, our patient is atypical in that she has responded remarkably well to treatment. We conclude that a multimodal approach including platinum based adjuvant chemotherapy with etoposide can be effective in similar patients. However, more robust studies with longer follow-up periods is necessary to establish a consensus regarding effective treatment options.

4. Disclaimer

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

Informed consent was obtained from the patient for publication of this case report and accompanying images.

Author contributions

All authors contributed equally to this manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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