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Uterine Tumors with Neuroectodermal Differentiation. A Report of 4 Cases

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Abstract We report four cases of uterine tumors with neuroectodermal differentiation. One tumor had neuroectodermal component only; in the three other tumors, the neuroectodermal component was admixed with another component, namely rhabdomyosarcoma (1 case), and endometrioid adenocarcinoma (2 cases). Histologically, the neuroectodermal component consisted of small to medium sized cells arranged in diffuse sheets. The tumor cells had round nuclei with stippled to coarsely granular chromatin, mostly with non-prominent nucleoli, and scant eosinophilic or amphophilic cytoplasm. Immunohistochemically, 4/4 tumors showed expression of vimentin, synaptophysin and CD56; 3/4 tumors were CD99 and NSE positive; 2/4 tumors showed focal expression of S-100 protein; and 1/4 tumors had focal dot-like cytoplasmic positivity for cytokeratin AE1/AE3. FLI-1 was negative in all cases. FISH examination was performed and none of the tumors showed rearrangement of EWSR1 gene. Uterine tumors with neuroectodermal differentiation are rare; to the best of our knowledge only 44 cases have been reported in the literature to date, referred to as Ewing sarcoma, peripheral PNET (pPNET), PNET (not otherwise specified) and uterine tumors with neuroendocrine differentiation.

Keywords Uterine tumors · PNET · Ewing sarcoma · EWSR1 gene · Neuroectodermal

Abbreviations

EWSR1	Ewing sarcoma breakpoint region 1
NOS	not otherwise specified
PNET	primitive neuroectodermal tumor

Introduction

Neuroendocrine and neuroectodermal tumors comprise an interrelated group of neoplasms, which include tumors with epithelial and neural lineage. Tumors with neuroendocrine differentiation include carcinoid, small cell neuroendocrine carcinoma and large cell neuroendocrine carcinoma. Tumors of neural lineage include neuroblastoma (classic and olfactory), paraganglioma / pheochromocytoma, central type PNET (medulloblastoma and supratentorial PNET), Ewing sarcoma / PNET and some others [1]. Tumors of both lineages can be found in the female genital tract. Tumors of epithelial lineage are not uncommon but tumors of neural lineage are rare in this location [2–4]. Based on the morphology and immunophenotype, most of the neuroectodermal tumors of the female genital tract have been referred to as PNETs. The diagnosis of PNET without further specification could be, however, confusing because

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it encompasses a spectrum of tumors which belong to the Ewing sarcoma / PNET group as well as primitive-appearing neuroectodermal tumors that are more closely related to central type PNETs. Almost all tumors of the Ewing sarcoma / PNET group have some form of EWSR1 (Ewing sarcoma breakpoint region 1) gene rearrangement, which is specific for this group of tumors [5]. Uterine tumors with neuroectodermal differentiation are rare; to the best of our knowledge only 44 cases of this tumor have been reported to date, referred to as Ewing sarcoma, peripheral PNET (pPNET), PNET (NOS—not otherwise specified) and uterine tumors with neuroendocrine differentiation [6–28]. However, in most of these cases diagnosed as pPNET or PNET (NOS), the analysis of EWSR1 gene rearrangement or immunohistochemical analysis of FLI-1 was not performed and the diagnosis was based on the histological findings and immunophenotype of the tumors only, mostly on expression of CD99. In our study, clinicopathological, morphological and immunohistochemical analysis (including analysis of FLI-1) of another 4 cases of uterine tumors with neuroectodermal differentiation is reported. In addition, the presence of EWSR1 gene rearrangement was investigated by fluorescence in situ hybridization (FISH) in all of the cases.

Materials and Methods

Four cases of uterine tumor with neuroectodermal differentiation were retrieved from the archives of the Department of Pathology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague. Available hematoxylin-eosin and immunoperoxidase stained slides were reviewed in all of the cases. Additional immunohistochemical examinations were carried out in all cases for the purposes of this study.

Immunohistochemistry was performed using the avidin–biotin complex method. All slides were processed manually. Details of the primary antibodies used are summarized in Table 1. For some antibodies, antigen retrieval was performed including pretreatment in 0.01 M citrate buffer (pH 6.0) or TRIS/EDTA buffer (pH 9.0) for 40 min in a water bath at 98°C or with 0.05% trypsin in 0.05 M TRIS-buffered saline pH 7.4.

Table 1 Primary antibodies used

Antibody	Dilution	Antigen retrieval[a]	Source
Cytokeratin AE1/AE3	1:50	WB, pH 6	Dako, Glostrup, Denmark
Cytokeratin CAM5.2	1:10	Trypsin	Becton-Dickinson, Mountain View, CA, USA
EMA	1:100	None	Dako
Muscle specific actin (clone HHF35)	1:100	None	Dako
Desmin	1:200	None	Dako
Vimentin	1:300	WB, pH 6	Bio Genex, San Ramon, CA, USA
S-100 protein	1:1600	None	Dako
Neurofilament protein 2F11	1:100	Trypsin	Dako
Myoglobin	1:100	Trypsin	Dako
Myogenin	1:50	WB, pH 6	Dako
Chromogranin A	1:50	None	Dako
Synaptophysin	1:25	WB, pH 6	Dako
NSE	1:400	None	Dako
GFAP	1:200	None	Dako
CD99	1:100	WB, pH 6	Dako
CD56	1:50	WB, pH 9	Novocastra, Newcastle, UK
CD10	1:100	WB, pH 6	NeoMarkers, Fremont, CA, USA
LCA	1:100	WB, pH 6	Dako
Estrogen receptor	1:40	WB, pH 6	Novocastra
Progesterone receptor	1:100	WB, pH 6	Novocastra
MIB-1	1:50	WB, pH 6	Dako
FLI-1	1:50	WB, pH 6	NeoMarkers

WB water bath

[a] See the "Material and Methods" section for details

In all cases, FISH was performed on 4-μm thick formalin-fixed paraffin-embedded sections of tumor using the LSI EWSR1 (22q12) Dual Color, Break Apart Rearrangement Probe (Vysis, Downer`s Grove, IL, USA) according to the manufacturer`s instructions. This probe consists of a mixture of two DNA probes. The first probe labeled in SpectrumOrange flanks the 5′ side of the EWSR1 gene. The second probe labeled in SpectrumGreen flanks the 3′ side of the EWSR1 gene. The known breakpoints within the EWSR1 gene are restricted to introns 7 through 10. In normal cells, two fusion signals are observed reflecting the two intact copies of EWSR1. A split signal indicates a rearrangement of the EWSR1 gene.

Results

Patients´ ages ranged from 63 to 80 years. Three patients presented with abnormal vaginal bleeding and the fourth one with abdominal pain. All patients underwent radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. Two patients received adjuvant therapy (one of them radiotherapy and other chemotherapy). Two patients are alive with no evidence of disease 8 and 29 month after the diagnosis. One patient was alive with the disease (intraabdominal metastases) 6 months after the diagnosis, however, then was lost to follow-up. One patient died of the disease 7 months after the diagnosis. Clinico-pathological features of the patients are summarized in Table 2.

Grossly, the tumors in all 4 cases arose in the uterine corpus with apparent invasion into the myometrium. The serosa was intact in all cases and there were no signs of cervical infiltration. In one case (Case 4), a fallopian tube metastasis 15 mm in diameter was present. Gross features of the tumors are summarized in Table 2.

Histologically, in all tumors the neuroectodermal component consisted of small to medium sized cells arranged in diffuse sheets. The tumor cells had round nuclei 5–11 μm in diameter with stippled to coarsely granular chromatin mostly with non-prominent nucleoli and scant eosinophilic or amphophilic cytoplasm. In 3 cases (Case 1, 2 and 3), the tumor cells were relatively uniform and the cells borders were ill defined (Fig. 1a–c). In the last case (Case 4), however, the tumor cells showed irregular nuclei with atypias. This tumor consisted of larger cells and the cells borders were apparent (Fig. 1d). In one tumor, rare pseudorosettes consisting of neoplastic cells clustered around blood vessels were found (Case 2) (Fig. 1c). In all cases, the tumor cells showed multiple mitotic figures including atypical mitoses (28–70 mitoses/ 10 HPF). Large areas of necrosis were found. Lymphatic space invasion was present in all cases. One tumor had only

Table 2 Clinico-pathological features of uterine tumors with neuroectodermal differentiation

	Age	Clinical presentation	pTNM/ FIGO stage	Gross features	Therapy	Status
Case 1	63	Vaginal bleeding	pT1cN1M0 FIGO IIIC	Tumor 50×45×30 mm Invasion > 1/2 of wall Lymph nodes 36/2	AH/BSO/L Chemotherapy (6 cycles ifosfamid/cis-platin)	DOD 7mo after diagnosis (pelvic, mesenterial and peritoneal metastases)
Case 2	80	Abdominal pain	pT1bN0M0 FIGO IB	Tumor 50×40×30 mm Invasion < 1/2 of wall Lymph nodes 31/0	AH/BSO/L Radiotherapy (60 Gy)	AWD 6mo after diagnosis (intraabdominal metastases), than LTF
Case 3	79	Vaginal bleeding	pT1bN0M0 FIGO IB	Tumor 45×30×30 mm Invasion < 1/2 of wall Lymph nodes 41/0	AH/BSO/L	NED, 29mo
Case 4	78	Vaginal bleeding	pT3aN0M0 FIGO IIIA	Tumor 75×70×55 mm Invasion < 1/2 of wall Fallopian tube metastasis 15 mm in diameter Lymph nodes 24/0	AH/BSO/L	NED, 8mo

NED no evidence of disease, *AWD* alive with disease, *mo* months, *AH/BSO/L* abdominal hysterectomy/ bilateral salpingo-oophorectomy/ lymphadenectomy, *DOD* died of disease, *LTF* lost to follow-up

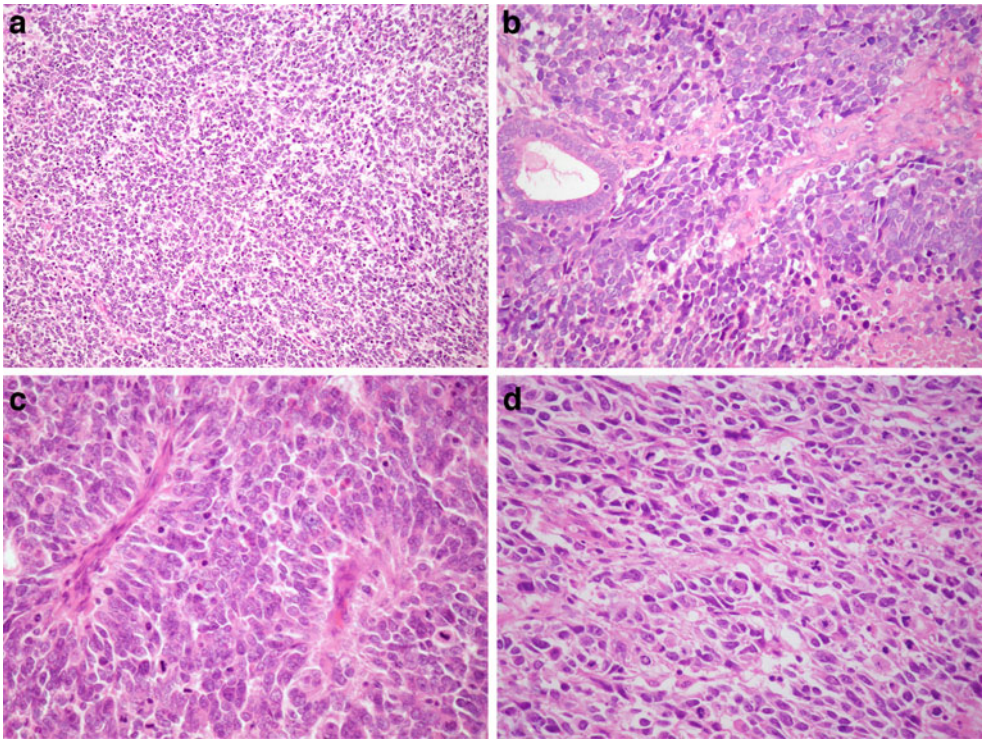

Fig. 1 Uterine tumors with neuroectodermal differentiation. **a**: Diffuse sheets of monomorphic tumor cells with ill defined cell borders (Case 3) (H&E, 200×). **b**: High power view of tumor cells arranged in diffuse sheets. Note the residual atrophic endometrial gland (Case 1) (H&E, 400×). **c**: Pseudorosetes consisted of neoplastic cells clustered around blood vessels (Case 2) (H&E, 400×). **d**: Tumor cells with irregular nuclei, prominent nucleoli and apparent cells borders (Case 4) (H&E, 400×)

neuroectodermal component (Case 4). In 3 tumors, the neuroectodermal component was admixed with endometrioid adenocarcinoma (Case 2 and 3) (Fig. 2), and rhabdomyosarcoma (Case 1) (Fig. 3). In mixed tumors, the neuroectodermal component represented the majority of the tumor in all 3 cases. In one case (Case 1), there were metastases in 2 of 36 lymph nodes. In this case of mixed tumor with minor component of rhabdomyosarcoma, the metastases consisted of neuroectodermal component only.

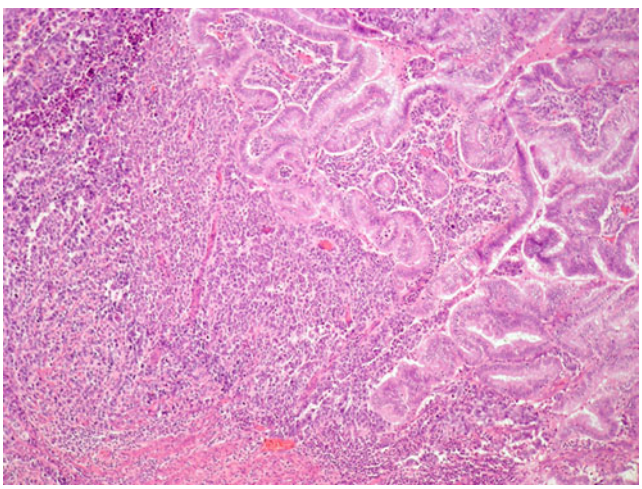

Fig. 2 Uterine tumor with neuroectodermal differentiation admixed with endometrioid adenocarcinoma (Case 2) (H&E, 100×)

Immunohistochemically, in all 4 cases the tumor cells showed expression of vimentin, synaptophysin and CD56 in the neuroectodermal component. The expression of vimentin was present in more than 75% of tumor cells in all cases. Synaptophysin showed diffuse strong expression in almost all cells in one case; another case showed strong expression in about 60% of cells and in 2 cases the expression was focal only. Membranous expression of CD56 was present in most tumor cells in 3 cases, and in 1 case the expression was just focal in about 10% of cells. From the other markers examined, membranous staining with CD99 was present in 3 cases. In 1 of these cases, staining was diffuse and strong. In 2 cases, staining was focal only. Three cases showed expression of NSE and 2 cases showed expression of chromogranin A. In 2 cases, S-100 protein expression was found in rare tumor cells. One case showed focal dot-like cytoplasmic staining with antibodies against cytokeratin AE1/AE3. Other markers examined including cytokeratin CAM5.2, EMA, desmin, myogenin, myoglobin, GFAP, neurofilament protein 2F11, FLI-1, muscle specific actin, CD10, LCA, estrogen and progesterone receptor were negative in the neuroectodermal component. The tumor cells in rhabdomyosarcoma component present in one case (Case 1) showed expression of desmin, myoglobin, myogenin and muscle specific actin. Examination of proliferative activity with monoclonal antibody MIB-1 showed nuclear positivity, which ranged from 20 to 80% of tumor cells. The immunohistochemical results are summarized in Table 3.

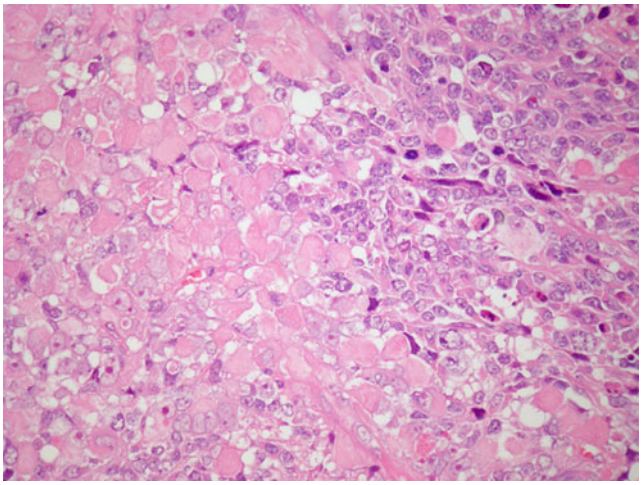

Fig. 3 Uterine tumor with neuroectodermal differentiation (right) with component of rhabdomyosarcoma (left) (Case 1) (H&E, 400×)

Discussion

Neuroendocrine and neuroectodermal tumors comprise an interrelated group of neoplasms, which include tumors with epithelial and neural lineage. Tumors with epithelial lineage include carcinoid tumor (well-differentiated endocrine neoplasms), and small or large cell neuroendocrine carcinoma. Tumors with neural characteristics include neuroblastoma (classic and olfactory), paraganglioma, pheochromocytoma, central type PNET (medulloblastoma and supratentorial PNET), Ewing sarcoma / PNET and some others [1]. Tumors of epithelial lineage are characterized by expression of some keratins, which are detectable in most of these lesions, whereas expression of vimentin is found only rarely. On the contrary, tumors of neural group are characterized by expression of vimentin. Keratin is not typically expressed in neural group of tumors, although aberrant expression of keratin could be found in some of them, especially in Ewing sarcoma/ PNET [29]. Neurofilament protein is variably co-expressed in both groups of tumor; however, in primitive tumors, such as neuroblastoma and PNET, only vimentin can sometimes be detected [1]. Generally, these tumors are characterized by expression of some neuroendocrine / neuroectodermal markers such as synaptophysin, chromogranin, CD56, CD57, and NSE. Some of these markers including synaptophysin, chromogranin and CD57 are relatively specific, whereas CD56 and NSE are rather non-specific for the neuroendocrine/ neuroectodermal differentiation and could be found in many other tumors without such differentiation [1].

Ewing sarcoma / primitive neuroectodermal tumor are defined as round cell sarcomas that show varying degrees of neuroectodermal differentiation. The term Ewing sarcoma has been used for undifferentiated tumors without evidence of neuroectodermal differentiation as assessed by light microscopy, immunohistochemistry and electron microscopy. The term pPNET has been used for tumors with apparent neuroectodermal features as demonstrated by one or more of these methods [30]. These tumors can occur in bones as well as extraskeletal locations. Extraskeletal tumors are most commonly found along the central axis in the paravertebral location, particularly chest wall. However, these tumors can arise in any soft tissues and rarely in some organs including kidney and lung [31, 32]. In female genital organs, these tumors can be found in vulva, vagina, cervix and ovary with the ovarian tumors being the most common [2–4, 33, 34].

Histologically, most cases of Ewing sarcoma / PNET consisted of uniform small round cells with round nuclei containing fine chromatin, scanty cytoplasm and indistinct cellular borders. However, some tumors show nuclear atypias or are composed of larger cells with vesicular nuclei and prominent nucleoli. In some cases, Flexner-Wintersteiner and Homer-Wright rosettes can be found and rare tumors show glial or ependymal differentiation [35]. The differential diagnosis of Ewing's sarcoma/ PNET is wide and correct diagnosis requires confirmation by ancillary methods including immunohistochemistry and analysis of EWSR1 gene rearrangement. Immunohistochemically, these tumors usually exhibit positivity for CD99, vimentin and FLI-1. However, expression of many other markers can be found including NSE, synaptophysin, chromogranin, S-100 protein and neurofilament protein. In addition, some of the tumors have focal positivity for

Table 3 Immunohistochemical results of the neuroectodermal component (% of positive tumor cells)

	Vim	Syn	CD56	CD99	NSE	CG	S-100	AE1/3	MIB-1	FLI-1
Case 1	75%	>90%	70%	–	–	30%	–	–	30%	–
Case 2	75%	60%	>90%	<5%	>90%	35%	<5%	–	30%	–
Case 3	>90%	<5%	10%	10%	10%	–	<5%	<5%	25%	–
Case 4	>90%	10%	>90%	>90%	<5%	–	–	–	75%	–

Other markers examined including GFAP, neurofilament protein, cytokeratin CAM5.2, EMA, muscle specific actin, desmin, myoglobin, myogenin, ER, PR, CD10 and LCA were negative

AE1/3 idicates cytokeratin AE1/AE3; *Syn* synaptophysin, *CG* chromogranin A, *Vim* vimentin; − negative result

cytokeratins [1, 29]. Membranous expression of CD99 is sensitive but not specific and can be found in lymphoblastic lymphoma, alveolar rhabdomyosarcoma, synovial sarcoma, some carcinomas (including endometrioid and serous adenocarcinoma) and many others [1, 22, 36]. Expression of FLI-1 protein as detected by polyclonal antibody has high specificity for vascular neoplasms and tumor of Ewing sarcoma / PNET group [37]. Detection of FLI-1 protein by means of monoclonal antibody shows higher sensitivity but lower specificity with positive result in number of other tumors such as malignant melanoma and some carcinomas [37, 38].

Virtually all tumors of Ewing sarcoma / PNET group had some form of EWSR1 gene rearrangement. Approximately 85% of cases show chromosomal translocation t(11;22) (q24;q12). Another 10–15% of cases have a translocation t(21;22) (q22;q12). In 1% or less, other rearrangements of EWS gene were described [5]. Detection of the fusion transcripts resulting from above mentioned translocations can be detected by RT-PCR [39]. Alternatively, the analysis of EWSR1 gene rearrangement using FISH method can be used since it detects all translocations involving this gene. However, this method does not specify the fusion type involved in the translocation.

Uterine tumors with neuroectodermal differentiation are rare. We have found only 44 cases of this tumor reported to date; most of them were single case reports with an exception of three series of 2, 4 and 17 cases [6–28]. These tumors were reported as Ewing sarcoma, peripheral PNET (pPNET), PNET (NOS) and uterine tumors with neuroendocrine differentiation. However, in most of these cases diagnosed as pPNET or PNET (NOS), the analysis of EWSR1 gene rearrangement or immunohistochemical analysis of FLI-1 was not performed and the diagnosis was based on the histological findings and immunophenotype of the tumors only, mostly on expression of CD99. However, expression of CD99 is not specific and can be found in many other tumors [1, 22]. Therefore, CD99 should be considered supportive but not diagnostic of Ewing sarcoma / pPNET. Sixteen of all reported cases have been subjected to molecular analysis of the EWSR1 gene, and EWSR1 gene rearrangement was detected in 4 of these cases [7, 24, 26, 27]. Immunohistochemical analysis of FLI-1 expression was performed in only 2 of all the reported cases, in both cases with positive results (one case showed rearrangement of EWSR1 gene) [27]. These tumors can be in pure form, or are associated with other tumors such as malignant mixed Müllerian tumor, endometrial stromal sarcoma and endometrioid or serous adenocarcinoma [10, 13, 22, 40]. Histologically, these tumors consist of diffuse sheets of primitive-appearing cells. Some of these tumors can have evidence of neural differentiation such as fibrillary background and rosette formation. Nevertheless, the origin of neuroectodermal tumors in the uterus remains unknown. Some authors suggest that these tumors are related to ectopically migrated neural crest cells at the time of fetal development [41]. Others suggest that these tumors are of Müllerian origin, which is supported by the fact that neuroectodermal uterine tumors can be associated with malignant mixed Müllerian tumor or other types of tumor with Müllerian differentiation [13, 39]. In the neuroectodermal uterine tumors associated with other types of tumor, the neuroectodermal component can represent a pattern of heterologous differentiation in a malignant mixed Müllerian tumor [11]. Pure uterine neuroectodermal tumors can represent monophasic differentiation in a malignant mixed Müllerian tumor [9, 13].

The differential diagnosis of uterine tumors with neuroectodermal differentiation included malignant lymphoma, alveolar rhabdomyosarcoma, poorly differentiated synovial sarcoma, endometrial stromal sarcoma, undifferentiated uterine sarcoma, high grade endometrioid adenocarcinoma and primary or metastatic carcinoma with neuroendocrine features. In most cases, the correct diagnosis can be achieved by analysis of histologic and immunohistochemical features of the tumor. Sometimes, the main problem lies in the distinction between small cell neuroendocrine carcinoma and uterine tumor with neuroendocrine differentiation that show considerable histologic and immunohistochemical overlapping features. However, small cell carcinomas usually express keratin, and expression of vimentin is found only exceptionally [1]. On the contrary, uterine tumors with neuroectodermal differentiation express vimentin in almost all cases. Aberrant keratin expression can be found in about 20% of PNETs, but it is usually focal only [1]. In addition, expression of CD99 occurs in some uterine tumor with neuroectodermal differentiation, whereas small cell carcinomas express this antigen rather rarely [42].

In conclusion, correct diagnosis of the uterine tumors with neuroectodermal differentiation requires immunohistochemical analysis using a panel of antibodies and analysis of the EWSR1 gene rearrangement. The diagnostic algorithm can be the same as proposed for such tumors in other locations [37]. Tumors with morphology suggestive of Ewing sarcoma/ PNET, which are vimentin, possibly some neuroendocrine/ neuroectodermal markers, and rarely focal cytokeratin positive, should be further analyzed with antibodies against CD99 and FLI-1. In addition, analysis of EWSR1 gene rearrangement should be performed. Expression of CD99 can be found in most of these tumors; however, it is not specific and should be considered supportive but not diagnostic of Ewing sarcoma / pPNET. Only tumors with rearrangement of EWSR1 gene should be classified as peripheral PNETs. Tumors without rearrangement of EWSR1 gene with morphology and immunophenotype suggestive of Ewing's sarcoma/ PNET that are

FLI-1 positive are suggestive of pPNET. The diagnosis of PNET, not otherwise specified, should not be used for tumors without rearrangement of the EWSR1 gene which are FLI-1 negative to avoid confusion with peripheral PNET. These tumors should be classified as uterine tumors with neuroectodermal differentiation. Alternatively, the term central type PNET was suggested for these tumors [11]. However, based on the CD99 negativity of central type PNET and common expression of this antigen by uterine neuroectodermal tumors without EWSR1 rearrangement, we prefer the term uterine tumors with neuroectodermal differentiation for these neoplasms. The presence of primitive neuroectodermal component can be a sign of potentially aggressive behavior of the tumor. However, it is necessary to analyze more cases in order to assess the prognostic significance of such differentiation and optimal treatment of these rare tumors.

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