Case report

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

Taku Homma,⁎ Takehiro Nakao, Toshiya Maebayashi, Toshiyuki Ishige, Hiroyuki Hao

Division of Human Pathology, Department of Pathology and Microbiology, Nihon University School of Medicine, 1-30 Ohyaguchikamimachi, Itabashi, Tokyo 173-0032, Japan

Department of Gynecology, Nihon University School of Medicine, 1-30 Ohyaguchikamimachi, Itabashi, Tokyo 173-0032, Japan

Department of Radiology, Nihon University School of Medicine, 1-30 Ohyaguchikamimachi, Itabashi, Tokyo 173-0032, Japan

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 in 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
component comprising atypical ganglion-like cells with a fibrillar 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 fibrillar 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 IN11 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 fibrillar 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 fibrillar 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
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 postsurgical 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. 2. Macroscopic and histopathological features of the uterine neuroectodermal tumor. The uterus was almost totally occupied 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.
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 bev-acizumab; 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.
| Case no | Age (y.o) | Symptom          | FIGO stage | Surgery                | Postoperative therapy | Prognosis |
|---------|-----------|------------------|------------|------------------------|-----------------------|-----------|
| 1       | 58        | Vaginal bleeding | IIIc       | + (unknown detail)     |                       | DOD       |
| 2       | 31        | Back pain        | IV         |                        | + (unknown regimen)   | DOD       |
| 3       | 72        | Vaginal bleeding | IIa        | ND                     | ND                    | ND        |
| 4       | 48        | Vaginal bleeding | IIIc       | ND                     | ND                    | ND        |
| 5       | 81        | Vaginal bleeding | ND         | +                      | Letrozole             | NED       |
| 6       | 66        | Pelvic mass      | IIb        | TAH, BSO               | +                     | NED       |
| 7       | 53        | Vaginal bleeding | ND         |                        |                       | ND        |
| 8       | 51        | Vaginal bleeding | ND         |                        |                       | ND        |
| 9       | 31        | Vaginal bleeding | ND         |                        |                       | ND        |
| 10      | 64        | Endocervical polyp | IIIc      | +                      | (unknown regimen)     | NED       |
| 11      | 64        | Vaginal bleeding | ND         |                        | (unknown regimen)     | NED       |
| 12      | 69        | Vaginal bleeding | IV         |                        |                       | ND        |
| 13      | 62        | Uterine fibroids | IIc        | TAH, BSO               |                       | ND        |
| 14      | 55        | Vaginal spotting | IIb        | TAH, BSO               | +                     | NED       |
| 15      | 52        | Vaginal pressure | IV         |                        |                       | ND        |
| 16      | 58        | Vaginal pressure | IV         |                        | +                     | NED       |
| 17      | 57        | Vaginal bleeding | IIc        |                        | (unknown regimen)     | NED       |
| 18      | 12        | Vaginal bleeding | IV         | TAH, LSO               |                       | ND        |
| 19      | 57        | Vaginal bleeding | IIc        | TAH, BSO, PALND        |                       | DOD       |
| 20      | 17        | Vaginal bleeding | IIc        | TAH, PLND, left uretectomy, bilateral ovarian wedge biopsy | Cisplatin             | NED       |
| 21      | 67        | Vaginal bleeding | IIc        | STAH, BSO              |                       | 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 | IIb        | TAH, BSO               |                       | NED       |
| 26      | 54        | Vaginal bleeding | IIa        | TAH, BSO, PLND         |                       | AWD       |
| Case no | Age (y.o) | Symptom               | FIGO stage | Surgery              | Postoperative therapy | Prognosis |
|--------|-----------|-----------------------|------------|----------------------|-----------------------|-----------|
| 27     | 78        | Vaginal bleeding      | Ib         | TAH, BSO, PLND       | −                     | NED       |
| 28     | 62        | Vaginal bleeding      | Ib         | TAH, BSO             | Vincristine           | DOD       |
|        |           |                       |            |                      | Cyclophosphamide     |           |
|        |           |                       |            |                      | Cisplatin             |           |
|        |           |                       |            |                      | teniposide            |           |
| 29     | 36        | Enlarged uterus       | Ib         | RH, BSO, PLND        | −                     | ND        |
| 30     | 47        | ND                    | Ib         | TAH, BSO, LND        | +                     | DOD       |
| 31     | 67        | ND                    | IIc        | TAH, BSO, LND        | +                     | DOD       |
| 32     | 71        | ND                    | IIc        | TAH, BSO, LND        | +                     | DOD       |
| 33     | 16        | Vaginal bleeding      | k          | TAH, BSO, omentectomy| Vincristine           | +         |
|        |           |                       |            |                      | Cyclophosphamide     |           |
|        |           |                       |            |                      | Doxorubicin           |           |
| 34     | 48        | Vaginal bleeding      | IIc        | TAH, BSO             | −                     | NED       |
| 35     | 68        | Vaginal bleeding      | I          | TAH, BSO             | −                     | NED       |
| 36     | 66        | Vaginal bleeding      | Ia         | TAH, BSO, omentectomy| +                     | NED       |
| 37     | 65        | Vaginal bleeding      | IIc        | TAH, BSO, PLND,     | Cisplatin             | AWD       |
|        |           |                       |            | PALND, omentectomy, upper vaginectomy |            |           |
| 38     | 15        | Abdominal pain        | I          | TAH, PLND            | −                     | NED       |
| 39     | 43        | Vaginal bleeding      | IIc        | TAH, BSO, PLND       | −                     | NED       |
| 40     | 58        | Vaginal bleeding      | IV         | TAH, BSO, right PLND, | Carboplatin           | DOS       |
|        |           | Abdominal pain        |            | segmental enterectomy, | Paclitaxel            |           |
|        |           | Total coloectomy      |            |                      |                       |           |
| 41     | 26        | Vaginal bleeding      | IV         | TAH, BSO, PLND,     | Cisplatin             | −         |
|        |           | Abdominal pain        |            | omentectomy          |                       | NED       |
| 42     | 50        | Abdominopelvic pain   | ND         | TAH, BSO, omentectomy| −                     | NED       |
| 43     | 63        | Vaginal bleeding      | IIc        | TAH, BSO, LND        | −                     | DOD       |
| 44     | 80        | Abdominal pain        | I          | TAH, BSO, LND        | −                     | AWD       |
| 45     | 79        | Vaginal bleeding      | IIa        | TAH, BSO, LND        | −                     | ND        |
| 46     | 78        | Vaginal bleeding      | IIa        | TAH, BSO, LND        | −                     | NED       |
| 47     | 32        | Abdominal pain        | IIIa       | TAH, BSO, PLND,     | Cisplatin             | +         |
|        |           |                       |            | PALND, omentectomy, upper appendectomy |            |           |
|        |           |                       |            |                      | Ifosfamide            |           |
|        |           |                       |            |                      | Adriamycin            |           |
|        |           |                       |            |                      | Vincristine           |           |
| 48     | 66        | Vaginal bleeding      | IVb        | TAH, BSO             | −                     | DOD       |

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| Case no | Age (y.o) | Symptom | FIGO stage | Surgery | Postoperative therapy | Prognosis |
|---------|-----------|---------|------------|---------|-----------------------|-----------|
| 49      | 32        | Pelvic pain | IV         | TAH, BSO, PLND | Cyclophosphamide, Doxorubicin, Dexamethasone, Holoxan, Cisplatin, Paclitaxel, Carboplatin, Docetaxel, Irinotecan, Celecoxib | AWD |
| 50      | 29        | Abdominal swelling and pain | IVb         | STAH, BSO, PLND, omentectomy, appendectomy, metastatic nodule resection | 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, Etoposide, Cisplatin, Bleomycin | NED |
| 53      | 12        | Vaginal bleeding | ND         | – | Cisplatin, Adriamycin, Cyclophosphamide, Etoposide, Bleomycin, Etoposide | NED |
| 54      | 56        | Vaginal bleeding | Ib         | TAH, BSO, PLND | Adriamycin, Cyclophosphamide, Etoposide, Cisplatin | NED |
| 55      | 59        | Vaginal bleeding | IIc        | TAH, BSO, PLND, PALND, omentectomy | Paclitaxel, Cisplatin | AWD |
| 56      | 30        | Vaginal bleeding | IVb        | – | Doxorubicin, Adriamycin, Cyclophosphamide, Etoposide, Docetaxel, Irinotecan, Celecoxib | DOD |
| 57      | 22        | Vaginal bleeding | I          | TAH, BSO, PLND, PALND, omentectomy | Cisplatin | NED |
| 58      | 24        | Adnexal mass | II         | TAH, BSO, omentectomy | Doxorubicin, Adriamycin, Cyclophosphamide, Etoposide | AWD |

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| Case no | Age (y.o) | Symptom | FIGO stage | Surgery | Postoperative therapy | Prognosis | Follow-up (month(s)) | Pathological findings | Component | Metastasis | Reference |
|---------|-----------|---------|------------|---------|----------------------|-----------|----------------------|----------------------|-----------|-----------|-----------|
| 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 | IIc | TAH, BSO, PLND, omentectomy | + (unknown regimen) | NED |  |  |  |  |  |
| 61      | 51        | Vaginal bleeding | III | TAH, BSO | + | 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 | ND | ND | TAH, BSO | + | ND |  |  |  |  |
| 66      | ND        | ND | ND | ND | TAH, BSO | ND | ND |  |  |  |  |
| 67      | 60        | Vaginal bleeding | IV | TAH, BSO, PALND | Carboplatin Etoposide | ND |  |  |  |  |  |
| 68      | 31        | Vaginal bleeding | IIIc | + | Carboplatin | + | NED |  |  |  |  |
| 69      | 62        | Vaginal bleeding | IVb | TAH, BSO, omentectomy | - | ND |  |  |  |  |  |

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| Case no | Follow-up (month(s)) | Prognosis | Tumor size (cm) | Pathological findings | Component | Metastasis | Reference |
|---------|----------------------|-----------|----------------|----------------------|-----------|-----------|-----------|
|         |                      |           |                |                      | 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        | Lung      | Hendrickson and Scheithauer (1986) |
| 18      | 25                   | ND        | NET            | −                    | +         |            | Lung      | Hendrickson and Scheithauer (1986) |
| 19      | 24                   | ND        | NET            | −                    | +         | ND        | Lung      | Hendrickson and Scheithauer (1986) |
| 20      | 10                   | ND        | NET            | −                    | +         | ND        | Lung      | 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 | Fukunaga et al. (1996) |
| 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 | Soremen et al. (1998) |
| 29      | ND                   | 11        | NET            | Endometrioid carcinoma | − | − | − | Taieb et al. (1998) |
| 30      | 18                   | 7.8       | NET            | EM carcinoma         | −         | −         | −         | 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            | −                    | −         | −         | −         | Kareladze et al. (2001) |
| Case no | Prognosis | Follow-up (month(s)) | Tumor size (cm) | Component | Metastasis | Reference |
|---------|-----------|----------------------|----------------|-----------|-----------|-----------|
|         |           |                      |                | 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    | Dundr et al. (2010) |
| 44      | 6         | 5.0 × 4.0 × 3.0      | NET            | EM carcinoma | –         | Mesenterium Peritoneum 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) |

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| Case no | Follow-up (month(s)) | Prognosis | Tumor size (cm) | Component | Metastasis | Reference |
|---------|---------------------|-----------|----------------|-----------|-----------|-----------|
| 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       | –         | –         | Shah et al. (2009) |
| 56      | 16                  |           | 18 × 20 × 21   | NET       | –         | –         | 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       | –         | – | – | Bättner et al. (2007) |
| 60      | 6                   |           | 10 × 8         | NET       | Adenocarcinoma | – | Vaginal vault | Bhardwaj et al. (2010) |
| 61      | ND                  |           | ND             | NET       | EM carcinoma | – | ND | Chiang et al. (2017) |

(continued on next page)
| Case no | Prognosis | Pathological findings | Reference |
|---------|-----------|-----------------------|------------|
| 62      | Follow-up | Tumor size (cm)       | Chung et al. (2017) |
| 63      |           |                       | Chung et al. (2017) |
| 64      |           |                       | Chung et al. (2017) |
| 65      |           |                       | Elizalde et al. (2016) |
| 66      |           |                       | Tosi et al. (2012)  |

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