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Case report

High grade sarcoma, with predominant neuroectodermal and minor embryonal rhabdomyosarcomatous tumor of the uterus: A case report

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ABSTRACT

Background: There have been few documented cases of combined primitive neuroectodermal and embryonal rhabdomyosarcomas (ERMS) in the uterus. Due to their rarity, there is no consensus on the optimal treatment for patients with primitive neuroectodermal tumor (PNET) and ERMS of the uterus. Studies on treatment and outcome are limited.

Case presentation: A 32 year-old female presented with heavy vaginal bleeding. Ultrasound revealed an 18 cm uterus with thickened endometrium. Histopathology revealed embryonal rhabdomyosarcoma. She underwent a total abdominal hysterectomy, bilateral salpingectomy, lymph node dissection, and omentectomy. Pathologic review confirmed a tumor with mainly central-type PNET and focally ERMS within the uterus and cervix. She was treated with adjuvant chemoradiation.

Conclusion: Treatment of the predominant tumor, PNET, should be the primary goal of therapy. Vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide with tumor directed radiation may be efficacious for the treatment of this specific high grade uterine sarcoma.

1. Introduction

Primary neuroectodermal tumors (PNETs) are a group of small round cell tumors that originate from neuroectodermal cells, commonly known to affect soft tissue and bone, but rarely the female genital tract (Stout, 1918; Hart et al., 1973). PNETs are divided into two major groups: central (derived from the central nervous system) and peripheral (tissues outside the central and autonomic nervous system). Eighty-five percent of PNETs demonstrate a characteristic rearrangement of the Ewing sarcoma (EWS) gene on chromosome 22, which creates the EWRS1/FLI1 fusion product t(11;22)q24q12 (Dundr et al., 2010). Tumors with this gene rearrangement are considered to belong to the EWS/peripheral primitive neuroectodermal tumor (pPNET) spectrum. Lack of an EWSR1 rearrangement excludes them from this family and are then considered central type PNETs regardless of shared histologic and immunohistochemical findings (Euscher et al., 2008). Central type PNETs tend to occur in children and young adults; neuroectodermal tumors, however, have been reported to occur in various sites and in older adults. Within the female genital tract, the ovary is the most common location of PNETs (Dizon et al., 2014).

Rhabdomyosarcoma is the most common soft tissue sarcoma in the first two decades of life, occurring in the head and neck region (35%) and genitourinary tract (25%), with the bladder, prostate and vagina as the most common sites (Dehner et al., 2012). Rhabdomyosarcoma of the uterus and/or cervix is uncommon, and most cases reported are the embryonal subtype; others include alveolar, pleomorphic, and undifferentiated (Cate et al., 2013).

There is no established optimal treatment for these rare tumors in the literature, especially in adults. There have only been four cases described with an embryonal rhabdomyosarcoma (ERMS) and a PNET within the same tumor (Stolnicu et al., 2012; Cate et al., 2013; Euscher et al., 2008; Dundr et al., 2010). In an effort to provide more understanding and therapeutic options for this rare malignancy, we report a case in which PNET and embryonal rhabdomyosarcoma are identified as unequal components of a single tumor in the uterus.

2. Case report

The patient is a 32 year-old gravida 1 para 1 who presented with heavy vaginal bleeding. A pelvic ultrasound revealed an enlarged 18 cm uterus with heterogeneous echotexture of the myometrium and abnormally thickened endometrium with cystic changes. Pathology from

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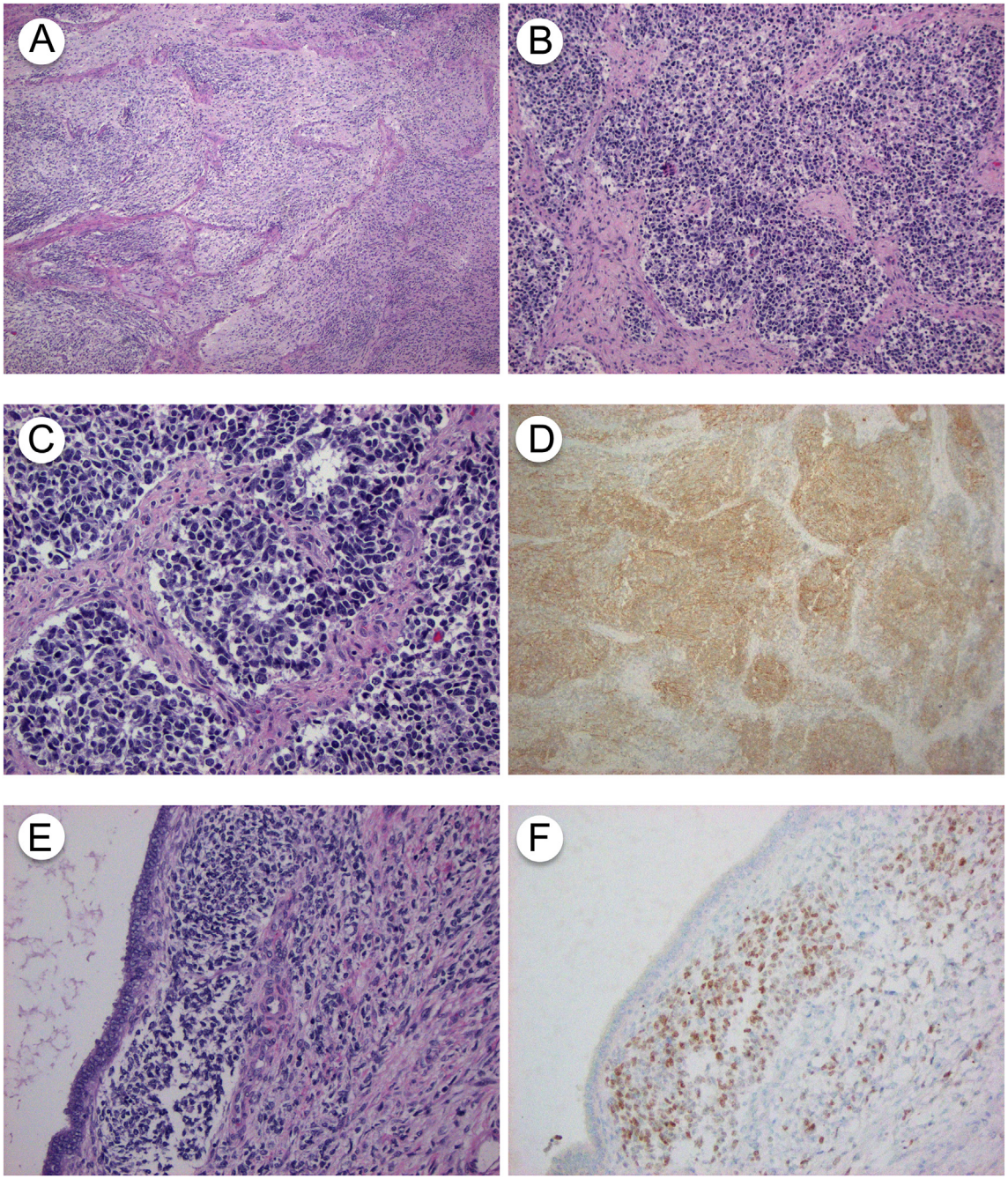

Fig. 1. A. Small blue cell tumor with fibrous septae (H&E 20×). B. Small blue cell tumor with hyperchromatic nuclei and scant cytoplasm (H&E 200×). C. Rosettes of tumor cells denoting neuroectodermal differentiation were focally present (H&E 400×). D. The neuroectodermal tumor cells were positive for synaptophysin. E. Native endometrial epithelium, with a concentration of embryonal rhabdomyosarcoma tumor cells (cambium layer) (H&E 200×). F. Staining for myogenic marker MyoD1 in the embryonal rhabdomyosarcoma. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

a dilation and curettage was concerning for rhabdomyosarcoma. The specimen was sent to another institution for a second opinion, confirming rhabdomyosarcoma, embryonal type. A CT scan revealed a diffusely enlarged uterus with markedly heterogeneous, ill-defined expansion of solid and cystic components of the endometrium extending to endocervix. There was concern for sarcomatous involvement and greater than 90% of myometrial involvement. Para-iliac lymph node prominence could not exclude metastatic disease. The patient was referred to gynecologic oncology and underwent a total abdominal hysterectomy, bilateral salpingectomy, pelvic and para-aortic lymph node dissection, omentectomy, and cystoscopy. Frozen specimen was interpreted as rhabdomyosarcoma. Histologic sections of the uterus and cervix demonstrated a high grade sarcoma, with a predominant neuroectodermal component (95%) and a minor embryonal rhabdomyosarcomatous component (5%), 9.5 cm in size, involving uterus, lower uterine segment and cervix. Extensive lymphovascular invasion was present, and one of three right pelvic lymph nodes was positive for metastasis. The tumor consisted predominantly of sheets of discohesive small cells with scant cytoplasm and ependymal-type rosette formation was seen in focal areas (Fig. 1A–D). On immunohistochemical stains, the tumor cells were positive for CD56 and synaptophysin, and negative for multiple keratin cocktails, GFAP, chromogranin, and TTF1. CD99

showed weak cytoplasmic staining. One area of tumor showed a different morphology, with scattered spindled to rounded tumor cells with dense eosinophilic cytoplasm, which showed immunoreactivity for desmin, myogenin, and MyoD1, supporting an embryonal rhabdomyosarcomatous component (Fig. 1E–F). Of note, the lymph node metastasis morphologically showed neuroectodermal differentiation. The EWS gene translocations were not detected in molecular analysis for small round cell sarcomas, thus the predominant neuroectodermal component favored PNET-central type.

The planned course of chemotherapy for her stage III uterine sarcoma consisted of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VAC/IE) every three weeks, based on a treatment protocol from Grier et al., 2003, a regimen commonly used for Ewing Sarcoma and PNET of bone, with the VAC component used for rhabdomyosarcoma. Vincristine 2 mg/m^2 and cyclophosphamide 1200 mg/m^2 were given on day one, and doxorubicin 37.5 mg/m^2 on days one and two, alternating with Ifosfamide 1800 mg/m^2 and etoposide 100 mg/m^2 days one through five, every 21 days. Pegfilgrastim was also administered. Local control with radiation therapy was planned to occur around week 12 or after 4–8 cycles, as per Grier et al. and NCCN guidelines.

The patient delayed initiation of chemotherapy (65 days from surgery to day 1 of cycle 1), and upon presentation for a port-a-cath placement, was found to have a new tumor palpable in the pelvis. A CT scan (performed 53 days postoperatively) confirmed a soft tissue pelvic mass measuring 5 cm by 3.9 cm in the cul-de-sac suspicious for metastatic disease. Prior to initiation of adjuvant chemotherapy, a Multi Gated Acquisition (MUGA) scan was obtained which demonstrated a normal left ventricle with a 73% ejection fraction. The patient was then given five cycles of VAC/IE, after which a PET CT scan showed no active disease. She received tumor directed radiotherapy which consisted of 4500 cGy in 25 fractions to the whole pelvis, followed by 1500 cGy in three fractions to the vaginal cuff. After completion of radiotherapy, the patient received four more cycles of VAC/IE. Another CT scan obtained at that time showed no evidence of disease, with resolution of the previous pelvic mass. The patient completed a total of 16 cycles of VAC/IE without adverse events. Of note, the patient received IE in the hospital over 5 days, and VAC was given over 2 days outpatient. She also received dactinomycin 1250 μg/m^2 in place of doxorubicin starting with cycle 6 to avoid cardiotoxicity. Six months after completion of therapy, the patient was found disease free on physical exam. A final CT scan (performed approximately 8.5 months after completion of chemotherapy) revealed no evidence of disease in the chest, abdomen or pelvis.

3. Discussion

The phenomenon of two distinct histological types within the same tumor is well known in the gynecologic tract, with carcinosarcomas being a typical example. However, the combination of PNET and ERMS within one tumor is rare. Table 1 summarizes the four cases described in current literature. The patients were in their second, third, and seventh decades of life. Our patient is in her fourth decade of life. Three patients presented with abnormal vaginal bleeding and one with uterine fibroids. Three patients received chemotherapy (one of them neoadjuvant with radiation, another adjuvant, and the other neoadjuvant). Two patients underwent hysterectomy with bilateral salpingo-oophorectomy (one with lymphadenectomy). Two patients are alive with no evidence of disease 18 and 36 months after diagnosis. Two other patients died of disease 7 and 22 months after diagnosis. The two pathological components of the tumors, PNET and ERMS, varied among the patients and were proportionally different from the present case. Molecular analysis did not detect the EWSR1 gene rearrangement in any of the cases, including our patient.

It is evident optimal treatment regimens have not been established for the aforementioned mixed histology tumors in the uterus, or for that

Table 1
Reported cases of uterine tumors with areas of neuroectodermal differentiation and rhabdomyosarcoma.

Author	Age	Clinical Presentation	Diagnosis	*EWSR1* rearrangements	Disease Extent	Therapy	Status
Stolnicu et al	12	Vaginal bleeding	ERMS, component of PNET	Not identified	Corpus	Chemotherapy (etoposide, cisplatin, bleomycin)	NED 36mo
Cate et al	25	Vaginal bleeding	60% ERMS, 40% PNET	Not identified	Corpus and cervix involvement	Chemoradiation (vincristine, adriamycin, cyclophosphamide, ifosfamide/VP-16), TH/BSO	NED 18mo
Euscher et al	62	Uterine fibroids	PNET, focal ERMS	Not identified	FIGO IIIC	Unknown	DOD 22mo
Dundr et al	63	Vaginal bleeding	PNET, minor ERMS	Not identified	FIGO IIC	TH/BSO/L, chemotherapy (ifosfamide, cisplatin)	DOD 7mo after diagnosis (pelvic, mesenterial and peritoneal metastases)

BSO, bilateral salpingo-oophorectomy; *DOD*, died of disease; *L*, lymphadenectomy; *NED*, no evidence of disease; *TH*, total hysterectomy.

Table 2
Clinical features of primary primitive neuroectodermal tumor of the uterine corpus (Shah et al., 2009).

Case	Age	FIGO stage	Surgery	Radiation	Chemo	Follow-up
Hendrickson and Scheithauer	12	IVB	TAH, LSO	Yes	Vincristine Doxorubicin Cyclophosphamide	Pelvic recurrence, 12mo, DOD, 2y
Karseladze et al	16	I	TAH, BSO, omentectomy	Yes	Vincristine Doxorubicin Cyclophosphamide	NED, 4y
Rose et al. Ward et al	17	IIIC	RH, PLND, bilateral ovarian wedge biopsy	Not done	Vincristine Doxorubicin Dactinomycin Cyclophosphamide Etoposide Cisplatin	NED, > 10y
Mittal et al	24	II	TAH, BSO, omentectomy	Not done	Vincristine Doxorubicin Cyclophosphamide Ifosfamide Etoposide	Persistent AWD, 1mo
Blattner et al	26	III	RH, PLND, bilateral ovarian transposition	Yes	Vincristine Doxorubicin Cyclophosphamide Ifosfamide Etoposide	NED, 16mo
Park et al	30	IVB	Not done	Not done	Vincristine Doxorubicin Cyclophosphamide Ifosfamide Etoposide	DOD, 16mo
Varghese et al	43	IIIC	TAH, BSO, PLND	Not done	Vincristine Doxorubicin Cyclophosphamide Etoposide	NED, 2mo

AWD, alive with disease; *BSO*, bilateral salpingo-oophorectomy; *DOD*, died of disease; *LSO*, left salpingo-oophorectomy, *NED*, no evidence of disease; *NR*, not reported; *PALND*, para-aortic lymphadenectomy; *PLND*, pelvic lymphadenectomy; *RH*, radical hysterectomy *SAH*, subtotal abdominal hysterectomy; *TAH*, total abdominal hysterectomy.

matter, even for the individual types—PNETs and rhabdomyosarcomas—in the uterus. This is due to their rarity and poor prognosis despite multimodal therapy. The current guidelines for treating PNET and rhabdomyosarcoma in adults are based on multimodality approaches established by NCCN guidelines for bone cancer and the Intergroup Rhabdomyosarcoma studies, which were investigations performed in younger populations. Since this patient's tumor was composed predominantly of neuroectodermal tissue (95%), the focus of therapy was directed at this aggressive tumor. The randomized trial from which this patient's treatment plan was derived, showed improved five-year event-free survival (69%) with the addition of I/E to the standard regimen for non-metastatic Ewing sarcoma, primitive neuroectodermal tumor of bone, and primitive sarcoma of bone (VAC) (Grier et al., 2003). This was in comparison to the five-year survival of 54% in the standard regimen. Overall survival was also significantly better among patients who received I/E versus those without (72% vs 61%). Shah et al., 2009, also suggested outcomes were improved for patients with PNETs of the uterus after the addition of I/E to standard VAC as opposed to treatment with carboplatin and paclitaxel (Table 2). Treatment for rhabdomyosarcomas alone have also included vincristine, actinomycin D, and cyclophosphamide with or without irradiation as described in the Intergroup Rhabdomyosarcoma Study Group (IRSG) (Raney et al., 2001). Donaldson et al., 2001 in IRS-IV, determined those with localized and unresectable or gross disease (i.e., Group III by IRSG) should receive conventional fractionated radiotherapy with chemotherapy. Thus, since VAC/IE have shown efficacy in PNET and ERMS, this combination of chemotherapy with tumor directed radiotherapy may be an effective approach in the treatment of high grade sarcoma with neuroectodermal and rhabdomyosarcomatous components of the uterus.

Conflict of interests statement

All authors included in this article have no conflict of interests.

Author contribution

LC made significant contribution to the conception, literature review, development, and writing of the manuscript. NL conducted the review of the patient's diagnosis, development of treatment plan, and helped revise the final manuscript. ME was instrumental in reviewing the patient's diagnosis, pathology, and helped revise the final manuscript. RWS provided scientific suggestions and helped revise the final manuscript. All authors approved the final version of the manuscript.

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