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Case report

Primitive neuroectodermal tumor of the uterus

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1. Introduction

Primitive neuroectodermal tumors (PNETs) were first described in 1973 by Hart and Earle to denote a group of tumors thought to be derived from fetal neuroectodermal cells and that had morphologic features of small round cell tumors with variable degrees of neural, glial, and ependymal differentiation (Hart and Earle, 1973).

This group of tumors also includes Ewing sarcoma, rhabdomyosarcoma, small-cell osteosarcoma, neuroblastoma, and hematolymphoid tumors. Uterine PNET appears to fall into two categories. Some have a chromosomal translocation of the Ewing sarcoma (EWS) gene on chromosome 22, which 90% of the time creates the EWSR1/FLI1 fusion product t(11;22)q24q12 (Delattre et al., 1994). This demonstrates histologic, inmunochemical, and biologic similarities to the EWS/peripheral primitive neuroectodermal tumor (pPNET). Central type PNETs tend to occur in children and young adults. They are usually seen along the central axis, particularly in the soft tissue and bone structures of the chest and abdomen. However, neuroectodermal tumors have been reported in a variety of visceral sites and in older adults (O'Sullivan et al., 2001). Small-cell carcinomas arising in the female genital tract are rare (Kim et al., 2004).

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To date, over 64 cases of primary uterine PNET have been reported in the literature (Ng, 2002; Dizon et al., 2013, Novo et al., 2015), the largest being a seventeen-patient case series by Euscher et al. (2008).

In this report we describe an unusual case of high-grade uterine tumor with neuroectodermal differentiation.

2. Case

A 60 year-old nulliparous woman with a past medical history of Raynaud's Syndrome, SLE (Systemic lupus erythematosus), CREST (calcinosis, Raynaud, esophageal dysmotility, sclerodactyly and telangiectasia) and nephrotic syndrome. She presented to her general practitioner complaining of vaginal bleeding and abdominopelvic pain. A pelvic ultrasound revealed an atrophic uterus with 45 mm of haematometra and 34 mm of diffuse endometrial thickness. Endometrial biopsy showed a diffuse proliferation of undifferentiated tumor cells. CT and MRI scan revealed a markedly enlarged uterus with a contiguous mass in the uterine fundus suggestive of uterine tumor (Fig. 1).

She was referred to Gynaecologic Oncology clinic for definitive surgical management. The patient underwent an exploratory laparotomy, radical hysterectomy, bilateral salpingo-oophorectomy and para-aortic lymphadenectomy. A 10 × 13 cm necrotic mass was found arising from the fundus (Fig. 2). The uterus contained a diffusely infiltrative tumor in the myometrium with involvement of the endometrium and serosal surface. The endometrial cavity was occupied by a polypoid mass with necrosis. Histologic sections demonstrated a poorly circumscribed tumor with infiltrative borders containing poorly differentiated epithelioid and spindle cells with a high nuclear/cytoplasm ratio (Fig. 3). The tumor also contained many areas of necrosis, massive vascular invasion and extranodal extension of metastasis in para-aortic lymph nodes. Several areas revealed tumor in an angiocentric pattern giving the appearance of pseudorosettes (Fig. 3). CD 99, Fli-1, and Vimentin were positive on immunohistochemical stains (Fig. 3). Final pathology revealed high-grade primitive neuroectodermal tumor and intraoperative findings were consistent with FIGO stage IV classification.

Following discussion of the patient's case at our multidisciplinary team discussion meeting, the decision was made to treat the patient with six cycles of adjuvant carboplatin and etoposide. Response to treatment was followed with physical examination and chest, abdomen and pelvic CT scan.

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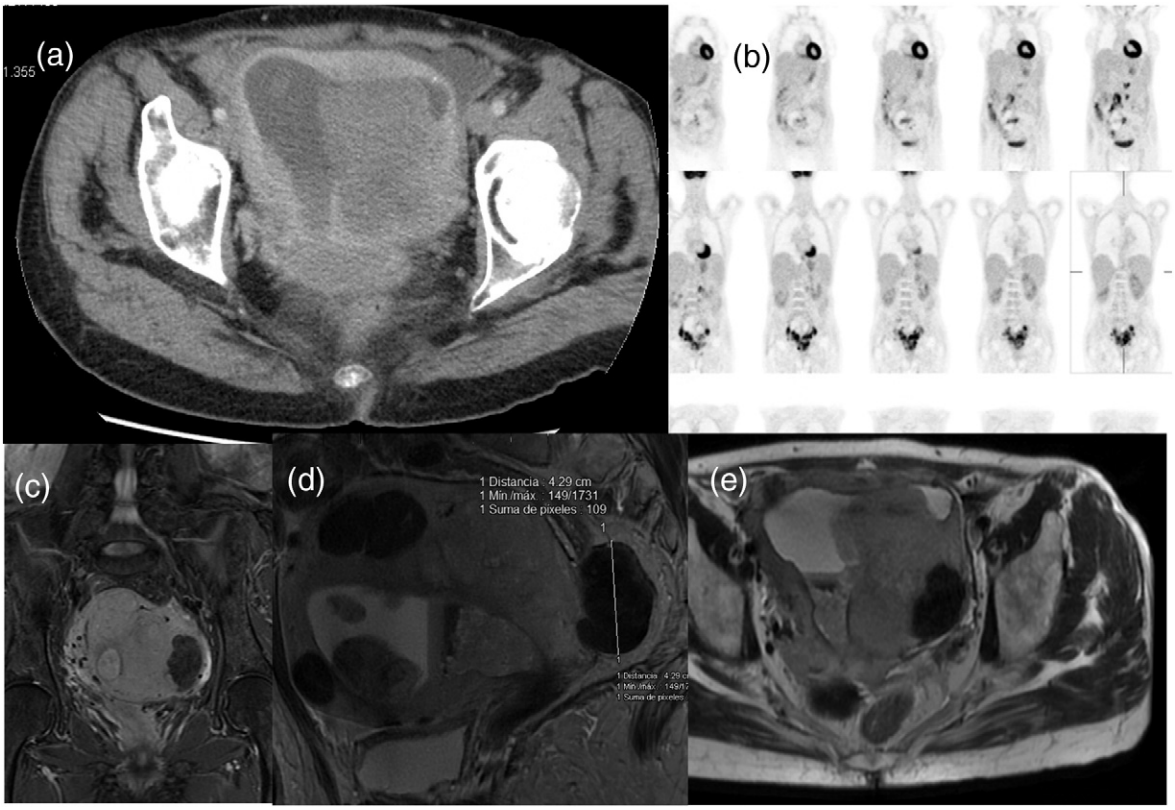

Fig. 1. CT (a) and MRI scan (c, d, e) revealed an enlarged uterus with a contiguous mass in the uterine fundus (a). The PET scan showed an hypermetabolic image in the pelvic region with poorly defined morphology occupying the cervical stump and Pouch of Douglas, hypermetabolism deposits in the mesentery and peritoneum compatible with mesenteric implants, and an image in the left pubis that, in this context, could be a metastasis (b).

She was initially asymptomatic for four months post surgery but then presented to her gynaecologist complaining of vaginal bleeding. Vaginal cytology and biopsy were positive for infiltration by the neuroectodermal tumor. Follow up CT chest scan revealed, in comparison with the previous CT, a pulmonary node of 3 mm on the right and low segment. Abdominal MRI revealed a pelvic mass in the recto-uterine pouch of 9.6 × 6.2 cm and minimum growth of two para-aortic lymph nodes. PET scan showed a hypermetabolic image in the pelvic region (Fig. 1).

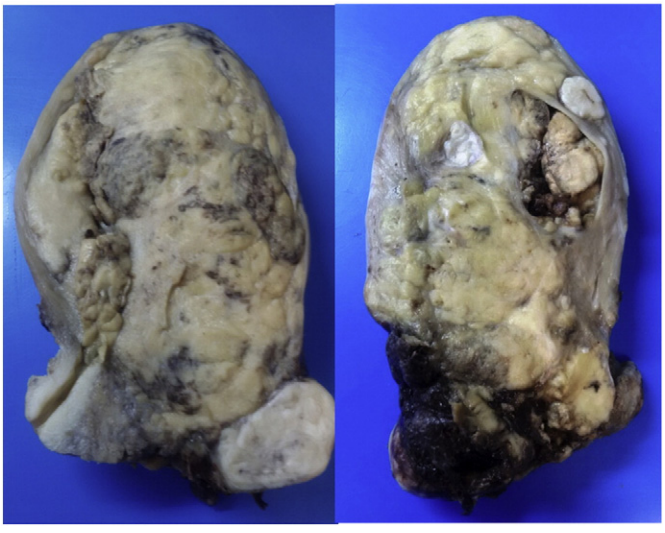

Fig. 2. Longitudinal section of the uterus showing a tumor with transmyometrial invasion and cervical involvement.

After receiving 6 cycles of chemotherapy, the patient was admitted into the hospital via A&E with a history of severe abdominal pain. She was diagnosed of intestinal subocclusion. An abdomino-pelvic CT was performed which showed trabeculated cystic pelvic mass of 10 cm which was filling up the entire minor and major pelvis. Small bowel distension and colic frame collapsed were found. However, it was unable to find the cause for this. Retroperitoneal lymph nodes were enlarged in comparison with previous CT.

This admission just coincided with the last chemotherapy cycle of the first line. A discussion was therefore carried out with the oncologist whether she should start with the second line of chemotherapy (carbo-taxol). As the chemotherapy causes the secondary pancytopenia, this treatment was rejected at this moment.

Radiology and cytology revealed the diagnosis of progression, and radiation was considered in the primary treatment. However, it was never administered because the patient was admitted two days after hospital discharge presenting abdominal pain and deceased the same day, seven months since the diagnosis.

3. Discussion

PNETs can be classified based on the degree of differentiation, location and genetic signatures into peripheral and central types. Peripheral-type PNET/EWING sarcoma is believed to originate from neural crest and occur outside of the central nervous system. cPNET/neuroblastoma are derived from the central neuraxis and involve central structures including the brain and spinal cord, and generally lack the EWSR1 gene rearrangement (Hart and Earle, 1973). The majority of primary uterine PNETs lack the EWSR1 gene translocation, as in our case, and therefore resemble a cPNET (Varghese et al., 2006).

PNETs belong to a group of small round cell tumors that are most commonly found in the central nervous system, soft tissues, or bones

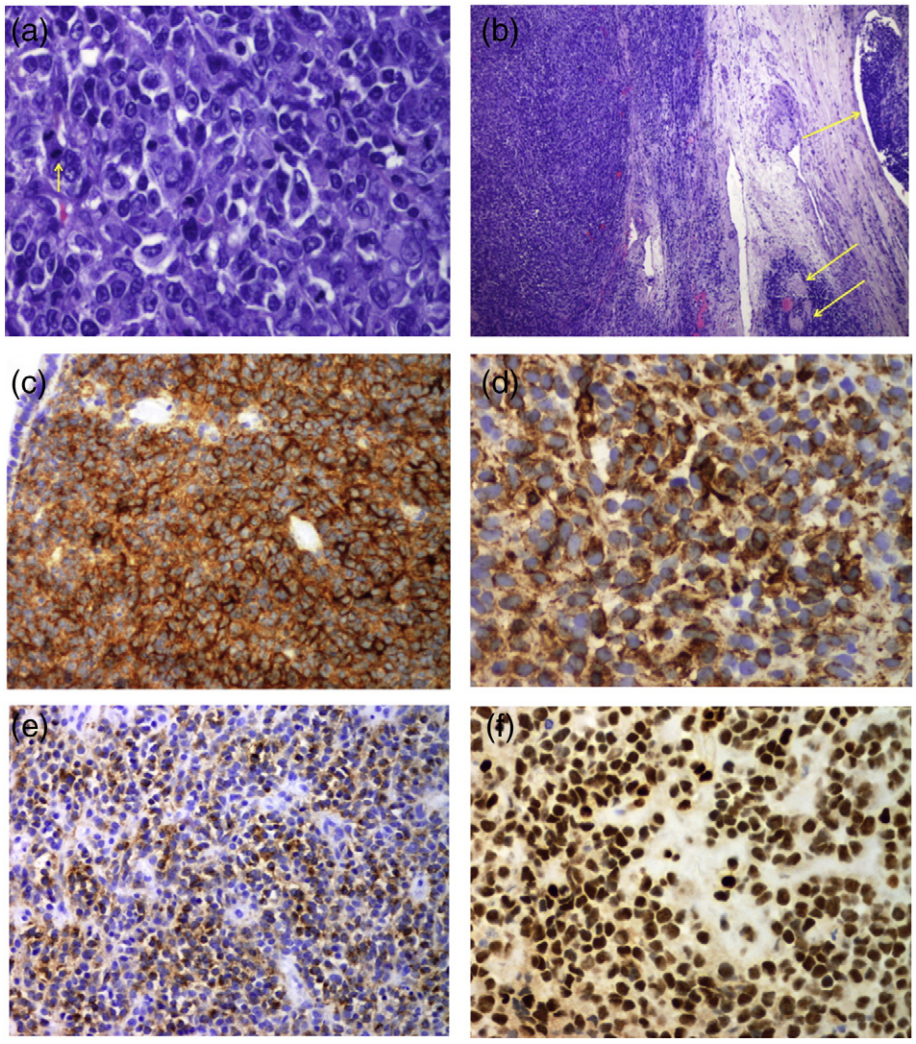

Fig. 3. (a) H&E photo (400×). High-power view of diffusely infiltrative tumor cells, arranged in trabeculae and cords, marked atypia and pleomorphism, and numerous mitotic figures (arrows). (b) H&E photo (40×). Cells are diffusely arranged with variable amounts of vague nesting and/or trabeculated pattern. Perivascular rosettes in a fibrillary background. Arrows indicate perineural infiltration and vascular invasion. Uterine myometrium infiltration by a poorly differentiated tumor with diffuse growth pattern "broadsheet". The tumor cells were positive for CD99 Strong reactivity of neoplastic cells for this marker (c), synaptophysin (d), Vimentin (e), FLI-1 (f). H&E photo (400×).

(Kim et al., 2004). Such tumors arising in the female genital tract are possibly among the least well characterized and have been reported in the vagina, cervix, uterus and ovary. The most common site in the female genital tract is the ovary (Odunsi et al., 2004), and the next commonest is the uterus. PNET of the uterus, however, is rare, and has been reported in less than 50 cases in the English literature. Various theories have been proposed as to the origin of the neuroectodermal tissues in the uterus. It has been suggested that benign glial tissue is originated from fetal central nervous system tissue implanted at the time of miscarriage. However, the finding of a glial tumor in a young, nulliparous patient led to the development of alternate theories, some have proposed that is related to ectopically migrated neural crest cells at the time of fetal development.

PNET's can present in pure form or admixed with other components, including endometrioid adenocarcinoma, adenosarcoma, carcinosarcoma (metaplastic carcinoma), and heterologous sarcoma.

Risk factors for uterine PNET are few, but include adolescent or postmenopausal age, Caucasian or Hispanic race. The most common presenting symptom is abnormal vaginal bleeding, and a uterine mass the most common finding on exam. Many uterine PNET cases are diagnosed at advanced stages highlighting their aggressive nature (Park et al., 2007). The differential diagnosis of uterine PNETs include tumors exhibiting neuroectodermal elements found in the central nervous system. 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. In our case FISH examination was performed which did not show rearrangement of EWSR1 gene.

In the largest case series on uterine PNETs by Euscher et al., CD99 was positive in seven out of nine cases tested for the marker. Also none of the 12 cases tested for typical EWSR1 rearrangement were positive. However, five cases of typical gene rearrangement are described in the literature (Euscher et al., 2008; Blattner et al., 2007).

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) occurs in most cases of Ewing's sarcoma. Given this association, genetic testing should be considered if other risk factors are present.

Due to the rare nature of the uterine PNET and the small number of case reports in the literature, it is difficult to determine the optimal course of treatment. Treatment for PNETs has included multimodal therapy with surgery, adjuvant chemotherapy, and radiation. 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.

The survival rate of our case was similar to previous ones published on the literature regarding patients diagnosed with Stage IV with the same features (Euscher et al., 2008). The two year survival of younger patients and postmenopausal patients has been reported as 75% and 32%, respectively (Odunsi et al., 2004). Factors that portend a poor prognosis for the PNET family of tumors include metastatic disease at presentation, primary extraosseous tumor, central or pelvic disease, age at diagnoses of 26 or older, tumor size greater than 8 cm, poor response to chemotherapy, absence of EWS-FL1 fusion gene, and elevated pretreatment LDH (Mittal et al., 2007).

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% (Blattner et al., 2007). 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 (Tsai et al., 2012). 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 (Novo et al., 2015).

4. Conclusion

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.

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 behaviour 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.

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 gynaecological examination.

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