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Case Report

Uterine adenosarcoma admixed with a primitive neuroectodermal tumour (PNET): a case report and review of the literature

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Summary

Herein the authors report a case of uterine adenosarcoma admixed with primitive neuroectodermal tumour (PNET) and review the literature on these rare neoplasms, as well as data files of their Gynaecologic Pathology Centre in Rome, Italy.

Key words: Uterine adenosarcoma; Primitive neuroectodermal tumour (PNET).

Introduction

Uterine adenosarcoma is an uncommon biphasic malignant mesenchymal neoplasm characterised by malignant stroma containing benign epithelial elements. The malignant stroma is classically a low-grade spindle cell sarcoma with no specific line of differentiation [1]. Heterologous mesenchymal elements are present in 20-25% of adenosarcomas and include mainly rhabdomyosarcoma, cartilage or fat. Uterine primitive neuroectodermal tumour (PNET) usually occurs as pure PNET. Very rarely does it occur in association with other uterine malignancies.

Case Report

A 51-year-old postmenopausal woman presented with vaginal bleeding and pelvic pain. Ultrasound scans revealed a large polypoid mass in the uterine cavity (33 mm). A fractional endometrial curettage yielded pink-tan, friable tissue fragments measuring 11 ×7×1.5 cm in aggregate. Histology revealed a lesion largely composed of undifferentiated sarcomatous areas and limited broad leaflike formations of spindled cells displaying low-to moderate grade cytologic atypia and an average of 4 mitoses/10 HPF, lined by benign epithelium. Myxoid or edematous degeneration, as well as necrotic areas of the malignant stroma were present (Figure 1a). The sarcomatous spindled tumour cells stained positively only with CD10 and p53 antibodies and focally with ER (Figure 1b).

Other tumoral areas, accounting for approximately 15% of the tumour mass, displayed sheets of small, round-to-oval dark cells with hyperchromatic nuclei and inconspicuous nucleoli, occasionally forming Homer-Wright rosettes (Figure 2a). Numerous mitotic figures could be made out. This cell component immunostained diffusely with CD99 (cell membrane) (Figure 2 b), and focally with synaptophysin, and showed a proliferation index of 45%, using Ki67 antibody. Despite being intermingled, no morphologic transition from one cell type to the next was observed. PET TC scan was performed and revealed an enlarged uterine cavity (58×67×46 mm) containing a markedly and heterogeneously enhancing growth. The mass did not appear to extend through the cervical or uterine wall. There was no evidence of metastasis noted within the extrauterine soft tissues or osseous structures. A total abdominal hysterectomy with bilateral salpingo-oophorectomy was then carried out.

Gross examination revealed a 10×5×5 cm uterus of symmetrical shape, lined by normal serosa. A residual, largely necrotic, exophytic mass of 2.8×2 was present in the endometrial cavity. On sectioning, the mass appeared to invade circumferentially the uterine wall up to the internal uterine os, without reaching the visceral serosa. Histology confirmed a uterine adenosarcoma with stromal sarcoma overgrowth and foci of PNET. The latter was diagnosed based on the morphological and immunohistochemical features, short of the support of molecular evidence, due to the lack of probe and primers for the fusion gene of EWSR1. The tumour involved < 50% of the myometrial thickness and presented microscopical deposits in the right ovary. The latters were devoid of the PNET component. No tumour deposits were observed in the parametrium and omentum (pT2a pNx). Microscopical examination of the uterine cervix revealed an adenofibroma of approximately 3 mm in diameter (Figure 3), the benign counterpart of adenosarcoma.

The patient underwent five cycles of an adjuvant chemotherapeutic regimen based on gemcitabine + docetaxel. She currently is without evidence of recurrent disease two years after completion of therapy.

Discussion

Adenosarcomas accounted for 6% of uterine sarcomas diagnosed during 11 years in a large Chinese hospital [2]. Search of the files of the Institute of Anatomical Pathology and Histology of Rome University "La Sapienza" from

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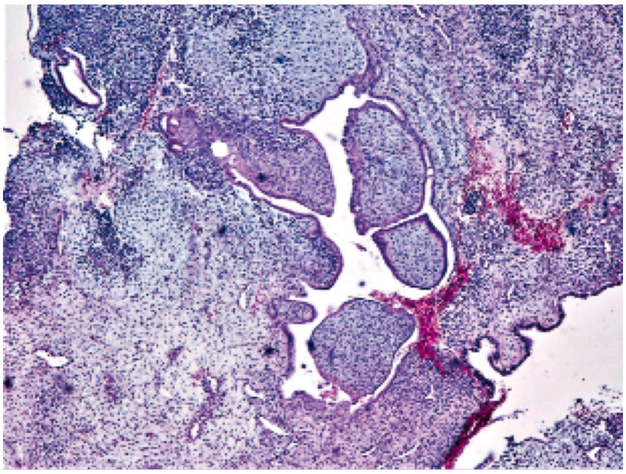
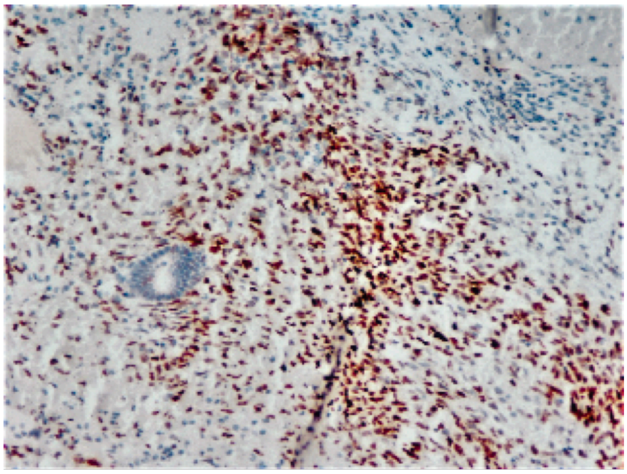

Figure 1. — (a) Histology of the endometrial polyp showing an undifferentiated sarcoma forming broad leaflike formations of spindled cells, lined by benign epithelium (Hematoxylin-Eosin ×50). (b) The sarcomatous tumour cells are immunostained with p53 (Avidin-biotin DAB ×250).

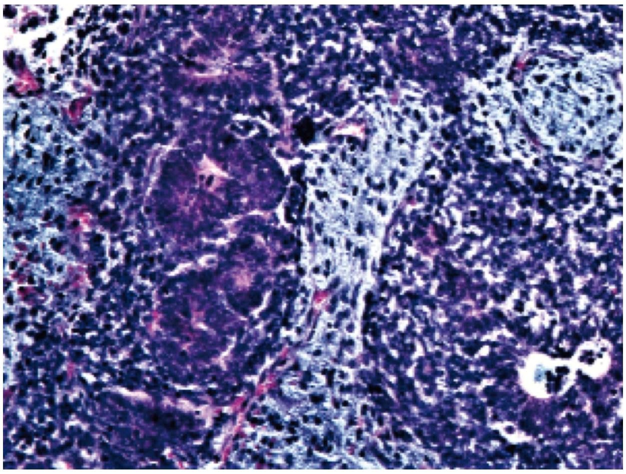
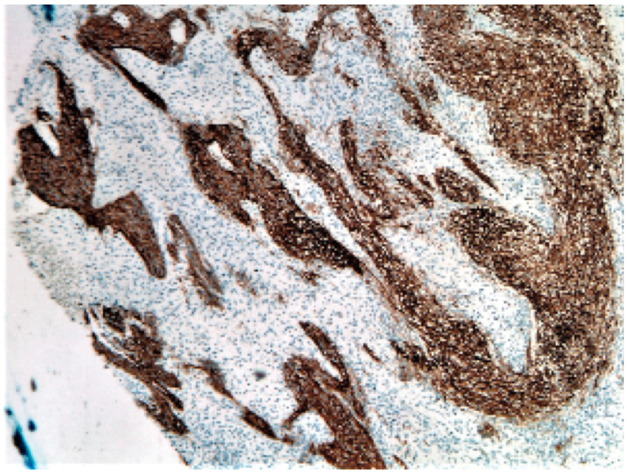

Figure 2. — (a) Homer-Wright rosettes characterise microscopically the PNET component (Haematoxylin-Eosin ×250). (b) CD99 immunostaining of the PNET component. The negative background is composed of undifferentiated sarcomatous cells (Avidin-biotin DAB ×250).

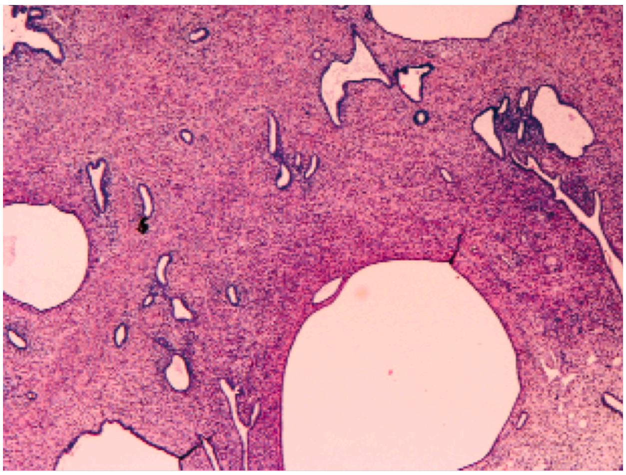

Figure 3. — Adenofibroma of the cervix, showing benign Müllerian glands in a slightly cellular stroma. This was an accidental microscopical finding in the hysterectomy specimen. (Haematoxylin-Eosin ×100).

2007 to 2017 retrieved six cases (Table 1) of uterine adenosarcoma and one case of uterine PNET, out of 24,768 gynaecological specimens, giving an overall incidence of 0.024% for uterine adenosarcoma and 0.0040% for uterine PNET. The only case of uterine PNET in the present series was combined with an adenosarcoma, and represents the case under discussion.

The mean age of the present patient series was 53 (range 26-71) years. In five instances, the tumour originated from the endometrium, while cervical origin accounted for only one case. The endometrial lesions measured an average of 9 (range 3 to 14) cm and most often (67%) appeared to invade only superficially into the uterine wall. Histology revealed stromal overgrowth in all, but one instance. No correlation between stage and mitotic count could be found (Table 1). Fifty percent of cases contained heterologous elements, rhabdomyosarcoma being the most common. The current case report showed, instead, large foci of PNET.

Table 1. — *Uterine adenosarcomas occurring in the present Institute from 2007 to 2017.*

	Age	Site	Size (cm)	Stromal mitoses /10 HPF	Myometrial invasion	Stromal overgrowth	Heterologous components	pTNM
1	71	Endometrial cavity	8.5×7×5	6	Superficial	No	No	pT1b
2	26	Endometrial cavity + cervix	10×4.5×2.5	40	Full-thickness	Yes	RMS	pT1c
3	68	Endometrial cavity	8×5×4.5	60	< 50%	Yes	RMS	pT1b
4	65	Endometrial cavity + proximal cervix + ovary	14×10×6	30	Parametrium	Yes	No	pT2a
5	36	Cervix + vagina	3	40	No	Yes	No	
6	51	Endometrial cavity + ovary	10×5×5	4	< 50%	Yes	Cartilage, PNET	pT2a

RMS = rhabdomyosarcoma; PNET = primitive neuroectodermal tumour; HPF = high power fields; case 6 = present case.

With the limitation of small numbers, the present data do not compare well with Shi *et al.*'s series of uterine adenosarcomas, where the nine affected patients showed an average age of 45 years (younger), a tumour diameter of 2 to 7 cm (smaller), lack of myometrial invasion in 37.5% (none in this series), absence of sarcomatous overgrowth, and metastatic disease (lymph nodes) in one instance [2]. In Shi *et al.*'s series, as in the present, rhabdomyosarcoma was the most common heterologous component (33% of cases). Analysis of larger series from different parts of the world may prove useful to pinpoint the differences in epidemiology and clinical features of these rare gynaecological sarcomas.

In the female genital tract, PNET usually occurs in the ovary or in the uterus. The cervix and vulva are rarely the primary sites with only five and two cases reported from each site, respectively [3].

PNET is considered to originate from neurocrest fetal cells (neuroectodermal tumour) and is interrelated with neuroendocrine tumours. Tumours with neuroendocrine differentiation include carcinoid, small cell neuroendocrine carcinoma and large cell neuroendocrine carcinoma, and are of epithelial lineage. Tumours of neural lineage include Ewing sarcoma / PNET and some others. Differently from neuroendocrine tumours, PNETs express immunohistochemically the antigen CD99 and FLI-1. PNETs are additionally characterized by reciprocal translocation between chromosomes 11 and 22, t (11, 22) [1], with typical EWSR1 gene rearrangement. However, the largest published case series on uterine PNETs, either pure or of combined phenotype, indicates that none of the 11 cases (8 pure, 3 mixed) tested for typical EWSRI rearrangement were positive [4]. Other studies indicate a percentage of EWSRI rearrange-ments of no more than 20% in uterine PNET [5]. Uterine PNETs lacking EWSRI rearrangements also lack im-munoreactivity for FLI-1 [5], a sensitive marker for Ewing sarcoma/PNET. These data clearly indicate that the tumours that have been referred to as PNET of the uterus, either in pure or combined form, although morphologically similar, are histogenetically heterogeneous, with the majority of them not expressing the characteristic EWSRI rearrange-ment. This reduces the importance of molecular confirma-tion for diagnosing uterine PNET. On the other hand, no significant difference in survival has been found related to ESWR1 rearrangement, whereas the two-year survival (46%) for uterine pure PNET (FIGO's annual report) [6] relates mainly with the surgical stage [7]. Of interest, the latest AJCC Cancer Staging Manual (2017) does not still provide staging criteria for uterine sarcomas other then adenosarcoma, leiomyosarcomas, and endometrial stromal sarcoma, leaving PNET staging in a grey area.

Uterine PNET can present in pure form or combined with other tumours, most often of known Müllerian origin. The present review of the literature yielded 30 cases of uterine PNET combined with other malignancies (Table 2). Other than adenosarcoma (two cases) [4, 8], PNET have been found admixed with endometrioid endometrial carcinoma (15 cases) [4, 9-12], malignant mixed Müllerian tumour (MMMT) (two cases) [4], high grade serous endometrial carcinoma (five cases) [12], rhabdomyosarcoma (four cases) [4, 9, 13-14], and endometrial stromal sarcoma (two cases) [4, 10]. A Müllerian derivation for at least some of these uterine PNET has been advocated, due to the prevalence of cases associated with a Müllerian neoplasm (Table 2). According to Euscher *et al.*, the neuroectodermal component in uterine PNET tumours combined with other epithelial components may represent a pattern of heterologous differentiation of the Müllerian epithelium, such as can be seen in uterine MMMT [4]. Some of them could else be a form of dedifferentiation in low-grade neoplasms or divergent differentiation in high-grade neoplasms [4]. PNET from gynaecological sites could not, after all, be derived from neurocrest fetal cells.

Some interesting features of combined uterine PNET have been indicated in the literature. When admixed with endometrioid endometrial carcinoma, the endometrioid component is well-differentiated, the PNET component shows a solid growth pattern, and the two components do not merge into each other, unlike that seen in MMMT [11, 12]. In the present authors' opinion, the absence of transition from one neoplasms to the other is suggestive of a collision tumour, and does not lend support to the theory of a common origin of the two histological components from the Müllerian epithelium.

According to Quddus *et al.*, as much as 7.1% of serous carcinomas of the endometrium and 12.5% of endometrioid endometrial carcinomas show a CD99-positive PNET component, accounting for at least 10% of the overall neoplas-

Table 2. — *Literature review of uterine composite PNETs.*

Ref.	Age	Other histological subtypes	PNET component	Spread	Treatment	Status
4	64	Adenosarcoma with sarcomatous outgrowth	Minor		nr	Lost to FU
	48	EEC	Minor		nr	Lost to FU
	66	Unclassified sarcoma (HG)	Major		Surgery+ hormone therapy	NED 41 mo
	62	RMS	Major		n.r	DOD 22 mo
	58	MMMT	Minor		CHT	NED 6 mo
	57	MMMT	Minor		CHT	NED 35 mo
7	58	EEC (IG)	Major (90%)	Myometrium, ileal and colon wall, left adnexa. 1/12 iliac right LN	CHT	DOD 11 mo (lung metastases)
8	50	Adenosarcoma	Major (80%)	Myometrium (FT), cervix, L parametrium, L external iliac LN	TAH+BSO+omentectomy+pelvi+ LA	Recurrence on vaginal vault 2 mo p.o. RT+ CHT for 6 mo. DF
9	63	RMS	Major	Myometrium	TAH, BSO, LN, CHT	DOD 7 mo (pelvic, peritoneal, mesenterial recurrence)
	80	EEC	Major	Myometrium	TAH, BSO, LN, RT	AWD 6 mo (abdominal mass)
	79	EEC	Major	Myometrium	TAH, BSO, LN	NED 29 mo
10	68	EEC (LG)	Major	Endometrium	TAH, BSO, RT	DF 5.5 yrs
	69	ESS (LG)	Minor	Superficial myometrium	TAH, BSO, LA, RT	DF 6 yrs
11	47	EEC	Major (90%)	myometrium	TAH, BSO, LA+RT	Pelvic recurrence 1yr, CHT 6 mo, DOD
	67	EEC	Major (90%)	myometrium	TAH, BSO, LA, CHT	Peritoneal recurrence, CHT 3 mo, DOD
	71	EEC	Major (90%)	myometrium	TAH, BSO, LA, CHT	Lung and peritoneal recurrence 4 mo, CHT, DOD
12	64-84	Serous carcinoma of endometrium (HG) (5 cases)	Minor	nr	nr	nr
	58-86	EEC (7 cases)				
13	25	Embryonal RMS	Minor (40%)	Endometrium, myometrium	Refused surgery. Neo-adjuvant CHT+RT. CHT. Simple hysterectomy	NED 18 mo
14	12	Botryoides RMS	Minor	Confined to the endometrial polyp	polypectomy	NED

EEC = endometrioid endometrial carcinoma; ESS = endometrial stromal sarcoma; MMMT = malignant mixed Müllerian tumour; RMS = rhabdomyosarcoma; HG = high-grade; IG = intermediate- grade; LG = low-grade; nr = not reported; TAH = total abdominal hysterectomy; BSO = bilateral salpingo-opherectomy; LN = lymph node excision; RT = radiotherapy; REC = recurrence; DF = disease-free; mo = months; CHT = chemotherapy; AWD = alive with disease; DOD = died of disease; FT = full thickness; L = left; R = right.

tic population [12]. In their study, CD-99 positive cells displayed either the typical solid growth pattern common to PNET, or were part of the serous neoplasia in that they showed epithelial morphology and often lined papillary projections. In the latter instance, CD-99-positive and CD99-negative cells did not differ morphologically [12]. Their findings need further confirmation, as an overlooked PNET component in classical serous or endometrioid endometrial carcinomas may impact prognosis. However, as CD99 positivity is not exclusive of PNET, and can be observed, for instance, in breast carcinoma, caution should be taken when reporting a neuroectodermal component showing atypical morphology (serous) in the gynaecological tract.

To the best of the present authors' knowledge, only two uterine adenosarcomas admixed with PNET have been published so far [4, 8]. Table 2 summarises literature data on uterine adenosarcoma with PNET. Similarly to the present case, Bhardwaj *et al.*'s reported case included a polypoid mass protruding from the cervical os [8]. Histology revealed a tumour largely composed of cells displaying PNET differentiation and a minor component (20%) of adenosarcoma [8]. No details were given for Euscher *et al.*'s case [4].

The present case predominantly showed the classic features of an adenosarcoma, formed by a high grade, undifferentiated stromal sarcoma (CD10+, ER+) and few benign endometrial glands. As in the present case, most uterine adenosarcomas show diffuse or multifocal expression of CD10, estrogen, and progesterone receptors in the stromal component [1], indicating an endometrial stromal differentiation of the spindled cell component. Heterologous ele-

Table 3. — *Literature review of immunophenotype and EWSR1 rearrangement of combined uterine PNET.*

Reference	Other histological component	Immunophenotype (+)	Immunophenotype (-)	EWSR1 rearrangement
4	EEC	CD99, SYN	CK, CROM-A	No signal
	HG unclassified sarcoma	SYN, NF, CD56		Not performed
	Adenosarcoma with sarcomatous overgrowth	SYN	CK	Negative
	RMS	SYN, NF	CK	Negative
	MMMT	CD99, SYN	CK	Not performed
	MMMT	SYN, NF	CK	Negative
7	EEC	CD99, VIM, SYN, PR, ER & EMA (focal)	CD10, AE1/AE3, CD45, DES, MYO, MSA	Negative
8	adenosarcoma	SYN; NSE	CD99, CROM-A, CK	Not performed
10	LG EEC LG ESS	NSE, VIM, CROM-A NSE,VIM, CROM-A, S-100	CYT, S-100 CYT	Not performed
11	EEC	CD99, AE1/AE3, CYT8, VIM, NSE	DES, SMA, MSA; CROM, SYN, NF	Positive
	EEC	CD99, VIM, NSE	AE1/AE3, CYT8, DES, SMA, MSA; CROM, SYN, NF	Positive
	EEC	CD99, VIM, NSE	AE1/AE3, CYT8, DES, SMA, MSA; CROM, SYN, NF	Positive
12	7 cases: EEC 5 cases: endometrial serous carcinoma	CD99 CD99		Not performed
13	RMS	CD99, SYN, CD56, p16	CK, CROM-A, DES, EMA, MYO, MyoD1	Negative
14	Botryoides RMS	CD99, NSE, VIM, SYN,	FLI-1	Negative

HG = high-grade; IG = intermediate- grade; LG = low-grade; CAL = calcitonin; CK = cytokeratins; CROM-A = chromogranin; DES = desmin; ER = estrogen recptor; INH = inhibin; MSA = muscle specific actin; MYO = myogenin; NF = neurofilament; NSE = neuron specific enolase; PR = progesterone receptor; SYN = synaptophysin; SMA = smooth muscle actin; VIM = vimentin; EEC = endometrioid endometrial carcinoma; ESS = endometrial stromal sarcoma; MMMT = malignant mixed Müllerian tumour; RMS = rhabdomyosarcoma; negative = no rearrangement by ISH.

ments in uterine adenosarcoma, such as cartilage or rhabdomyoblasts, appear to carry no prognostic significance alone and to occur most commonly in the presence of sarcomatous overgrowth [1].

In the past literature cases of "PNET" other than those described in Table 2 were reported in association with a MMMT [15, 16]. However, presently only neurectodermal malignancies composed entirely of immature neural tissue with a limited capacity for several different degrees of differentiation, forming sheets, tubules, rosettes, pseudorosettes, or medullary tubules, are considered to belong to the ES/PNET family. Homer Wright rosettes are a marker for PNET [1]. Gersell *et al.* and Fukunaga *et al.* cases contained mature neural elements such as ganglion cells, or glia, and expressed GFAP, which is not a feature of PNET [15, 16]. Rare cases of combined rhabdomyosarcoma and PNET have been also described [4, 9, 13, 14] (Table 2).

PNET areas may be difficult to recognise when admixed with other sarcomas, or with high-grade uterine carcinomas. The PNET component in the present case was easily identifiable through morphology and positive results with synaptophysin and CD99. On immunohistochemistry, most of the reported combined uterine PNET are variably positive for CD99 and FLI-1 (Table 3). However, as CD99-negative PNET cases do exist (Table 3), testing the neoplastic cells with a larger immunohistochemical panel for markers of neural differentiation, including synaptophysin, CD56, and NSE may be useful in doubtful instances.

Pure PNET is extremely aggressive with dismal outcome. When treated with local therapies such as surgery or radiation therapy, Ewing sarcoma family of tumours have a relapse rate of 80–90% and an extremely high mortality rate. Factors affecting prognosis of uterine PNET, either pure or in combination with other neoplasms, are not yet clarified and risk criteria are mostly derived from the information obtained from extragenital PNET and Ewing's sarcomas. Additionally, it is not yet clear whether the presence of a PNET component may add to the unfavourable prognosis of a high grade adenosarcoma of the uterine corpus.

Conclusion

PNET can coexist with uterine adenosarcoma. Awareness of the occurrence and recognition of PNET foci in other uterine sarcomas or in carcinomas, may prove important to ascertain whether these combined neoplasms may possess a different behaviour and require specific treatment.

References

[1] Pinto A., Howitt B.: "Uterine adenosarcoma". *Arch. Pathol. Lab. Med.*, 2016, *140*, 286.

[2] Shi Y., Liu Z., Peng Z., Liu H., Yang K., Yao X.: "The diagnosis and treatment of Mullerian adenosarcoma of the uterus". *Austr. New Zealand J. Obstet. Gynaecol.*, 2008, *48*, 596.

[3] Akbayir O., Gungorduk K., Rafioglu G., Gulkilik A., Yavuz E., Tekirdag A.I., *et al.*: "Primary primitive neuroectodermal tumor of the uterus: A case report". *Arch. Gynecol. Obstet.,* 2008, *277*, 345.

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

[5] Fadare O.: "Heterologous and Rare Homologous Sarcomas of the Uterine Corpus: A Clinicopathologic Review". *Adv. Anat. Pathol.,* 2011, *18*, 60.

[6] Creasman W.T., Odicino F., Maisonneuve P., Quinn M.A., Beller U., Benedet J.L., *et al.*: "Carcinoma of the corpus uteri. FIGO 26th annual report on the results of treatment in gynecological cancer". *Int. J. Gynaecol. Obstet.*, 2006, *95*, 105.

[7] Bartosch C., Vieira J., Teixeira M.R., Lopes J.M.: "Endometrial endometrioid adenocarcinoma associated with primitive neuroectodermal tumor of the uterus: a poor prognostic subtype of uterine tumors". *Med. Oncol.*, 2011, *28*, 1488.

[8] Bhardwaj M., Batrani M., Chawla I., Malik R.: "Uterine primitive neuroectodermal tumor with adenosarcoma: a case report". *J. Med. Case Rep.*, 2010, *4*, 195.

[9] Dundr P., Fischerová D., Povýšil C., Berková A., Bauerová L., Cibula D.: "Uterine tumors with neuroectodermal differentiation. A report of 4 cases". *Pathol. Oncol. Res*., 2010, *16*, 601.

[10] Daya D., Lukka H., Clement P.B.: "Primitive neuroectodermal tumors of the uterus; a report of four cases". *Hum. Pathol.*, 1992, *23*, 1120.

[11] Sinkre P., Albores-Saavedra J., Miller D.S., Copeland L.J., Hameed A.: "Endometrial endometrioid carcinomas associated with Ewing sarcoma/peripheral primitive neuroectodermal tumor". *Int. J. Gynecol. Pathol.*, 2000, *19*, 127.

[12] Quddus M.R., Rashid L., Sung C.J., Steinhoff M.M., Zhang C., Lawrence W.D.: "Ewing's sarcoma/peripheral primitive neuroectodermal tumor (ES/PNET) differentiation in endometrial serous carcinomas". *Reprod Sci.*, 2009, *16*, 591.

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

[14] Stolniku S., Goyenaga P., Hincu M., Marian C., Murillo R., Nogales F.F.: "Embryonal (botryoides) rhabdomyosarcoma of the uterus harboring a primitive neuroectodermal tumor component". *Int. J. Gynecol. Pathol.*, 2012, *31*, 387

[15] Fukunaga M., Nomura K., Endo Y., Ushigome S., Aizawa S.: "Carcinosarcoma of uterus with extensive neuroectodermal differentiation". *Histopathology,* 1996, *29*, 565.

[16] Gersell D.J., Duncan D.A., Fulling K.H.: "Malignant mixed mullerian tumor of the uterus with neuroectodermal differentiation". *Int. J. Gynecol. Pathol.*, 1989, *8*, 169.

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