Gynecologic Oncology Reports 24 (2018) 65–77

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Uterine corpus tumor with neuroectodermal differentiation and frequent ganglion-like cells in a postmenopausal woman

Taku Homma[a,*], Takehiro Nakao[b], Toshiya Maebayashi[c], Toshiyuki Ishige[a], Hiroyuki Hao[a]

[a] Division of Human Pathology, Department of Pathology and Microbiology, Nihon University School of Medicine, 1-30 Ohyaguchikamimachi, Itabashi, Tokyo 173-0032, Japan
[b] Department of Gynecology, Nihon University School of Medicine, 1-30 Ohyaguchikamimachi, Itabashi, Tokyo 173-0032, Japan
[c] Department of Radiology, Nihon University School of Medicine, 1-30 Ohyaguchikamimachi, Itabashi, Tokyo 173-0032, Japan

ARTICLE INFO

Keywords:
Postmenopausal woman
Uterus
Malignant neoplasm
Neuroectodermal tumor
Ganglion-like cell

1. Introduction

Uterine neuroectodermal tumors (NETs) are uterine neoplasms with a poor prognosis (Elizalde et al., 2016; Euscher et al., 2008; Novo et al., 2015; Prat et al., 2014). They are pathologically classified into 2 groups: 1) those resembling central nervous system (CNS) embryonal tumors (central-type NETs) (Euscher et al., 2008; McLendon et al., 2016; Prat et al., 2014), and 2) those resembling peripheral primitive neuroectodermal tumors/Ewing sarcomas (peripheral-type NETs) (Elizalde et al., 2016; Novo et al., 2015; Prat et al., 2014). Uterine NETs are also associated with endometrial adenocarcinomas, carcinosarcomas, and high-grade sarcomas (Prat et al., 2014). However, the pathogenesis of NETs remains unknown because of the rarity of this type of malignancy (Elizalde et al., 2016; Euscher et al., 2008; Novo et al., 2015; Prat et al., 2014). Here, we present a patient with a rare uterine NET comprising frequent ganglion-like cells.

2. Case report

A 62-year-old Japanese woman was receiving medications for cellulitis and deep vein thrombosis of her right and left lower extremities. During follow-up visits for these ailments, contrast-enhanced computed tomography (CT) revealed a solid uterine tumor exhibiting heterogeneous enhancement (Fig. 1A) with multiple swollen intra-pelvic and para-abdominal aortic lymph nodes. The uterine mass exhibited hypointensity and high intensity on T1-weighted (Fig. 1B) and T2-weighted (Fig. 1C) pelvic magnetic resonance imaging, respectively. As the patient also complained of vaginal bleeding, she was admitted to our hospital for further examinations. Blood tests revealed elevated levels of the following tumor markers: carcinoembryonic antigen, 14.8 ng/mL (normal, < 5 ng/mL); carbohydrate antigen (CA) 19-9, 1300 U/mL (normal, < 40 U/mL); CA125, 68 U/mL (normal, < 35 U/mL); and neuron-specific enolase (NSE), 77.4 ng/mL (normal, < 16.3 ng/mL). Endometrial biopsy was performed, and the specimen was diagnosed as a leiomyosarcoma. There were para-abdominal aortic lymph node metastases (Fig. 1D), resulting hydronephrosis of both kidneys (Fig. 1E). One month later, the patient underwent total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), and partial omentectomy. However, her renal dysfunction did not improve and her general condition gradually worsened to a level that precluded postoperative chemotherapy or radiation therapy. She died of multiple organ failure 2 months after the discovery of the tumor.

3. Pathologic findings

The resected uterus comprised almost entirely of a milky-whitish tumor with necrosis, measuring 15 × 9 cm in size (Fig. 2A). The tumor was histopathologically classified as a highly malignant cellular neoplasm (Fig. 2B) and was mainly composed of small naked neoplastic cells (Fig. 2C). The following additional histological components were noted: atypical ganglion-like cells with a fibrillary background (Fig. 2D), endometrial adenocarcinoma with squamous differentiation (Fig. 2E), rhabdoid-like cells (Fig. 2F), atypical spindle cells resembling skeletal muscular cells, and an atypical cartilaginous component. The

* Corresponding author.
E-mail address: homma.taku@gmail.com (T. Homma).

https://doi.org/10.1016/j.gore.2018.04.003
Received 11 January 2018; Received in revised form 10 April 2018; Accepted 15 April 2018
Available online 17 April 2018

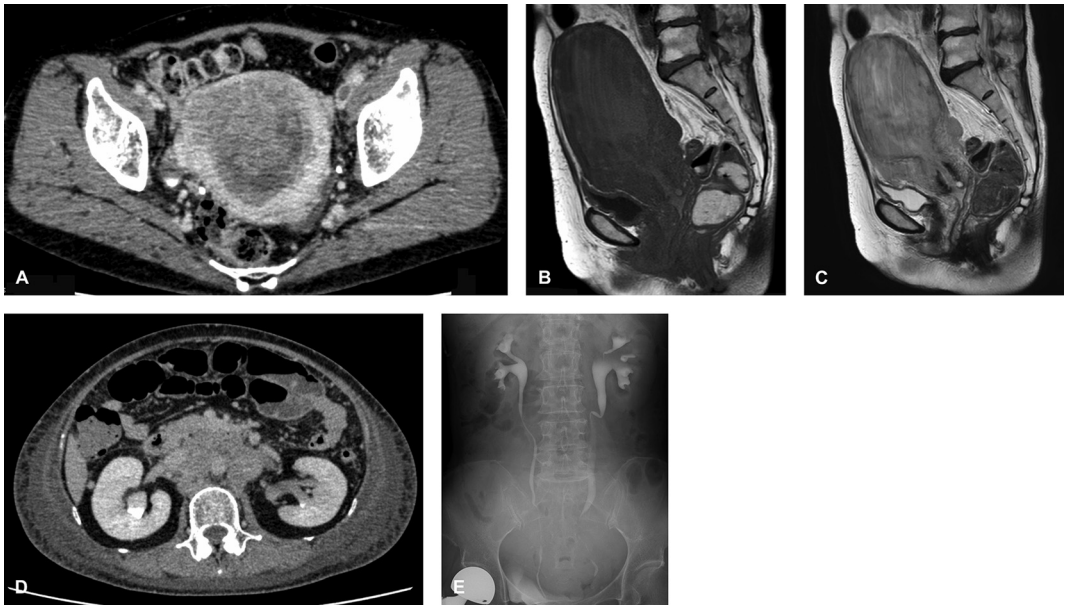

Fig. 1. Radiological features of the uterine tumor and hydronephrosis. Contrast-enhanced computed tomography (CT) showed the large solid uterine tumor with heterogeneous enhancement (A). Magnetic resonance imaging showed the uterine tumor with slightly heterogeneous hypointensity on T1-weighted imaging (B) and hyperintensity on T2-weighted imaging (C). CT showed prominent para-aortic lymph node metastases (D), resulting bilateral hydronephrosis (drip infusion pyelography; E).

component comprising atypical ganglion-like cells with a fibrillary background occupied approximately 92% of the uterine tumor. The neoplasm directly infiltrated the parametrium and had metastasized to both ovaries as well as the major omentum.

Immunohistochemically, the small naked neoplastic cells showed varying degrees of immunoreactivity for vimentin, CD99, CD56, S100, synaptophysin (Fig. 3A), alpha-smooth muscle actin (α-SMA), neurofilament (NF), and chromogranin A (CGA). Both the atypical ganglion-like cells and fine fibrillary background were positive for synaptophysin (Fig. 3B), S100, CD56, CD99, and NF. The atypical ganglion-like cells were also positive for CGA. A few neuronal nuclei (NeuN)-positive atypical ganglion-like cells and glial acidic protein (GFAP)/oligodendrocyte lineage transcription factor 2 (Olig2)-positive fibrillary astrocytes were also detected (Fig. 3C). The endometrial adenocarcinoma with a squamous differentiation component was diffusely positive for cytokeratin (CK) AE1/AE3 (Fig. 3D) and epithelial membrane antigen (EMA), and was focally positive for vimentin. The squamous differentiation component showed p40 immunoreactivity. The rhabdoid-like cells revealed immunoreactivity for vimentin, synaptophysin, CGA, and NF, suggesting small ganglion cells, whereas it was negative for S-100, human melan black-45 (HMB-45), GFAP, Olig2, NeuN, epithelial markers (cytokeratin [CAM5.2], EMA, and pan-CK [AE1/AE3]), and muscular markers (desmin, myogenin, and α-SMA). Nuclear INI1 protein immunoreactivity was preserved in the tumor, including in the rhabdoid-like cells (Fig. 3E). α-SMA-positive atypical spindle cells were intermingled with the epithelial and neuronal components. The MIB-1 labeling index was > 50% in the small round neoplastic cells (Fig. 3F) and approximately 20% in the ganglion-like cells with fibrillary background. No neoplastic cells were positive for melanoma (HMB-45 and melan-A) or skeletal muscle (desmin and myogenin) markers. Based on these features, the pathological diagnosis was uterine NET with frequent ganglion-like cells.

Widespread dissemination of the uterine NET was found on autopsy. The uterine neoplastic cells had metastasized or disseminated to the lungs, liver, appendix vermiformis, urinary bladder, ureters, Douglas' pouch, peritoneum, mesenterium, and lymph nodes (para-aortic, peritracheal, and peri-pancreatic). The metastatic cells were mainly comprised of NET with ganglion-like cells and a fibrillary background; however, no metastases of the carcinomatous or sarcomatous components were noted. Both kidneys showed mild hydronephrosis that was secondary to tumor spreading. No remarkable changes were noted in the heart, alimentary tract, pancreas, gallbladder, thyroid gland, or adrenal glands.

4. Discussion

Uterine NET is rare; only 69 patients with this tumor type have been reported in the English-language literature to date (Table 1). Clinically, uterine NET usually occurs in postmenopausal women and presents with vaginal bleeding (Euscher et al., 2008; Prat et al., 2014). Indeed, 78.7% of the patients with uterine NETs listed in Table 1 experienced vaginal bleeding, and 72.9% of them were over 40 years old. Approximately 50% of these uterine neoplasms are found to have metastasized to the extra-uterine tissues/organs at diagnosis (Prat et al., 2014). The major metastatic sites of uterine NETs are the lymph nodes via the lymphatic system (Daya et al., 1992; Odunsi et al., 2004; Shah et al., 2009; Park et al., 2007; Elizalde et al., 2016) and lungs/liver via the vasculature (Bartosch et al., 2011; Gersell et al., 1989; Hendrickson and Scheithauer, 1986; Shah et al., 2009; Sinkre et al., 2000; Yi et al., 2015), as was also observed in our patient. Although the standard treatment for uterine NETs normally involves surgery (TAH + BSO) with or without chemotherapy and/or radiotherapy (Elizalde et al., 2016), we recommend that lymph node dissection also be performed when possible. However, the necessity of omentectomy in patients with uterine NETs remains unconfirmed because it has been performed in too few patients who underwent TAH + BSO (Table 1).

As for the prognosis of patients with uterine NETs, Euscher et al. (2008) reported a mortality rate of 47% in their largest uterine NET series; furthermore, the 2-year survival rate of postmenopausal patients with uterine NET was reported to be approximately 30% (Elizalde et al., 2016; Prat et al., 2014). Consistent with previous reports, our patient was also a postmenopausal woman with minimal vaginal bleeding, and had a uterine tumor with lymphadenopathy at the time of diagnosis. She died 2 months after the uterine mass was diagnosed despite undergoing TAH, BSO, and omentectomy; however, lymph node dissection was not possible. As such, our patients' uterine NET was consistent

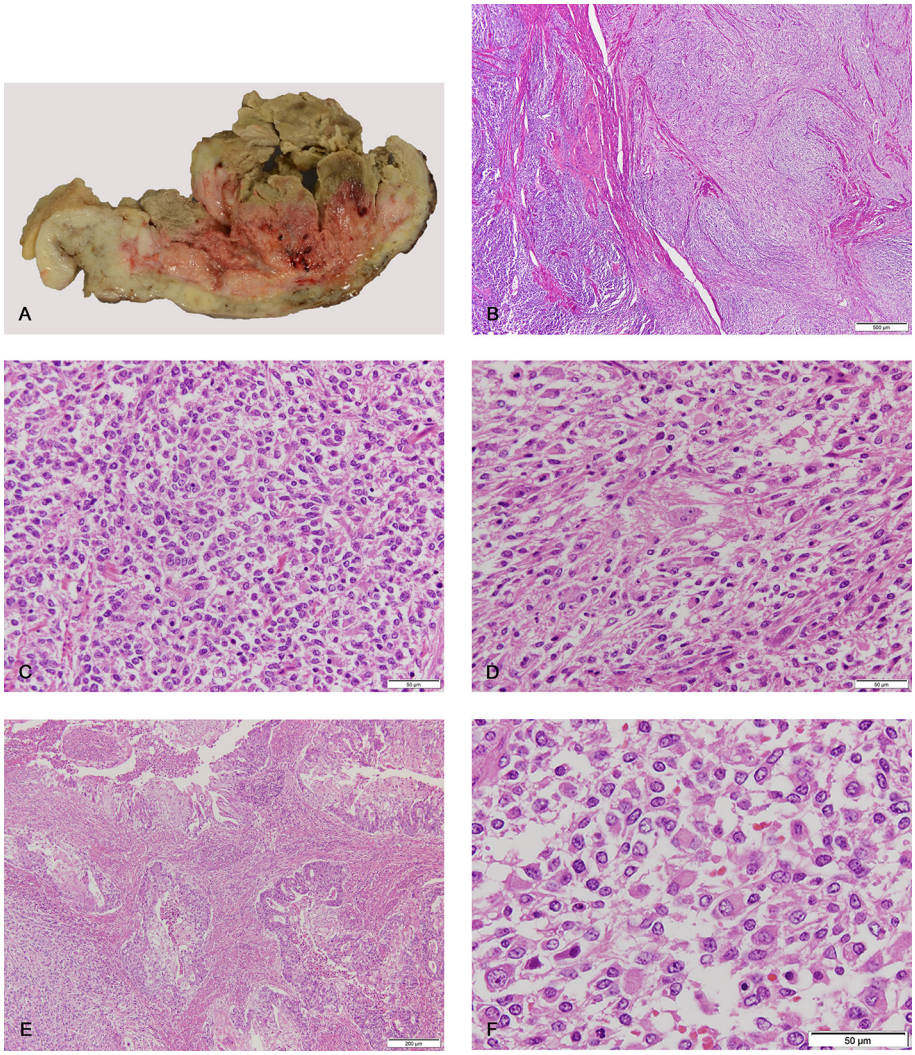

Fig. 2. Macroscopic and histopathological features of the uterine neuroectodermal tumor. The uterus was almost totally occued by the neoplasm (A, sagittal section of the uterus). Histopathologically, the uterine tumor was a highly cellular neoplasm (B, hematoxylin and eosin [H&E]) mainly composed of small round neoplastic cells (C, H&E) and ganglion-like cells with fibrillary background (D, H&E). Moreover, components of adenocarcinoma with squamous metaplasia (E, H&E) and rhabdoid-like cells (F, H&E) were intermingled in the tumor.

with previously reported tumors that had poor prognoses. Of the 69 patients with uterine NETs previously reported in the English-language literature (Table 1), 36% died of their uterine tumors after a mean post-surgical duration of 14.1 months (range, 2–26 months), 50% were free of disease after a maximum follow-up period of 72 months, and 14% were alive with disease after a maximum follow-up period of 38 months. Furthermore, the mean follow-up duration from diagnosis to death in the non-surviving patients was 14.5 ± 8.4 months. Taken together, uterine NETs may not necessarily have as poor a prognosis as previously thought (Elizalde et al., 2016; Euscher et al., 2008; Novo et al., 2015; Prat et al., 2014).

The histopathology of uterine NET is characterized by a monotonous population of small- to medium-sized round neoplastic cells growing in sheets, nests, and/or cords, with or without fibrillary backgrounds and rosette formations (Euscher et al., 2008; Prat et al., 2014). Some central-type NETs have been reported to show pathological features similar to those of medulloblastoma, medulloepithelioma, glioblastoma, and/or ependymoma (Chiang et al., 2017). Uterine NETs may also include other histologic elements, such as endometrial adenocarcinoma, carcinosarcoma, and/or high-grade sarcoma (Euscher et al., 2008; Prat et al., 2014). Our patient's uterine NET had heterologous carcinosarcoma as a minor component, which has also been described in previous reports (Euscher et al., 2008; Prat et al., 2014). However, frequent ganglion-like cells with a fibrillary background were detected as a major component in our patient, whose NET resembled a ganglioneuroblastoma (McLendon et al., 2016). To the best of our knowledge, this uterine NET subtype is extremely rare, although a patient with a uterine NET comprising foci resembling ganglioneuroma was reported by Hendrickson and Scheithauer (1986).

Immunohistochemical analyses of our patient's tumor showed that the NET component expressed CD99, synaptophysin, NSE, and NF. Although rare, GFAP immunoreactivity is characteristic of CNS-type NETs (Prat et al., 2014). In addition to neuronal markers such as synaptophysin and NF, our patient's tumor also expressed the glial markers GFAP and Olig2. Moreover, an α-SMA immunoreactive spindle cell component and both a vimentin and epithelial marker immunoreactive component were detected, suggesting leiomyosarcoma and endometrial adenocarcinoma, respectively, intermingled as minor components within the neuroectodermal component. *EWSR1* rearrangement has been recently reported as a characteristic genetic finding of peripheral-type uterine NETs (Novo et al., 2015); however, we were unable to perform genetic analysis to test for *EWSR1* rearrangement.

Surgery (TAH + BSO) with or without chemotherapy and/or radiotherapy is the standard treatment for uterine NETs (Elizalde et al.,

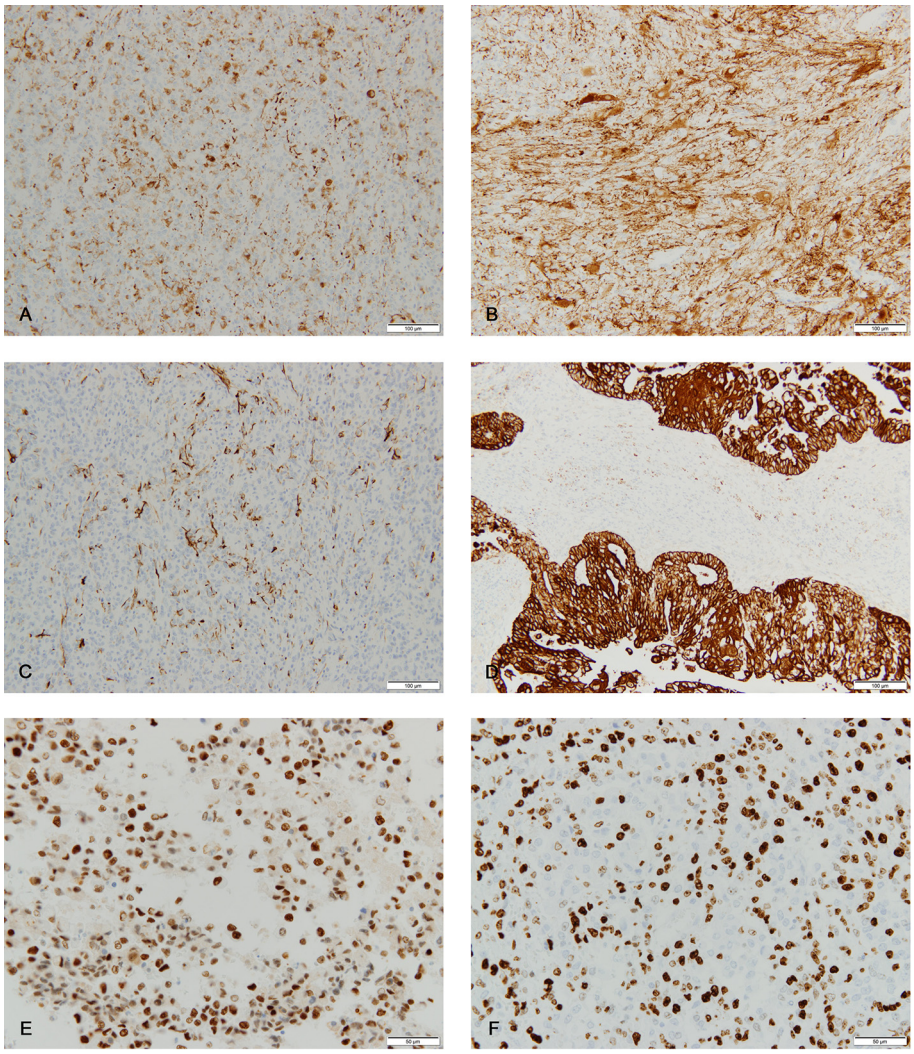

Fig. 3. Immunohistochemical features of the uterine neuroectodermal tumor. Small round neoplastic cells (A) and ganglion-like cells with fibrillary background (B) showed immunoreactivity for synaptophysin. Furthermore, glial acidic protein (GFAP)-positive astrocytes were also intermingled (C, GFAP), suggesting a central-type neuroectodermal tumor. The adenocarcinoma component was immunopositive for cytokeratin AE1/AE3 (D, AE1/AE3). Nuclear INI1 protein expression was preserved in the tumor, including in the rhabdoid-like cells (E, INI1). The tumor showed a high MIB-1 labeling index at the area of small round neoplastic cells (F, Ki-67).

2016). As described in Table 1, approximately 92% of patients with uterine NETs underwent surgery, while 72% received chemotherapy and only 36% received radiotherapy. Therapeutic treatment regimens for gynecologic NETs might be selected according to their subtypes, such as NETs resembling medulloblastoma and Ewing sarcoma/peripheral primitive NETs (Chiang et al., 2017). Furthermore, Novo et al. (2015) recently reported a patient with uterine NET treated with surgery and adjuvant chemotherapy using cisplatin, etoposide, and bevacizumab; their patient experienced no recurrence for 48 months. Although our patient was treated with TAH + BSO, she died of multiple organ failure 1 month after surgery owing to the metastasis of multiple tumors that comprised mainly of NET resembling ganglioneuroblastoma (according to autopsy results). In retrospect, treating the ganglioneuroblastoma with total tumor resection followed by chemoradiotherapy with temozolomide should have been considered for our patient, as it was previously reported that 2 patients with cerebral ganglioneuroblastoma treated with this regimen were free of tumor recurrence or progression after 12 and 14 months of follow-up, respectively (Schipper et al., 2012). Interestingly, as shown in Table 1, 42% of the patients with uterine NETs who underwent radiotherapy died of their disease, whereas 32% were free of disease. Although surgery with or without chemotherapy and/or radiotherapy is the standard treatment for uterine NETs (Elizalde et al., 2016), postoperative radiotherapy for such patients might need to be reconsidered. Nevertheless, the accumulation of additional patient data and detailed clinical and pathological analyses are required to devise better treatment modalities for uterine tumors.

Although the pathogenesis of primary uterine NETs remains poorly understood, several possibilities have been suggested, including 1) that they originate from the implantation of aborted fetal tissue in the uterus (Chiang et al., 2017; Fukunaga et al., 1996; Rose et al., 1987; Siddon and Hui, 2010; Young et al., 1981), 2) that they originate from abnormal migrated neural crest cells in the uterus (Chiang et al., 2017; Fukunaga et al., 1996; Rose et al., 1987), and 3) that they are of Müllerian origin (Chiang et al., 2017; Daya et al., 1992; Fukunaga et al., 1996; Gersell et al., 1989; Young et al., 1981). Liao and Choi (1986) reported that malignant mixed Müllerian tumors showed GFAP immunoreactivity; our patient had heterologous carcinosarcoma intermingled within the uterine NET as the minor component. Based on our clinicopathological findings, our patient's tumor appeared to have been of Müllerian origin.

In conclusion, uterine NETs with frequent ganglion-like cells such as the tumor diagnosed in our patient are extremely rare; their pathogenesis is poorly understood and afflicted patients have poor prognoses. Therefore, the accumulation of clinicopathological data from additional patients is needed to establish more effective treatment modalities for patients with these types of tumors.

Author contributions

Taku Homma: Pathological examination, manuscript preparation.
Takehiro Nakao: Patient care, data collection.

Table 1
Clinicopathological feature of 69 uterine neuroectodermal tumor cases.

Case no	Age (y.o)	Symptom	FIGO stage	Surgery	Postoperative therapy		Prognosis
					CT	RT	Alive/died
1	58	Vaginal bleeding Palpable mass	IIIc	+ (unknown detail)	−	−	DOD
2	31	Back paine	IV	−	+ (unknown regimen)	+	DOD
3	72	Vaginal bleeding	Ia	ND	ND	ND	DOD
4	48	ND	IIIc	ND	ND	ND	ND
5	81	Vaginal bleeding	ND	ND	ND	ND	ND
6	66	Pelvic mass	IIIc	+ (unknown detail)	Letrozole	−	NED
7	53	Vaginal bleeding	ND	ND	ND	ND	DOD
8	51	Vaginal bleeding	ND	ND	ND	ND	DOD
9	31	Vaginal bleeding	ND	ND	ND	ND	DOD
10	64	Endocervical polyp	IIb	TAH, BSO	+ (unknown regimen)	+	NED
11	64	Vaginal bleeding Pain	ND	ND	ND	ND	ND
12	69	Vaginal bleeding	IV	ND	ND	ND	ND
13	62	Uterine fibroids	IIIc	ND	ND	ND	DOD
14	55	Vaginal spotting	Ib	TAH, BSO	+ (unknown regimen)	−	NED
15	52	ND	IV	ND	ND	ND	NED
16	58	Vaginal pressure	IV	−	+ (unknown regimen)	−	NED
17	57	ND	IIIc	−	+ (unknown regimen)	−	NED
18	12	Vaginal bleeding	IV	TAH, LSO	Cyclophosphamide Doxorubicin Adriamycin Dactinomycin Vincristine	−	DOD
19	57	Vaginal bleeding	IIIc	TAH, BSO, PALND	Cisplatin Vinblastine Bleomycin	+	DOD
20	17	Vaginal bleeding Pelvic mass	IIIc	TAH, PLND, left uretectomy, bilateal ovarian wedge biopsy	Vincristine Cisplatin Daunorubicin Dactinomycin Cyclophosphamide Etoposide	−	NED
21	67	Vaginal bleeding Enlarged uterus	IIIc	STAH, BSO	Cisplatin Doxorubicin Carboplatin 5-FU	+	DOD
22	68	Vaginal bleeding	IVb	TAH, BSO, PLND	−	+	DOD
23	69	Vaginal bleeding	I	TAH, BSO, PLND	−	+	NED
24	68	Vaginal bleeding	I	TAH, BSO	−	−	NED
25	72	Vaginal bleeding	Ib	TAH, BSO	−	−	DOD
26	54	Vaginal bleeding	IIIa	TAH, BSO, PLND	Cyclophosphamide Cisplatin adriamycin 5-FU	−	AWD

(*continued on next page*)

Table 1 (*continued*)

Case no	Age (y.o)	Symptom	FIGO stage	Surgery	Postoperative therapy		Prognosis
					CT	RT	Alive/died
27	78	Vaginal bleeding	Ib	TAH, BSO, PLND	−	−	NED
28	62	Vaginal bleeding	Ib	TAH, BSO	Vincristine Cyclophosphamide Cisplatin tenisopid	+	DOD
29	36	Enlarged uterus	Ib	RH, BSO, PLND	−	+	ND
30	47	ND	IIb	TAH, BSO, LND	+ (unknown regimen)	+	DOD
31	67	ND	IIIc	TAH, BSO, LND	+ (unknown regimen)	−	DOD
32	71	ND	IIIc	TAH, BSO, LND	+ (unknown regimen)	−	DOD
33	16	Vaginal bleeding	Ic	TAH, BSO, omentectomy	Vincristine Cyclophosphamide Doxorubicin	+	NED
34	48	Vaginal bleeding Pelvic mass	IIIc	TAH, BSO	−	−	NED
35	68	Vaginal bleeding	I	TAH, BSO	−	−	NED
36	66	Vaginal bleeding	Ia	TAH, BSO, omentectomy PLND, PALND	ND	−	NED
37	65	Vaginal bleeding	IIIc	TAH, BSO, PLND, PALND, omentectomy, upper vaginectomy	Cisplatin Adriamycin Etoposide	+	AWD
38	15	Abdominal pein Pelvic mass	I	TAH, PLND	Carboplatin Etoposide	−	NED
39	43	Vaginal bleeding Uterine enlargement	IIIc	TAH, BSO, PLND	Cytoxan Adriamycin Vincristine Etoposide	−	NED
40	58	Vaginal bleeding Abdominal pain	IV	TAH, BSO, right PLND, segmental enterectomy, total coloectomy	Carboplatin Paclitaxel	−	DOS
41	26	Vaginal bleeding	IV	TAH, BSO, PLND, omentectomy	Cisplatin Etoposide Avastin	−	NED
42	50	Abdominopelvic pain	ND	TAH, BSO, omentectomy	Carboplatin Etoposide	−	NED
43	63	Vaginal bleeding	IIIc	TAH, BSO, LND	Ifosfamide Cisplatin	−	DOD
44	80	Abdominal pain	Ib	TAH, BSO, LND	−	+	AWD
45	79	Vaginal bleeding	Ib	TAH, BSO, LND	−	−	NED
46	78	Vaginal bleeding	IIIa	TAH, BSO, LND	−	−	NED
47	32	Abdominal pain	IIIa	TAH, BSO, PLND, PALND, omentectomy, appendectomy	Cisplatin Ifosfamide Adriamycin Vincristine	+	AWD
48	66	Vaginal bleeding	IVb	TAH, BSO	Cisplatin	+	DOD

(*continued on next page*)

Table 1 (*continued*)

Case no	Age (y.o)	Symptom	FIGO stage	Surgery	Postoperative therapy		Prognosis
					CT	RT	Alive/died
		Pelvic pain			Cyclophosphamide Doxorubicin Dexamethasone		
49	32	Vaginal bleeding Abdominal pain	IV	TAH, BSO, PLND	Holoxan Mens Cisplatin Paclitaxel Carboplatin	−	AWD
50	29	Abdominal swelling and pain	IVb	STAH, BSO, PLND, omentectomy, appendectomy, metastatic nodule resection	Docetaxel Carboplatin Vincristine Adriamycin Cyclophosphamide Ifosfamide Etoposide	+	AWD
51	63	Constipation	ND	TAH, BSO	Cyclophosphamide Vincristine Adriamycin	−	NED
52	25	Vaginal bleeding	ND	TAH, BSO	Vincristine Adriamycin Cyclophosphamide Ifosfamide Etoposide	+	NED
53	12	Vaginal bleeding	ND	−	Etoposide Cisplatin Bleomycin	−	NED
54	56	Vaginal bleeding	Ib	TAH, BSO, PLND	Ifosfamide Etoposide Cisplatin	−	NED
55	59	vaginal bleeding	IIIc	TAH, BSO, PLND, PALND, omentectomy	Carboplatin Paclitxel Cisplatin	+	AWD
56	30	Vaginal bleeding	IVb	−	Doxorubicin Ifosfamide Vincristine Carboplatin Etopiside Docetaxel Irinotecan Celecoxib	+	DOD
57	22	Vaginal bleeding	I	TAH, BSO, PLND, PALND, omentectomy	Cisplatin Doxorubicin	− −	NED
58	24	Adnexal mass Fever Lower abdominal pain	II	TAH, BSO, omentectomy	Vincristine Adriamycin Cyclophosphamide Ifosfamide Etoposide	−	AWD

(*continued on next page*)

Table 1 (*continued*)

Case no	Age (y.o)	Symptom	FIGO stage	Surgery	Postoperative therapy		Prognosis
					CT	RT	Alive/died
59	26	Pelvic mass (found at cesarean section)	III	Modified TAH, PLND, bilateral ovarian transposition	Vincristine Doxorubicin Cytoxan Mensa ifosfamide Etoposide	+	NED
60	50	Vaginal bleeding	IIIc	TAH, BSO, PLND, omentectomy	+ (unknown regimen)	+	NED
61	51	Vaginal bleeding	III	TAH, BSO	+ (unknown regimen)	−	ND
62	50	Vaginal bleeding	III	TAH, BSO	−	−	ND
63	31	Vaginal bleeding	III	TAH, BSO	−	−	ND
64	26	Vaginal bleeding	I	TAH, BSO	−	−	ND
65	64	ND	III	TAH, BSO	+ (unknown regimen)	−	ND
66	ND	ND	ND	TAH, BSO	ND	ND	ND
67	60	Vaginal bleeding Abdominal pein	IV	TAH, BSO, PALND	Carboplatin Etoposide	−	ND
68	31	Vaginal bleeding Abdominal pain	IIIc	+ (unknown detail)	Cisplatin Etoposide	+	NED
69	62	Vaginal bleeding	IVb	TAH, BSO, omentectomy	−	−	DOD

Case no	Prognosis	Pathological findings					Reference
	Follow-up (month(s))	Tumor size (cm)	Component			Metastasis	
			Major component	Minor component	Ganglion cells		
1	2	ND	NET	−	−	ND	Euscher et al. (2008)
2	20	ND	NET	−	−	ND	Euscher et al. (2008)
3	11	ND	NET	−	−	ND	Euscher et al. (2008)
4	ND	ND	EM carcinoma	NET	−	ND	Euscher et al. (2008)
5	ND	ND	NET	–	−	ND	Euscher et al. (2008)
6	41	ND	NET	High grade sarcoma	−	ND	Euscher et al. (2008)
7	22	ND	NET	−	−	ND	Euscher et al. (2008)
8	12	ND	NET	−	−	ND	Euscher et al. (2008)
9	26	ND	NET	EM hyperplasia with atypia	−	ND	Euscher et al. (2008)
10	36	ND	NET	−	−	ND	Euscher et al. (2008)
11	ND	ND	Adenosarcoma	NET	−	ND	Euscher et al. (2008)
12	ND	ND	NET	Rhabdomyosarc-oma	−	ND	Euscher et al. (2008)
13	22	ND	NET	−	−	ND	Euscher et al. (2008)
14	38	ND	NET	−	−	ND	Euscher et al. (2008)

(*continued on next page*)

Table 1 (*continued*)

Case no	Prognosis	Pathological findings					Reference
	Follow-up (month(s))	Tumor size (cm)	Component			Metastasis	
			Major component	Minor component	Ganglion cells		
15	6	ND	NET	–	–	ND	Euscher et al. (2008)
16	6	ND	Carcinosarcoma	NET	–	ND	Euscher et al. (2008)
17	35	ND	Carcinosarcoma	NET	+	ND	Euscher et al. (2008)
18	25	ND	NET	–	+	Lung	Hendrickson and Scheithauer (1986)
19	24	ND	NET	–	+	Lung Retroperitoneum	Hendrickson and Scheithauer (1986)
20	10	ND	NET	–	+	–	Rose et al. (1987)
21	6	ND	NET	–	ND	–	Daya et al. (1992)
22	12	7.5	NET	–	+	LNs (supraclavicular)	Daya et al. (1992)
23	72	2	NET	EM stromal sarcoma	ND	–	Daya et al. (1992)
24	60	2	NET	EM carcinoma	ND	–	Daya et al. (1992)
25	8	6.5 × 3.5 × 3.0	NET	–	–	ND	Molyneux et al. (1992)
26	3	8.5 × 8.0 × 6.5	NET	Carcinosarcoma	–	–	Fukunaga et al. (1996)
27	9	6	NET	Cartilaginous component	–	–	Fraggetta et al. (1997)
28	18	4 × 2	NET	–	–	Terminal ileum Cecum	Sørensen et al. (1998)
29	ND	11	NET	–	–	–	Taïeb et al. (1998)
30	18	7.8	NET	Endometrioid carcinoma		Pelvis	Sinkre et al. (2000)
31	3	4.5	NET	EM carcinoma		Peritoneum	Sinkre et al. (2000)
32	4	6	NET	EM carcinoma		Lung Peritoneum	Sinkre et al. (2000)
33	48	ND	NET	–	–	–	Karseladze et al. (2001)

(*continued on next page*)

Table 1 (*continued*)

Case no	Prognosis	Pathological findings					Reference
	Follow-up (month(s))	Tumor size (cm)	Component			Metastasis	
			Major component	Minor component	Ganglion cells		
34	6	ND	NET	EM carcinoma	–	–	Ng et al. (2002)
35	10	ND	NET	–	–	ND	Venizelos et al. (2004)
36	24	4 × 3.5 × 2	NET	–	–	–	Odunsi et al. (2004)
37	12	7	NET	–	–	Vagina Obturator lymph nodes	Odunsi et al. (2004)
38	12	6 × 7	NET	–	–	–	Peres et al. (2005)
39	2	13.3	NET	–	–	Left adnexa	Varghese et al. (2006)
40	11	12	NET	EM carcinoma	–	Lung	Bartosch et al. (2011)
41	48	5.8 × 4.2	NET	–	–	–	Novo et al. (2015)
42	16	15	NET	–	–	–	Dizon et al. (2013)
43	7	5.0 × 4.5 × 3.0	NET	Rhabdomyosarcoma	–	Pelvis Mesenterium Peritoneum	Dundr et al. (2010)
44	6	5.0 × 4.0 × 3.0	NET	EM carcinoma	–	Intraabdominal metastasis	Dundr et al. (2010)
45	29	4.5 × 3.0 × 3.0	NET	EM carcinoma	–	–	Dundr et al. (2010)
46	8	7.5 × 7.0 × 5.5	NET	–	–	–	Dundr et al. (2010)
47	38	3	NET	–	–	–	Celik et al. (2009)
48	24	6 × 4	Carcinosarcoma	NET		Lung LNs (left supraclavicula, right axillary)	Gersell et al. (1989)
49	24	9 × 6.5	NET	–	–	Peritoneal seeding	Aminimoghaddam et al. (2015)
50	18	3.0 × 2.5 × 2.0	NET	–	–	Liver	Yi et al. (2015)

(*continued on next page*)

Table 1 (*continued*)

Case no	Prognosis	Pathological findings					Reference
	Follow-up (month(s))	Tumor size (cm)	Component			Metastasis	
			Major component	Minor component	Ganglion cells		
51	24	13.0 × 10.0	NET	–	–	–	Shimada et al. (2014)
52	18	7.6 × 4.0 × 5.9	Rhabdomyosarcoma	NET	–	Vagina	Cate et al. (2013)
53	36	12	Rhabdomyosarcoma	NET		–	Stolnicu et al. (2012)
54	41	4.0 × 3.5 × 2.0	NET	–	–	–	Ren et al. (2011)
55	12	1.1	NET	–	–	Lymph nodes (mediastinal, paraaortic) Vaginal cuff pelvic wall Lung liver	Shah et al. (2009)
56	16	18 × 20 × 21	NET	–	–	Lymph nodes (paraaortic, pelvic) Omentum Thoracolumbar spine Right humerus Left lower rib Left femur	Park et al. (2007)
57	10	7.6 × 6.1	NET	–	–	–	Akbayir et al. (2008)
58	1	9 × 10	NET	–	–	Residual tumor	Mittal et al. (2007)
59	16	7.0 × 5.0	NET	–	–	–	Blattner et al. (2007)
60	6	10 × 8	NET	Adenosarcoma	–	Vaginal vault	Bhardwaj et al. (2010)
61	ND	ND	NET	EM carcinoma	–	ND	Chiang et al. (2017)

(*continued on next page*)

Table 1 (*continued*)

Case no	Prognosis	Pathological findings				Metastasis	Reference
	Follow-up (month(s))	Tumor size (cm)	Component				
			Major component	Minor component	Ganglion cells		
62	ND	ND	NET	EM carcinoma	–	ND	Chiang et al. (2017)
63	ND	ND	NET	Carcinosarcoma	–	ND	Chiang et al. (2017)
64	ND	ND	NET	–	–	ND	Chiang et al. (2017)
65	ND	ND	NET	–	–	ND	Chiang et al. (2017)
66	ND	ND	NET	–	–	ND	Chiang et al. (2017)
67	ND	10 × 13	NET	–	–	Pelvis LNs (para-aortic, retropetitoneal)	Elizalde et al. (2016)
68	24	ND	NET	–	–	/	Tsai et al. (2012)
69	2	15 × 9	NET	Carcinosarcoma	+	Peritoneum Liver Appendix vermiformis	present case

y.o., years old; FIGO, International Federation of Gynecology and Obstetrics; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oopholectomy; PLND, pelvic lymph node dissection; PALND, paraaortic lymph node dissection; CT, chemotherapy; RT, radiation therapy; DOD, die of disease; NED, no evidence of disease; AWD, alive with disease; ND, no data; NET, neuroectodermal tumor; EM, emdometrial

Toshiya Maebayashi: Radiology imaging examination.
Toshiyuki Ishige: Pathological examination.
Hiroyuki Hao: Supervisor, manuscript preparation.

Funding disclosure

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

The authors thank Mrs. Yukari Hirotani of the Department of Pathology, Nihon UniversitySchool of Medicine for her excellent technical assistance.

References

Akbayir, O., Güngördük, K., Rafioğlu, G., Gülkilik, A., Yavuz, E., Tekirdağ, A.I., Odabaş, E., 2008. Primary primitive neuroectodermal tumor of the uterus: a case report. Arch. Gynecol. Obstet. 277, 345–348.

Aminimoghaddam, S., Seifirad, S., Abbasi Dezfouli, G., Abbasi, N., Zare Mahrjardi, A., Razavi, S.M., Mahmoudzadeh, F., 2015. Uterine primitive neuroectodermal tumor. Arch. Iran. Med. 18, 260–262.

Bartosch, C., Vieira, J., Teixeira, M.R., Lopes, J.M., 2011. Endometrial endometrioid adenocarcinoma associated with primitive neuroectodermal tumour of the uterus: a poor prognostic subtype of uterine tumours. Med. Oncol. 28, 1488–1494.

Bhardwaj, M., Batrani, M., Chawla, I., Malik, R., 2010. Uterine primitive neuroectodermal tumor with adenosarcoma: a case report. J. Med. Case Rep. 28, 195.

Blattner, J.M., Gable, P., Quigley, M.M., McHale, M.T., 2007. Primitive neuroectodermal tumor of the uterus. Gynecol. Oncol. 106, 419–422.

Cate, F., Bridge, J.A., Crispens, M.A., Keedy, V.L., Troutman, A., Coffin, C.M., Fadare, O., 2013. Composite uterine neoplasm with embryonal rhabdomyosarcoma and primitive neuroectodermal tumor components: rhandomyosarcoma with divergent differentiation, variant of primitive neuroectodermal tumor, or unique entity? Hum. Pathol. 44, 656–663.

Celik, H., Gurates, B., Karaoğlu, A., Yavuz, A., Dagli, F., Ozercan, R., 2009. Uterine primitive neuroectodermal tumor: a case report. Arch. Gynecol. Obstet. 279, 259–261.

Chiang, S., Snuderl, M., Kojiro-Sanada, S., Quer Pi-Sunyer, A., Daya, D., Hayashi, T., Bosincu, L., Ogawa, F., Rosenberg, A.E., Horn, L.C., Wang, L., Iafrate, A.J., Oliva, E., 2017. Primitive neuroectodermal tumors of the female genital tract: a morphologic, immunohistochemical, and molecular study of 19 cases. Am. J. Surg. Pathol. 41, 761–772.

Daya, D., Lukka, H., Clement, P.B., 1992. Primitive neuroectodermal tumors of the uterus: a report of four cases. Hum. Pathol. 23, 1120–1129.

Dizon, A.M., Kilgore, L.C., Grindstaff, A., Winkler, M., Kimball, K.J., 2013. High grade primitive neuroectodermal tumor of the uterus: a case report. Gynecol. Oncol. Case Rep. 19, 10–12.

Dundr, P., Fischerová, D., Povýšil, C., Berková, A., Bauerová, L., Cibula, D., 2010. Uterine tumors with neuroectodermal differentiation. A case report of 4 cases. Pathol. Oncol. Res. 16, 601–608.

Elizalde, C.R., Yagüe, A., Fernandez, J., Dieste, P., Puente, M.J., Hernandez, J., 2016. Primitive neuroectodermal tumor of the uterus. Gynecol. Oncol. Rep. 18, 25–28.

Euscher, E.D., Deavers, M.T., Lopez-Terrada, D., Lazar, A.J., Silva, E.G., Malpica, A., 2008. Uterine tumors with neuroectodermal differentiation – a series of 17 cases and review of the literature. Am. J. Surg. Pathol. 32, 219–228.

Fraggetta, F., Magro, G., Vasquez, E., 1997. Primitive neuroectodermal tumour of the uterus with focal cartilaginous differentiation. Histopathology 30, 483–485.

Fukunaga, M., Nomura, K., Endo, Y., Ushigome, S., Aizawa, S., 1996. Carcinosarcoma of the uterus with extensive neuroectodermal differentiation. Histopathology 29, 565–570.

Gersell, D.J., Duncan, D.A., Fulling, K.H., 1989. Malignant mixed müllerian tumor of the uterus with neuroectodermal differentiation. Int. J. Gynecol. Pathol. 8, 169–178.

Hendrickson, M.R., Scheithauer, B.W., 1986. Primitive neuroectodermal tumor of the endometrium: report of two cases, one with electron microscopic observations. Int. J. Gynecol. Pathol. 5, 249–259.

Karseladze, A.I., Filipova, N.A., Navarro, S., Llombart-Bosch, A., 2001. Primitive neuroectodermal tumor of the uterus: A case report. J. Reprod. Med. 46, 845–848.

Liao, S.Y., Choi, B.H., 1986. Expression of glial fibrillary acidic protein by neoplastic cells of müllerian origin. Virchows Archiv. B 52, 185–193.

McLendon, R., Ng, H.K., Judkins, A.R., Huang, A., Eberhart, C.G., Kool, M., Fuller, G.N., Pfister, S., Sarkar, C., 2016. Other CNS embryonal tumours. In: Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavenee, W.K. (Eds.), WHO Classification of Tumours of the Central Nervous System. International Agency for Research on Cancer, Lyon, pp. 206–208.

Mittal, S., Sumana, G., Gupta, M., Gupta, B., 2007. Primitive neuroectodermal tumor of

the uterus: a case report. Int. J. Gynecol. Cancer 17, 524–527.
Molyneux, A.J., Deen, S., Sundaresan, V., 1992. Primitive neuroectodermal tumour of the uterus. Histopathology 21, 584–585.
Ng, S.B., Sirrampalam, K., Chuah, K.L., 2002. Primitive neuroectodermal tumours of the uterus: a case report with cytological correlation and review of the literature. Pathology 34, 455–461.
Novo, J., Bitterman, P., Guirguis, A., 2015. Central-type primitive neuroectodermal tumor of the uterus: case report of remission of stage IV disease using adjuvant cisplatin/etoposide/bevacizumab chemotherapy and review of the literature. Gynecol. Oncol. Rep. 14, 26–30.
Odunsi, K., Olatinwo, M., Collins, Y., Withiam-Leitch, M., Lele, S., Spiegel, G.W., 2004. Primary primitive neuroectodermal tumor of the uterus: a report of two cases and review of the literature. Gynecol. Oncol. 92, 689–696.
Park, J.Y., Lee, S., Kang, H.J., Kim, H.S., Park, S.Y., 2007. Primary Ewing's sarcoma-primitive neuroectodermal tumor of the uterus: a case report and literature review. Gynecol. Oncol. 106, 427–432.
Peres, E., Mattoo, T.K., Poulik, J., Warrier, I., 2005. Primitive neuroectodermal tumor (PNET) of the uterus in a renal allograft patient: a case report. Pediatr. Blood Cancer 44, 283–285.
Prat, J., Palacios, J., Oliva, E., Wells, M., 2014. Miscellaneous tumours. In: Kurman, R.J., Carcangiu, M.L., Herrington, C.S., Young, R.H. (Eds.), WHO Classification of Tumours of Female Reproductive Organs. Lyon, International Agency for Research on Cancer, pp. 151–152.
Ren, Y.L., Tang, X.Y., Li, T., 2011. Ewing sarcoma-primitive neuroectodermal tumor of the uterus: a clinicopathologic, immunohistochemical and ultrastructural study of one case. Arch. Gynecol. Obstet. 283, 1139–1143.
Rose, P.G., O'Toole, R.V., Keyhani-Rofagha, S., Qualman, S., Boutselis, J.G., 1987. Malignant peripheral primitive neuroectodermal tumor of the uterus. J. Surg. Oncol. 35, 165–169.
Schipper, M.H., van Duinen, S.G., Taphoorn, M.J., Kloet, A., Walchenbach, R., Wiggenraad, R.G., Vecht, C.J., 2012. Cerebral ganglioneuroblastoma of adult onset: two patients and a review of the literature. Clin. Neurol. Neurosurg. 114, 529–534.
Shah, J.P., Jelsema, J., Bryant, C.S., Ali-Fehmi, R., Malone, J.M., 2009. Carboplatin and paclitaxel adjuvant chemotherapy in primitive neuroectodermal tumor of the uterine corpus. Am. J. Obstet. Gynecol. 200, e6–e9.
Shimada, C., Todo, Y., Okamoto, K., Akashi, D., Yamashiro, K., Hasegawa, T., 2014. Central type primitive neuroectodermal tumor/neuroblastoma of the uterus: a case report. J. Obstet. Gynaecol. Res. 40, 2118–2122.
Siddon, A., Hui, P., 2010. Glial heterotopia of the uterine cervix: DNA genotyping confirmation of its fetal origin. Int. J. Gynecol. Pathol. 29, 394–397.
Sinkre, P., Alores-Saavedra, J., Miller, D.S., Copeland, L.J., Hameed, A., 2000. Endometrial endometrioid carcinomas associated with Ewing sarcoma/peripheral primitive neuroectodermal tumor. Int. J. Gynecol. Pathol. 19, 127–132.
Sørensen, J.B., Schultze, H.R., Madsen, E.L., Hølund, B., 1998. Primitive neuroectodermal tumor (PNET) of the uterine cavity. Eur. J. Obstet. Gynecol. Reprod. Biol. 76, 181–184.
Stolnicu, S., Goyenaga, P., Hincu, M., Marian, C., Murillo, R., Nogales, F.F., 2012. Embryonal (botryoides) rhabdomyosarcoma of the uterus harboring a primitive neuroectodermal tumor component. Int. J. Gynecol. Pathol. 31, 387–389.
Taïeb, S., Cabaret, V., Bonodeau, F., Leblanc, E., Besson, P., 1998. MRI of primitive neuroectodermal tumor of the uterus. J. Comput. Assist. Tomogr. 22, 896–898.
Varghese, L., Amesen, M., Boente, M., 2006. Primitive neuroectodermal tumor of the uterus: a case report and review of literature. Int. J. Gynecol. Pathol. 25, 373–377.
Venizelos, I.D., Zafrakas, M., Dragoumis, K., Tzevelekis, P., Kellartzis, D., Bontis, J., 2004. Primitive neuroectodermal tumor (PNET) of the uterine isthmus. Eur. J. Gynaecol. Oncol. 25, 384–386.
Yi, T., Wang, P., Lin, L., Jiang, W., 2015. Ewing's sarcoma/peripheral primitive neuroectodermal tumors of the uterus confirmed with fluorescence in situ hybridization in a 29-year-old Chinese female: a case report and published work review. J. Obstet. Gynaecol. Res. 41, 478–482.
Young, R.H., Kleinman, G.M., Schully, R.E., 1981. Glioma of the uterus. Report of a case with comments on histogenesis. Am. J. Surg. Pathol. 5, 695–699.