Clinical Case Report

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Clinical management of a unique case of PNET of the uterus during pregnancy, and review of the literature

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Abstract

Rationale: PNETs (primitive neuroectodermal tumors) are a family of highly malignant neoplasms characterized by small round cells of neuroepithelial origin. They usually involve bone and soft tissues, and have a higher incidence in childhood.

Patient concerns: In this case report, we describe the obstetric and oncological outcome of a huge mass diagnosed as a leiomyoma in a 39-year-old pregnant woman who complained of low back pain, dysuria, and urinary frequency at 22 weeks of gestation.

Diagnoses: During the 25th week of pregnancy, the patient was referred to our hospital at night with severe anemia and suspected hemoperitoneum. She underwent an emergency caesarean section, delivering a female fetus weighing 400 g, with an Apgar score of 7 at 1 minute and 9 at 5 minutes.

Intervention: During surgery, we found a huge uterine sarcoma-like metastatic tumor, invading the pelvic peritoneum and parametria bilaterally; the adnexae seemed disease-free. We performed a type B radical hysterectomy, bilateral salpingo-oophorectomy, pelvic peritonectomy, omentectomy, appendectomy, and excision of a bulky lymph node. Seven days after delivery, staging computed tomography (CT) scan demonstrated a large lombo-aortic lymph node compressing the left renal vein and we completed debulking with a second surgery, including diaphragmatic peritonectomy and excision of a huge lymph node by lombo-aortic lymphadenectomy, requiring partial reconstruction of an infiltrated renal vein.

Outcome: Ten days after the second surgery, echo-color Doppler showed a regular microcirculation in the left kidney. The patient was discharged after 10 days, and the baby after 1 month, both in good health.

Histological examination revealed a uterine body cPNET (central primitive neuroectodermal tumor) orienting the clinical management toward chemotherapy with cisplatin and etoposide.

Lessons: PNETs are aggressive neoplasms, usually diagnosed at an advanced stage. Due to their low incidence, universally accepted guidelines are still unavailable. Radical surgery leaving no macroscopic residual disease is mandatory in advanced stages. A good fertility-sparing procedure can be performed only in young women at early stages of disease, when the wish for childbearing is not yet fulfilled.

Abbreviations: DSRCT = Desmoplastic Small Round Cell Tumours, EFT = Ewing's family of tumours, FISH = Fluorescence in situ hybridisation, PNETs = primitive neuroectodermal tumours, SCCOHT = small-cell carcinoma of the ovary, hypercalcaemic type.

Keywords: central primitive neuroectodermal tumor (cPNET), neoplasm, pregnancy, uterus

1. Introduction

PNETs (primitive neuroectodermal tumors) are a family of highly malignant neoplasms characterized by small round cells of neuroepithelial origin. They usually involve bone and soft tissues, and have a higher incidence in childhood. This is the second case to be diagnosed, at the advanced stage, in a pregnant uterus at emergency cesarean section, but in our case, there was a maternal indication in view of the clinical picture, not a fetal indication as in Blattner case.[1] PNETs were first described in 1973 as a group of small round cell tumors that arise from mesenchymal progenitor cells, belonging to a spectrum of neoplastic diseases known as Ewing family of tumors (EFT).[2,3] PNETs mostly affect Caucasian and Hispanic young adults and adolescents, and feature a male predominance.[4] PNETs of the genital tract are rare; they can share some genetic rearrangements such as translocations involving the *EWS-FLI1* genes, as in peripheral PNET or also CIC-DUX4.[5–8] To date, 112 cases of primary uterine PNET have been reported in the literature (see Table 1),[9,10] including the present case; the largest series is the 17-patient case series reported by Euscher et al.[9,10]

Differential diagnosis is with desmoplastic small round cell tumors (DRSCTs), belonging to Ewing Sarcoma family of tumors, and small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT). SCCOHT is a very rare and aggressive

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The authors report no conflicts of interest.

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Table 1

PNET of the uterus: review of the literature.

Ref.	Age	c/p	Tumors associated	Clinical presentation	Serum Ca125 level before treatment	Pregnant, gestational age at diagnosis	Site	Stage	Surgery	Adjuvant therapy	Survival and follow-up
Khosla et al[47]	28	NR	No	Cervical mass at routine gyn-ob evaluation	NR	Yes, 10 wks	Cervical	IB2	TOP + RH +(BSO+LNS?)	Adriamycin, IE, for total of 6 weeks/adjuvant + (RT?)	DFI 33 mo postsurgery
Venizelos et al[48]	68	NR	No	Vaginal bleeding	NR	No	Uterine isthmus	NR	NR	NR	NR
Goda et al[19]	19	NR	No	Vaginal discharge abdominal pain; tenesmus and difficulty in passing urine	NR	No	Cervical and vaginal mass	IVA (walls of urinary bladder and rectum)	Not performed	CAV + pelvic RT (50.40Gy/ 28 fractions to whole pelvis + boost to tumor alone 5.40 Gy / 3 fractions)	Improvement in symptoms; mass markedly reduced in size.
Bhardwaj et al[12]	50	C	No	Postmenopausal bleeding with polypoid mass emerging from endocervix	NR	No	Uterus, left parametrium and cervix	IIIC (one left external iliac lymph node)	TAH, BSO, OM and pelvic lymph node sampling Vaginal vault relapsed in 2 mo	3 cycles of RT + 6 cycles of CT (6 mo after surgery)	Vaginal vault relapse regressed. disease-free until 2010
Aminimoghaddam et al[49]	32	NR	No	Abdominal pain and fever, AUB	Negative	No	Uterus	IIIA (perimetrium)	Emergency laparotomy with TAH, BSO, PLND	Cisplatin and ifosfamide/ mesna + RT II line CT (Carboplatin +paclitaxel)	Recurrence (ascites and tumor relapse) after 17 mo from diagnosis. Ten mo later, new relapse: palliative treatment. F-up until 17 mo later, but prognosis quite poor.
Masoura et al[50]	23	P	No	Abdominal pain, AUB	NR	No	Cervix and pelvic lymph nodes	IVB (broncho-pulmonary infiltrations with regional nodes)	Surgical excision (?)	CT (only 1 course)	Death (MOF)
Loverro et al[6]	17	P	No	Abdominal pain	NR	No	Uterus without endometrial involvement	IB (mass $>$ 5 cm, in particular 10 cm)*	FSS (Diagnostic laparoscopy and local excision of the mass by laparotomy).	CT (IVADo) +RT (Protocol EpSSGRMS2005)	Free of disease until now
Tsao et al[13]	24	NR	No	Cervical mass at routine gyn-ob evaluation	NR	Yes, 8 wks	CERVIX	?	RH with bilateral ovarian transposition and periaortic lymphadenectomy	alternating courses of (CAV) and ifosfamide, etoposide (IE) neoadjuvant and adjuvant + RT	NED, 24 mo
Elizalde et al[10]	60	NR	No	Abdominal pain, AUB	NR	No	Uterus	IIIC2 (para-aortic nodes)	RH, BSO, and para-aortic lymphadenectomy	6 cycles of carboplatin and etoposide	After 4 mo: vaginal bleeding and pulmonary node Died after 7 mo from diagnosis with cystic abdominal mass, retroperitoneal relapse.
Dizon et al[39]	50	NR	No	Abdominopelvic pain and soreness	407	No	Uterus without endometrial involvement	IB	RH, BSO, debulking, omentectomy	6 cycles of adjuvant carboplatin and etoposide	No evidence of disease 16 months following completion of treatment
Bartosch et al[51]	58	C	EEC	Vaginal bleeding, abdominal pain, weight loss	NR	No	Uterus	IV	TAH, BSO, segmental enterectomy, total colectomy, right PLND	Carboplatin paclitaxel	Died after 11 mo, of sepsis from pyelonephritis
Celik et al[52]	32	NR	No	Abdominal pain, pelvic mass, intra-abdominal hemorrhage	NR	No	Uterus	IIIA	TAH, BSO, PLND, PALND, OM, appendectomy	Cisplatin Ifosfamide Adriamycin Vincristine	NED, 38 mo
Bhardwaj et al[53]	50	C	No	Vaginal bleeding, pelvic mass, polypoid mass emerging from introitus	NR	No	Uterus	IIIC	TAH, BSO, OM, PLND	Unknown chemotherapy regimen	NED, 6 mo
Odunsi et al[35]	66	NR	No	Vaginal bleeding	NR	No	Uterus	I	TAH, BSO, OM, PLND, PALND	Not done	NED, 2
Odunsi et al[35]	65	NR	No	Vaginal bleeding	NR	No	Uterus	IIIC	TAH, BSO, OM, PLND, PALND, upper vaginectomy	Cisplatin Doxorubicin Etoposide Paclitaxel	AWD, 12 mo Lung metastasis, 3 mo
Karseladze et al[55]	16	NR	No	Vaginal bleeding	NR	No	Uterus	I	TAH, BSO, OM	VDC	NED, 4
Hendrickson and Scheithauer[56]	12	NR	No	Vaginal bleeding, pelvic mass	NR	No	Uterus	IVB	TAH, LSO	VDC	Pelvic recurrence, 12 mo DOD, 2 y
Hendrickson and Scheithauer[56]	57	NR	No	Vaginal bleeding, uterine mass	NR	No	Uterus	IIB	TAH, BSO, PALND		Lung metastasis, 5 mo DOD, 2 y

(*continued*)

Table 1
(continued).

Ref.	Age	c/p	Tumors associated	Clinical presentation	Serum Ca125 level before treatment	Pregnant, gestational age at diagnosis	Site	Stage	Surgery	Adjuvant therapy	Survival and follow-up
Ward et al[57]	17	NR	No	Vaginal bleeding, pelvic mass	NR	No	Uterus	IIIC	RH, PLND, bilateral ovarian wedge biopsy	Cisplatin Vinblastine Bleomycin Vincristine Cisplatin Doxorubicin Dactinomycin Cyclophosphamide Etoposide	NED, 10 y
Rose et al[58]	17	NR	No	AUB, pelvic mass	NR	No	Uterus	NR	TAH, BSO, PLND	CT not known	NED, 5 y
Tarafdar Luna Laila et al[44]	20	NR	No	Pelvic heaviness and abdominal pain. Mild anemia, uterine, and left adnexal mass at US	22,4	No	Uterus	IV B (liver metastasis)	TAH+BSO+ OM	6 cycles ifosphamide, urometaxane, etoposide ◊ reduced residual tumor II line: CAV + Dacarbazine (only 1 cycle)	2 wks after surgery: ascites, negative at cytology 9 mo after surgery: huge ascites (6 L drained), pleural effusion and hepatomegaly AWD, under follow-up
Daya et al[46]	67	C (GI)	NR	Vaginal bleeding, enlarged uterus with a huge polypoid mass extending from the fundus to the isthmus	NR	No	Uterine corpus	IIIC	Subtotal hysterectomy, BSO	Pelvic RT + combined CT (Cisplatin Doxorubicin) II line CT: intraperitoneal Cisplatin followed by Carboplatin 5-FU	Persistent DOD, 6 mo
Daya et al[46]	68	C (Astr-GI)	Several leyomas	Vaginal bleeding, polypoid mass from posterior wall, pain in region of upper left tibia, enlarged uterus	NR	No	Uterine corpus	IVB (tibia metastasis)	TAH, BSO, right PLND	Cisplatin RT to left upper tibia with symptomatic relief	Persistent with supraclavicular node relapse DOD, 12 mo
Daya et al[46]	69	C (GI)	ESS	Vaginal bleeding, polypoid mass from the fundus	NR	No	Uterine corpus	IA	TAH, BSO, PLND	Pelvic RT	NED, 6 y
Daya et al[46]	68	C (GI)	EEC	Vaginal bleeding, endometrial polyps	NR	No	Uterine corpus	IA	TAH, BSO	Vaginal vault cesium insertion	NED, 5 y
Molyneux et al[59]	72	NR	No	Vaginal bleeding	NR	No	Uterus	I	TAH, BSO	Not done	DOD, 8 mo
Fragetta et al[60]	78	NR	No	Vaginal bleeding	NR	No	Uterus	IB	TAH, BSO, PLND	Not done	NED, 9 mo
Sørensen et al[61]	62	NR	No	Vaginal bleeding	NR	No	Uterus	I	TAH, BSO	Vincristine Cyclophosphamide Cisplatin	DOD, 18 mo
Taïeb et al[62]	36	NR	No	Uterine enlargement	NR	No	Uterus	I	RH, BSO, PLND	Not done	NR
Ng, Siok Bian et al[4]	48	NR	No	Vaginal bleeding	NR	No	Uterus	IIIC	TAH, BSO	Not done	NR
Blattner et al[1]	26	P	No	Intraoperative finding as a soft tissue mass at the lower uterine segment, distinct from the placenta)	NR	Yes, at term	Uterus (lower uterine segment) and paracervical mass	III B (paracervical mass, a questionable positive surgical margin at the anterior parametrial segment)	1st surgery: C-section and manual removal of the mass for histological examination 8 wks after C-section and staging CT modified RH, PLND, bilateral ovarian transposition	4 courses of VDC/IE every 3 wks. 4500 cGy of whole pelvic RT Then 12 courses of VDC/IE every 3 wks	NED, 16 mo after completion of therapy
Mittal et al[63]	24	NR	No	Fever, abdominal pain, pelvic mass	NR	No	Uterus	II	TAH, BSO, OM	VDC/IE	Recurrence, 1 month
Akbayır et al[64]	22	NR	No	Vaginal bleeding, adnexal mass	NR	No	Uterus	I	TAH, BSO, PLND, PALND, OM	Cisplatin Doxorubicin	NED, 10 mo
Peres et al[65]	15	NR	NR	Abdominal pain, fever, pelvic mass	NR	No	Uterus	I	TAH, PLND	Carboplatin Etoposide	NED, 12 m
Varghese et al[11]	43	NR	No	Vaginal bleeding, uterine enlargement	NR	No	Uterus	IIIC	TAH, BSO, PLND	Cytoxan Adriamycin Vincristine Etoposide	NED, 2 mo
Park, Jeong-Yeol, et al[20]	30	NR	No	Vaginal bleeding, uterine enlargement	NR	No	Uterus	IVB	None	VDC/IE	DOD, 16
Mashriqi, Nazia, et al[66]	49	P	No	Vaginal bleeding, lower abdominal pain	NR	No	CERVIX	II B, right parametrium	RH with upper vaginectomy, BSO Nephrostomy and exploratory laparotomy	Neoadjuvant CT: 2 Courses of cisplatin and etoposide + RT 5040 cGy over 28	Metastases to lumbar spine, pelvis, and bladder. distal colonic obstruction due to an extensive

(*continued*)

Table 1

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Ref.	Age	c/p	Tumors associated	Clinical presentation	Serum Ca125 level before treatment	Pregnant, gestational age at diagnosis	Site	Stage	Surgery	Adjuvant therapy	Survival and follow-up
									with diverting loop colostomy	fractions of 180cGy each Adjuvant CT: VDC/IE, 4 cycles (renal failure)	pelvic tumor. New lung metastases, DOD 10 mo
Shah et al[67]	59	NR	No	Vaginal bleeding, pelvic mass	NR	No	Uterus	IIIC	TAH, BSO, PLND, PALND, OM	Paclitaxel Carboplatin	AWD, 12 mo
Majeed et al[68]	27	NR	No	Vaginal bleeding, uterine Mass	NR	No	Uterus	NR	TAH/BSO	Vincristine+ Etoposide+ Doxorubicin+ Ifosfamide/ Vincristine+ Ifosfamide	NED, 2 y
Ren et al[69]	56	NR	No	Vaginal bleeding	NR	No	Uterus	IB	TAH, BSO, PLND	Ifosfamide Etoposide Cisplatin	NED, 41 mo
Fukunaga et al[70]	54	NR	No	Unknown	NR	No	Uterus	NR	TAH, BSO	Cyclophosphamide Cisplatin Doxorubicin 5-FU	AWD, 3 mo
Venizelos et al[48]	68	NR	No	Vaginal bleeding	NR	No	Uterus	I	TAH, BSO	Not done	NED, 10 mo
Euscher et al[9]	58	NR	No	Vaginal bleeding with palpable mass	NR	No	Uterus	IIIC	Unknown surgery	Not done	DOD, 2 mo
Euscher et al[9]	31	NR	NR	Back pain from metastatic disease	NR	No	Uterus	IV	Not done	Unknown	DOD, 20 mo
Euscher et al[9]	72	NR	NR	Vaginal bleeding	NR	No	Uterus	IA	Unknown	Unknown	DOD, 11 mo
Euscher et al[9]	48	NR	NR	Unknown	NR	No	Uterus	IIIC	Unknown	Unknown	Unknown
Euscher et al[9]	81	NR	NR	Vaginal bleeding	NR	No	Uterus	Unknown	Unknown	Unknown	Unknown
Euscher et al[9]	66	NR	NR	Pelvic mass	NR	No	Uterus	IIIC	Unknown	Letrozole	NED, 41 mo
Euscher et al[9]	53	NR	NR	Vaginal bleeding	NR	No	Uterus	Unknown	Unknown	Unknown	DOD, 22 mo
Euscher et al[9]	51	NR	NR	Vaginal bleeding	NR	No	Uterus	Unknown	Unknown	Unknown	DOD, 12 mo
Euscher et al[9]	31	NR	NR	Vaginal bleeding	NR	No	Uterus	Unknown	Unknown	Unknown	DOD, 26 mo
Euscher et al[9]	64	NR	NR	Cervical polyp	NR	No	Uterus	IIB/possible IIIC	TAH, BSO	Unknown	NED, 36 mo
Euscher et al[9]	64	NR	NR	Vaginal bleeding with pain	NR	No	Uterus	Unknown	Unknown	Unknown	Unknown
Euscher et al[9]	69	NR	NR	Unknown	NR	No	Uterus	IV by imaging	Unknown	Unknown	Unknown
Euscher et al[9]	62	NR	NR	Uterine fibroids	NR	No	Uterus	IIIC	Unknown	Unknown	DOD, 22 mo
Euscher et al[9]	52	NR	NR	Unknown	NR	No	Uterus	IV	Unknown	Unknown	NED, 6 mo
Euscher et al[9]	58	NR	NR	Vaginal pressure with passage of tissue	NR	No	Uterus	IV	Not done	Unknown	NED, 6 mo
Euscher et al[9]	57	NR	NR	Unknown	NR	No	Uterus	IIIC	Not done	Unknown	NED, 35 mo
Stolnicu et al[71]	12	NR	NR	Vaginal bleeding with passage of tissue	NR	No	Uterus	Unknown	Not done	BEP	NED, 36 mo
Cate et al[44]	25	NR	NR	Vaginal bleeding, uterine inversion and prolapse	NR	No	Uterus	Unknown	TAH	Not done	NED, 18 mo
Dizon et al[39]	50		No	Abdominopelvic pain	407	No	Uterus	Unknown	TAH, BSO, OM	Carboplatin, Etoposide	NED, 16 mo
Yi et al[44]	29	NR	No	Abdominal swelling and pain	NR	No	Uterus	IVB	TAH, BSO, PALND, PLND, OM	Neoadjuvant docetaxel and carboplatin. CAV	AWD, 18 mo Liver metastasis
Novo et al/Gynecologic[44]	26	C	No	Vaginal bleeding, uterine mass	372 10 at last follow-up	No	Uterus	IV	TAH, BSO, OM, PLND	Carboplatin Etoposide Avastin	NED, 61 mo
Shimada et al[44]	63	C	No	NR	NR	No	Uterus and peritoneal dissemination	IIIC para-aortic lymph node metastasis	Cytoreductive debulking surgery	CAV	No evidence of disease at 24 mo after surgery
Xiao et al[14]	52	NR	No	AUB and uterine enlargement	13.7 84.5 (relapse)	No	Cervix	IIA	TAH+BSO+ PLND + cytoreductive surgery	PVB 2 courses	Pelvic recurrence, after 6 mo DOD, 9 mo
Xiao et al[14]	59	NR	No	AUB, pelvic mass prolapsed from vagina	706.5	No	Cervix	IVB (widespread disseminated tumor of the abdominopelvic cavity)	TAH+BSO+ PLND + partial small bowel resection	Not done	DOD (MOF after 15 d)
Xiao et al[14]	43	NR	No	Incidental finding by other operation	37	No	Right round ligament	IA	TAH+bilateral salpingectomy +bilateral ovarian	Not done	NED, 87 mo

(*continued*)

Table 1

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Ref.	Age	c/p	Tumors associated	Clinical presentation	Serum Ca125 level before treatment	Pregnant, gestational age at diagnosis	Site	Stage	Surgery	Adjuvant therapy	Survival and follow-up
									wedge resection+ PLND		
Xiao et al[14]	31	NR	No	Abdominal pain and pelvic mass	96	No	Right broad ligament	IIB	TAH+BSO+ PLND +pelvic tumorectomy	PEI, 1 course	Lost to follow-up
Xiao et al[14]	37	NR	No	Pelvic mass+AUB	184.4	No	Uterine corpus	III	RH	VDCA + IE, 1 course	DOD, 8 mo
Xiao et al[14]	31	NR	No	AUB+ uterine enlargement	44	No	Uterine corpus	Unavailable	RH	PEI, 4 courses	Under treatment
Xiao et al[14]	18	NR	No	Abdominal pain+AUB	71 28.7	No	Uterine corpus	IIA	RH	PAC 2 courses BEP, 4 courses	Pelvic recurrence, 62 mo NED, 145 mo
Russin et al[72]	60	NR	No	Vaginal bleeding	NR	No	Uterus	IB	TAH+BSO+LND	VAC for 6 wks + RT	Alive at 16 mo, NED
Sato et al[54]	44	NR	No	Irregular vaginal bleeding	NR	No	Cervix	IB2	TAH+BSO+LND, second look after 6 mo	Cisplatin, VP16, cyclophosphamide (Cytoxan), doxorubicin (Adriamycin)	Alive, 6 mo, NED
Horn et al[73]	26	NR	No	Suspect cervical smear	NR	No	Cervix	IB1	TAH+BSO+LND	RT to metastases. 3 y later: lung metastases, 5FU and cisplatin/palliative	Died 4.2 y after diagnosis
Cenacchi et al[74]	36	NR	No	Irregular vaginal bleeding	NR	No	Cervix	IB2	TAH without BSO	NO	Alive 18 mo, NED
Pauwels et al[75]	45	NR	No	Irregular vaginal bleeding	NR	No	Cervix	IB2	TAH	Pelvic RT	Alive 42 mo, NED
Malpica and Moran[76]	35	NR	No	Vaginal bleeding	NR	No	Cervix	IB1	TAH+BSO+LND	Adjuvant chemotherapy/ regimen not reported	Alive 5 mo, NED
Malpica and Moran[76]	51	NR	No	Vaginal bleeding	NR	No	Cervix	IB2	TAH+BSO+LND	Adjuvant chemotherapy/ regimen not reported	Alive 18 mo, NED
Snijders-Keilholz and Ewing[77]	21	NR	No	Intermenstrual bleeding	NR	No	Cervix	IB2	TAH without BSO	Six courses of DIME/ neoadjuvant; 5 courses of VIA/adjuvant	Alive 27 mo, NED
Farzaneh et al[78]	43	NR	No	Purulent vaginal discharge	NR	No	Cervix	IB2	TAH+BSO+LNS	12 wks of VAC alternating with IE/neoadjuvant 12 weeks of VAC alternating with IE/ adjuvant	Alive 4 y, NED
Benbrahim et al[79]	25	NR	No	Irregular vaginal bleeding	NR	No	Cervix	IIb	Conisation with brachytherapy	Four cycles of Adriamycin and Cytoxan/neoadjuvant + RT	Alive 8 y, NED
Arora et al[80]	23	NR	No	Irregular bleeding, dysuria	NR	No	Cervix	NR	TAH+BSO+LND	One cycle of CAV, followed by 2 cycles of cis/VP16/ neoadjuvant + RT	Alive, 4 y NED
Masoura et al[50]	23	NR	No	Irregular bleeding, abdominal pain	NR	No	Cervix	IV	TAH+BSO	Cisplatin once/adjuvant	Died, 12 d
Li et al[81]	27	NR	No	Contact bleeding, abdominal pain	NR	No	Cervix	IIIB	Unresectable	VAC alternating with IE/ definitive chemotherapy	Alive at 6 mo, NED
Eskiyörük et al[82]	63	NR	No	Mass-like submucosal degenerated myoma nodule in the uterine cavity on ultrasonographic examination	NR	No	Miometrium	III C (positivity of left iliac lymph nodes at postoperative PET)	TLH + BSO	EVAIA After severe renal failure and granulocytopenic fever ◊VAC-IE combination	NED, not reported time of follow-up
Eskiyörük et al[82]	17	P	No	Uterine masses like myoma	NR	No	Miometrium	NR (2nd surgery was done at another hospital)	"Myomectomy" 2nd surgery: TLH +BSO	VAC and ifosfamide-etoposide for 52 wks	NED, 61 mo
Chiang[8]	66	C Me	No	Vaginal bleeding	NR	No	Uterus	III	TH+BSO†	Multiagent adjuvant CT, regimen not known	DOD, 6 m
Chiang[8]	51	C Mb	No	Vaginal bleeding	NR	No	Uterus	III	TH+BSO†	No	NED
Chiang[8]	50	C Mb	No	Vaginal bleeding	NR	No	Uterus	III	TH+BSO†	No	NA
Chiang[8]	31	C Me	No	Vaginal bleeding	NR	No	Uterus	III	TH+BSO†	No	NA
Chiang[8]	26	P	No	Vaginal bleeding	NR	No	Uterus	I	TH+BSO†	No	NA
Chiang[8]	68	C Mb	No	NA	NR	No	Uterus	IV	TH+BSO†	No	DOD, 12 mo
Chiang[8]	64	C Mb	No	NA	NR	No	Uterus	III	TH+BSO†	Multiagent adjuvant CT, regimen not known	NED
Chiang[8]	NA	C Mb	No	NA	NR	No	Uterus	NA	TH+BSO†	No	NA
Dundr et al[45]	63	C	RMS	Vaginal bleeding	NR	No	Uterine corpus	IIIC	Abdominal RH+BSO+ PLND	CT (6 courses cis-platin +ifosphamide)	

(*continued*)

Table 1
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Ref.	Age	c/p	Tumors associated	Clinical presentation	Serum Ca125 level before treatment	Pregnant, gestational age at diagnosis	Site	Stage	Surgery	Adjuvant therapy	Survival and follow-up
											DOD 7 mo after diagnosis (pelvic, mesenteric, and peritoneal metastases)
Dundr et al[45]	80	C	EEC	Abdominal pain	NR	No	Uterine corpus	IB	Abdominal RH+BSO+ PLND	RT (60 Gy)	AWD 6 mo after diagnosis (intraabdominal metastases), then lost to follow-up)
Dundr et al[45]	79	C	EEC	Vaginal bleeding	NR	No	Uterine corpus	IB	Abdominal RH+BSO+ PLND	None	NED, 29 mo
Dundr et al[45]	78	C	No	Vaginal bleeding	NR	No	Uterine corpus	IIIA	Abdominal RH+BSO+ PLND	None	NED, 8 mo
Gersel et al[83]	66	C, GI	MMMT	Pelvic mass prolapsed from vagina	NR	No	Uterus	IIIC (Para-aortic firm nodes noted but not biopsied)	TAH+BSO	Neoadjuvant whole pelvic irradiation 4800Rad CT after relapse: 2 courses of cisplatin, cyclophosphamide, doxorubicin, dexamethasone.	18 mo after surgery pulmonary metastasis, abdominal pain, ascites Reduced pulmonary nodules after CT, but new nodal metastasis (left supraclavicular and right axillary nodes). DOD, 2 years
Quddus et al[84]	67 (avarage from 12 cases)	Mostly P	5 ESCs cases + 7 EECs cases	NR	NR	No	Uterus	All the cases presented at IIIC stage	NR	NR	NR
Our case	39	C	No	Shock state with severe anemia, hypovolemia, and abundant hemoperitoneum with an abdominal mass	166, 5 (after 1st emergent surgery)	YES, 25th week	Uterus, parametrium, peri-adnexal tissues, colic and peritoneal dissemination (paracolic, colic, pelvic, diaphragm, Morrison pouch); hepatic hilum parenchymal node.	IIIC paracaval (including a large lymph node infiltrating the left renal vein) and pelvic lymph nodes,	First surgery: emergency caesarean section and type B RH + pelvic peritonectomy +omentectomy+ appendectomy. 2nd surgery, after staging CT scan: PALND*, cytoreductive surgery until NED.	Cisplatin 25/m^2 days 1–3 + Etoposide 100 mg/mg days 1–3 q 21 for 6 courses	Free of disease until now (24 mo)

STAGE FIGO defined according to primitive lesion. Astr = Astrocytoma, AUB = abnormal uterine bleeding, AWD = alive with disease, BEP = bleomycin, etoposide, and cisplatin, BSO = bilateral salpingo-oophorectomy, C/P = central/peripheral PNET based on immunophenotypic or biological features, CAV = Vincristine, Cyclophosphamide, Adriamycin, CS = carcinosarcoma, CT = chemotherapy, DFI = disease-free interval, DOD = died of disease, EEC = endometrial endometrioid carcinoma, ESS = endometrial stromal sarcoma, EVAIA = ifosfamide, dactinomycin, adriamycin, etoposide, vincristine, uromitexan, and G-CSF, FSS = fertility sparing surgery, GI = Glioblastoma, IVADo = ifosfamide, vincristine, actinomycin D, and doxorubicin, LSO = left salpingo-oophorectomy, Mb Medulloblastoma, Me Medulloepithelioma, MMMT = Mixed Malignant Müllerian tumor, MOF (Multi Organ Failure), NED = no evidence of disease, NR = not recorded, OM = omentectomy, PAC = cisplatin, epirubicin, and cyclophosphamide, PALND; pelvic and para-aortic lymph node dissection, PEI = cisplatin, epirubicin, and ifosfamide, PLND = pelvic lymph node dissection, RH = radical hysterectomy, RMS = rhabdomyosarcoma, RT = radiotherapy, TAH = total abdominal hysterectomy, Termination of pregnancy (TOP), TLH = total laparoscopic hysterectomy, VDC/IE = vincristine, doxorubicin, cyclophosphamide, and etoposide+ifosfamide/mesna, VDCA = vincristine, actinomycin D, and doxorubicin

* We also dissected a large lymph node infiltrating the left renal vein, by interruption and reconstruction.

† Chiang et al[8] wrote that 2 of the 8 patients had lymph node dissection, but did not specify which patients underwent the procedure.

‡PNETs that arise from the myometrium, without involvement of the endometrium, are classified by FIGO 2009 sarcoma staging; PNETs of the endometrium are staged as endometrial cancer, while PNETs of the cervix are classified as cervical cancer, according to FIGO 2009.

malignant tumor affecting children and young women, characterized by SMARCA4 protein loss and hypercalcemia.

PNETs can be subdivided into 2 major categories: central type, composed by small round cells displayed more or less like central nervous tumors, and peripheral type or extra-osseous Ewing sarcoma, composed entirely by sheets of small round cells and sometimes rosettes.[8] Most primary uterine PNETs belong to the central type PNET, so they lack the *EWSR1* gene translocation, as in our case, even if they share some morphological features with the peripheral types.[8,11] In the case series of uterine PNETs collected by Euscher et al,[9] CD99 was positive in 7 of 9 cases tested for the marker; all 12 cases were tested for the typical EWSR1 rearrangement, but yielded negative results.[1]

2. Case report

In this case report, we describe the obstetric and oncological outcome of a huge mass diagnosed as a leiomyoma, operated at 25 weeks of gestational age in a 39-year-old pregnant woman with a previous obstetric history of 1 spontaneous abortion and 1 vaginal delivery. Written informed consent was given by the patient. The project has been approved by the local Ethics Committee and conforms to the provisions of the Declaration of Helsinki in 1995.

The patient had never had previous surgery, and denied any previous health problems. Since the first trimester screening had evidenced a borderline risk for 21 trisomy, she underwent amniocentesis showing a normal female karyotype. However, the morphological US examination, at 22 gestational weeks, demonstrated a huge (9 cm) abdominal mass, classified as a leiomyoma; at this time, the patient started to complain of low back pain, dysuria, and urinary frequency.

During the 25th week, the patient was referred to our tertiary level hospital for severe anemia, hemoperitoneum, and persistent hypovolemia, despite the administration of 5 units of blood.

A worsening state of shock and increasing abdominal effusion with the ultrasound features of hemoperitoneum dictated an urgent caesarean section, performed by longitudinal laparotomy. After removing 400 mL of blood, we found a huge solid mass, crumbly and strictly adhering to the whole anterior surface of the uterus. LSCS (lower segment caesarean section) was not possible, so we performed a posterior vertical section (see Fig. 1) in order to achieve an "en bloc" extraction of the fetus, placenta, and amniotic sac. The neonate was alive and well, weighing 400 g, with an Apgar score of 7 after 1 minute and 9 at 5 minutes.

The uterus was dislocated and expanded by the presence of numerous confluent scirrous nodules, distributed from the fundus up to the front face, and also involving the parametria. The adnexae seemed to be macroscopically normal, but we decided on radical salpingo-oophorectomy.

Considering the vast uterine involvement by the tumor, reaching a maximum diameter of about 35 cm, we proceeded with a type B radical hysterectomy,[84,85] associated with pelvic peritonectomy, omentectomy, and appendectomy. Manual exploration of the retroperitoneum highlighted extensive lymphadenopathy, extending from the pelvic retroperitoneum up to the renal level; the visual and palpable mean diameter of pelvic lymph nodes was 5 to 6 cm.

Perioperatively, we transfused 6 units of plasma and 5 units of red blood cells.

In view of the severe anemia and the emergency nature of the caesarean section, we postponed a nodal debulking until after appropriate instrumental staging and histological diagnosis.

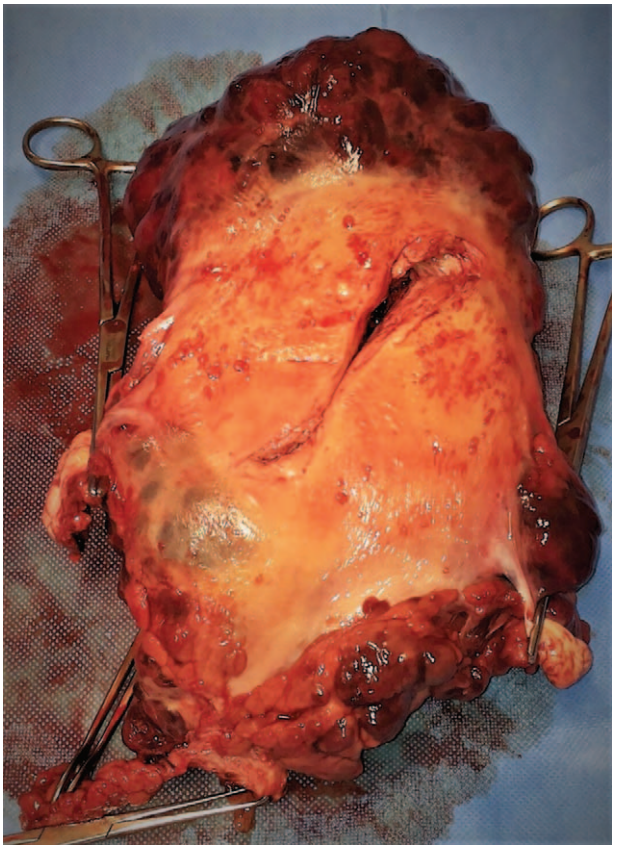

Figure 1. Uterus grossly involved by neoplasia with a sagittal caesarean cut on its posterior face; ovaries were macroscopically free of disease, but we removed them in order to be radical.

Oncological serum markers were investigated in the early postpartum period, showing slight positivity of CA 125 [166.5 U/mL (normal value, n.v., 0.0–30.0 U/mL)] and AFP [21.6 ng/ml (n.v. 0.0–8.0 ng/mL)]. The patient also showed a mild reduction of renal function [serum creatinine 1.33 mg/dL (n.v. 0.51–0.95 mg/dL); eGFR 50 mL/min (n.v. >90 mL/min) and severe hypoalbuminemia [1.7 g/dL (n.v. 3.4–5.0 g/dL)].

The serum calcium level after the first surgery was 8.2 mg/ dL [n.v. 8.5–10.1 mg/dL] with albumin 1.8 g/dL [n.v. 3.4–5.0 g/dL], versus 7.9 mg/dL with serum albumin 2.7 g/dL at discharge.

CT scan, performed 1 week after caesarean section, demonstrated multiple bulky lymph nodes in the hypogastric-obturatory, peri-aortic, intercavo-aortic regions, the largest measuring 6 x 5 cm in high retrocaval position, causing caval compression and anterior dislocation of the left vein (see Fig. 2).

Bulky nodes also distorted both common iliac vessels and the ureters, causing bilateral hydro-nephrosis. There were moderate ascites, as well as focal and partial thrombosis of the inferior vena cava under the renal vein and right iliac vessel, each extending for about 2 cm. The peritoneum was thickened both against the abdominal wall and on the visceral side, up to the diaphragm.

Two weeks after the first surgery, we completed debulking with a second surgery including diaphragmatic peritonectomy and excision of a huge lymph node by lombo-aortic lymphadenectomy (see Fig. 3).

We dissected a large lymph node infiltrating the left renal vein, by interruption and reconstruction of the vein. The left renal vein lesion was linear and without loss of substance, so it was possible

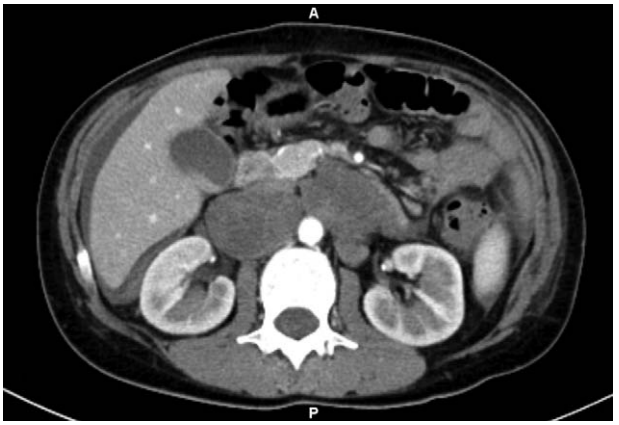

Figure 2. CT scan of the abdomen demonstrated many bulky lymph nodes, the largest measuring 6×5 cm in high retrocaval position. This one caused a caval compression and an anterior dislocation of the left vein with a focal thrombosis from kidney level until the right common iliac vein.

to repair it by prolene running whipstitches, after upstream and downstream clamping with vascular loops.

During the second surgery, 9 units of red blood cells and 2 units of plasma were transfused; the great quantity of transfusions was justified by the peculiar anatomic dislocation of the enlarged lymph-nodes. After the second surgery, the renal function was completely restored (serum creatinine 0.78 mg/dL and eGFR 96 ml/min). The patient was discharged after 10 days, while the neonate remained in the neonatal intensive unit for 1 month. They were both discharged in good health.

Ten days after the second surgery, echo-color Doppler showed normal microcirculation resistance indices in the left kidney and a normal patency of the reconstructed left renal vein.

Histological examination revealed a uterine body PNET (peripheral primitive neuroectodermal tumor) with diffuse lymph

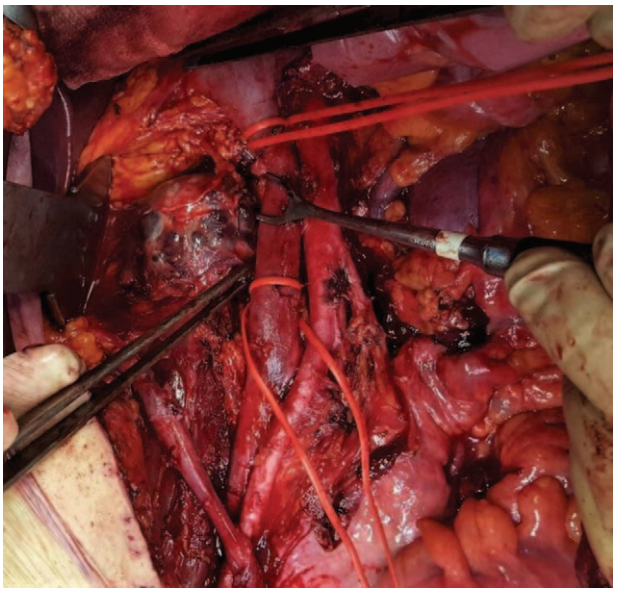

Figure 3. From the right side: a huge retrocaval bulky lymph node under the renal vein level, then inferior vena cava and aorta, both isolated from other bulky lymph nodes.

invasion of the vascular space, involving the uterus, omentum, and epiploic nodules, posterior parametrium, peri-adnexal tissues, but not the ovaries and tubes. The tumoral cells were undifferentiated, round, small, and monomorphic with a tendency to form nests.

The results of immunohistochemistry are summarized in Table 2 and Fig. 4.

The histological findings after the second surgery confirmed the diagnosis of metastasis of a uterine body PNET (primitive neuroectodermal tumor) to the paracaval lymph node, ovarian veins bilaterally, obturatory lymph nodes bilaterally, sigmoid and ascendant epiploon, paracolic peritoneum, diaphragm nodule, caecum peritoneal node, Morrison peritoneum, hepatic hilum parenchymal node, and vaginal cuff.

Because the restaging CT after the second surgery showed mild ascites and a small pulmonary nodule at the right lung apex, measuring less than 5 mm, with mesenteric-infra-mesocolic lymph nodes of borderline radiological significance, a histological re-evaluation was performed.

The new immunohistochemistry is also summarized in Table 2; FISH (fluorescence in situ hybridization) study demonstrated negativity for EWS (Ewing sarcoma), a 22q12 translocation, WT1, and CIC rearrangement (with BAC Bacteria Artificial Chromosome probe library RP11).

Clinical management was therefore adjuvant chemotherapy consisting of 6 courses as follows: Cisplatin 25/m^2 days 1–3 + Etoposide 100 mg/mg days 1–3 q 21. The ascites disappeared after 3 courses of chemotherapy and Ca125 reached a negative value, 19.46 U/mL after the fourth course.

The patient has completed therapy, and at 2 year's follow-up, she is in good general health with a good performance status (ECOG PS 0), and her daughter is also well.

3. Discussion

Primitive neuroectodermal tumors (PNETs) belong to a group of small round cell tumors that are most commonly found in the central nervous system, soft tissues, or bones (Kim et al).[5] They are rare in the female genital tract; the ovary is their preferred site (Odunsi et al).[35] There were less than 50 cases of PNET of the uterus reported in the English literature,[6,12] before the present case report. Pregnancy should not delay diagnosis of this potentially aggressive tumor. This case is only the second to be reported with onset in the uterine body during pregnancy.[1]

Risk factors for uterine PNET have a bimodal distribution, during adolescence or in postmenopausal age. A uterine localization usually presents with abnormal uterine bleeding if there is endometrial involvement; in any case, uterine PNETs are characterized by an aggressive behavior (Park et al).[20] Ca125 may play a role as an important marker for the prognosis and follow-up of PNET of the female internal genital tract.[14]

The present case is the only one in literature to be diagnosed during the second trimester of pregnancy, mimicking a large uterine fibroma with an acute clinical onset due to sudden severe anemia and hemoperitoneum.

The devastating disease spread in an otherwise normally evolving pregnancy and required an unusual access to the uterine cavity to deliver the fetus from a grossly altered, bleeding uterus, and 2-step surgery in order to complete the debulking, as well as demanding reconstruction of an infiltrated left renal vein.

Our case is also a rare example of caesarean section through the posterior uterine wall; this has previously been described in literature in 3 cases of torsion of a pregnant uterus due to a large

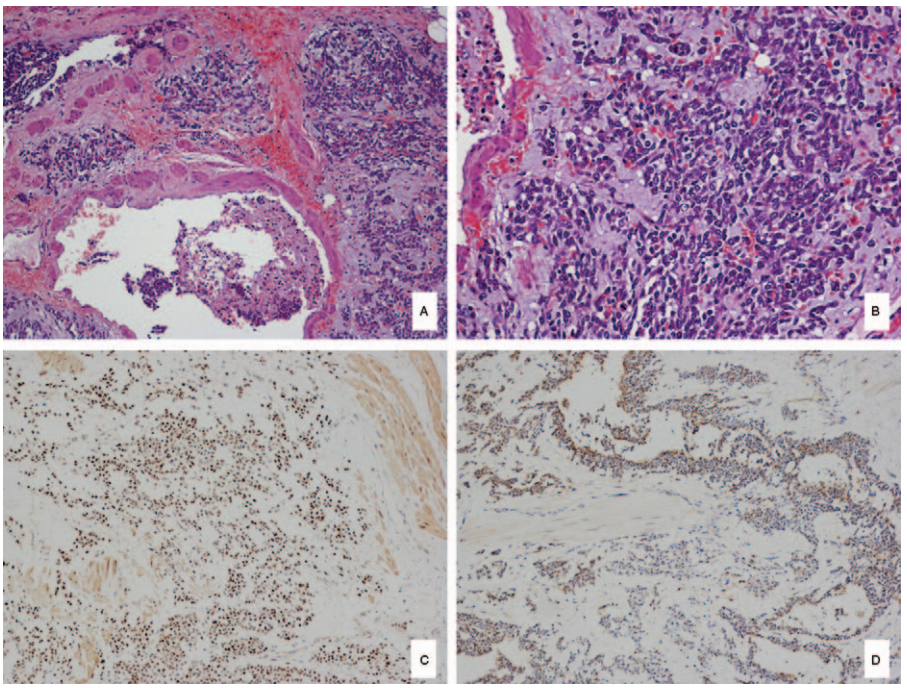

Figure 4. PNET, pathological characteristics: (A,B) Histologic examination showed undifferentiated neoplasms composed of diffuse sheets, nests, and cords of noncohesive monomorphic small blue/basaloid cells (H-E: 100x, 200x). The neoplastic cells showed mild and focal immunoreactivity for (C) WT1 and (D) CD99.

Table 2

Immunohistochemistry results.

Marker	Result	Results reported in literature
CD 99	Positive (dot wise)	Positive (dot wise)
WT1	Positive (dot wise)	Positive (dot wise)
p16	Not tested	Positive (dot wise)
BRG1	Not tested	Negative
INI-1	Not tested	Positive (dot wise)
CK pool	Negative	CK AE1-AE3 Positive; CK 5/6 Positive
PAX8	Not tested	Negative
ER	Not tested	Positive 70%
PgR	Not tested	Positive >90%
Vimentin	Negative	Not tested
HHF35	Negative	Not tested
Desmin	Negative	Positive
Podoplanin, caldesmin, myogenin, smooth muscle alpha-actin e (1A4)	Not tested	Negative
NSE	Negative	Not tested
Chromogranin (A and B)	Negative	Negative
Melan-A	Negative	Negative
SOX10	Not tested	Negative
Synaptophysin	Negative	Negative
Protein S100	Negative	Negative
EMA	Not tested	Negative
GCDFP15	Negative	Not tested
CD3; CD10; CD20; CD34; CD 56; CD138	Negative (CD 56 not tested)	Negative (CD 3; CD 20; CD 138 not tested)
TTF1	Negative	Not tested
Inhibin	Negative	Negative
HMB45	Negative	Negative
Myeloperoxidase	Negative	Not tested
BCL1	Not tested	Negative
SF1	Not tested	Negative
SALL4	Not tested	Negative
Mib-1 (proliferation index)	Not tested	Mild

myoma[15–17] and one of a severe placenta percreta precluding ordinary LSCS.[18]

During the 2-year postsurgical follow-up, we were pleased to observe the normal clinical health status of the patient, and of a healthy baby girl, who is developing well.

The histological diagnosis was very challenging, strongly influencing the therapeutic choice. PNETs are characterized by small, uniform round malignant cells with rounded vesicular nuclei bearing small nucleoli; the surrounding cytoplasm is scanty and ill defined; the N/C ratio is increased, with a high mitotic activity. Central PNETs show sheets of poorly differentiated small blue cells with an architecture that mimics tumors of the CNS: neuropil islands, ependymal rosettes, vascular pseudo rosettes, pseudostratified neuroepithelium with tubular spaces, and multi-layered tubular rosettes and neuroblastic rosettes. Peripheral PNET or extraosseous Ewing sarcoma is composed entirely by sheets of small round cells and sometimes rosettes without a CNS-like architecture.[8] Immunochemistry can also show diffuse membranous CD99, a highly specific marker, but also vimentin, intranuclear FLi-1, and sometimes keratin cocktails (CAM 5.2; AE1/AE3).[8,19,20]

In our case, the tumoral cells were undifferentiated, round, small, and monomorphic with a tendency to form nets; immunohistochemistry showed focal CD 99 and WT1 expression, but was negative for vimentin (see Fig. 4).

FISH or PCR evaluation could add information to the diagnosis. In fact, peripheral PNETs harbor chromosomal translocations that codify for chimeric transcripts, usually involving EWSR1 (22q12) with a spectrum of other Ewing sarcoma transcription factors. EWSR1 can often form a chimeric couple with FLI 1 (11q24) (85%) or ERG (21q22) (5–10%). EWSR1 may also match with ETV1, E1AF, or FEV; in other cases, there is no translocation involving EWSR1, such as CIC-DUX4 or BCOR –CCNB3.[4,7,20–22]

However, the distinction between peripheral and central PNETs is not easy because the morphological and immunophenotype characteristics commonly overlap. In the literature, however, only in few cases, the presence or absence of EWSR1 translocations has been specified.

Moreover, PNET tumors require differential diagnosis with other comparable conditions.[8] Desmoplastic small round cell tumors (DRSCTs), such as pPNETs, belong to the ESTs family: DRSCT could mimic PNET. DRSCT are aggressive neoplasms that predominantly occur intra-abdominally in young people, mostly males, and are characterized by a recurrent translocation EWSR1-WT1 t (11; 22) (p13; q12).[22,23]

Another condition that could mimic DRSCT or PNETs is small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), identified by Dickersin et al in 1982 as a unique entity.[24] In 82% of SCCOHTs, there is SMARCA4 protein loss (BRG1gene), which is extremely rare in all other primary ovarian tumors, just 0.4%. On the basis of morphologic and molecular affinities between SCCOHT and atypical teratoid/malignant rhabdoid tumors (MRTs), some authors have proposed a new name: MRT of the ovary. MRTs arise more frequently during childhood in the kidney. Rarely they can be seen in adults and extra-kidney sites, such as the female genital tract. Most MRTs, including tumors arising in the brain, called atypical teratoid/rhabdoid tumors [AT/RTs], host inactivating mutations in SMARCB1 (INI-1; SNF5; BAF47).[25,26] Other MRTs of the ovaries, without the SMARCB1 alteration, harbor a similar mutation involving the *SMARCA4* gene (also called BRG1) as also occurs in SCCOHT, so both can be denominated MRTOs.[26–32] In the 150 cases of SCCOHT described by Young et al in 1994,[33] hypercalcemia was found in 49 of the 79 patients (62%) with documented preoperative calcium levels; similar data were confirmed in the review by Callegaro-Filho et al.[34] In literature, SCCOHT at surgery was unilateral in 148 cases (99%), and extraovarian spread was present in about 50% of cases. SCCOHT was found during routine examinations in pregnancy in 2 cases during caesarean section and in 2 other cases during clinical evaluation in puerperium. When preoperative and postoperative serum calcium levels were tested, their values returned to normal after removal of the tumor while, in many cases, the calcium level rose once more at the time of the recurrence.[33] Moreover, SCCOHT usually spreads inside the pelvis and abdomen as an ovarian cancer. Involvement of abdominal and pelvic lymph nodes or even the presence of parenchymal liver metastases have also often been observed. Rarely, distant metastases are observed, spreading to the lungs, brain, and bones.[33]

According to Young et al,[33] SCCOHT has an epithelial origin based on immunohistochemical (IHC) staining and electron microscopy findings of an abundantly dilated rough endoplasmic reticulum. SCCOHT can also show a morphological signature, unlike other small cell carcinomas, consisting in a predominance of large cells with an abundant cytoplasm.[33] However, in our case, the serum calcium value was always borderline, at the lower extreme of the normal range and the ovaries were both free of disease at pathological examination excluding SCCOHT, and MRTO in general, from a clinical point of view.

Finally, a genital tract that has the morphological and immunophenotypic characteristics of a neuroectodermal tumor, in the absence of EWSR1-associated translocations, could be considered as a central PNET, as in our case (see Table 3).

In the Table 1, we have reviewed 111 cases of PNET of the uterus, including ours, which brings the total to 112 cases. The average age of onset is 45.64 years, the median being 49.5 years. The mean pre-treatment Ca 125 value is 199.14 U/mL, suggesting therefore only a peritoneal surface irritation and not an actual peritoneal neoplasia. The most common clinical presentation is vaginal bleeding (66.33%) and, showing similar rates, the presence of a pelvic mass (22.77%) and of abdominal pain (21.78%). There was a concomitant pregnancy only in 4 of the 101 cases. Pregnancy interruption was the precipitating cause in w of these, while in a third case (Blattner et al[1]), PNET was found incidentally at the operating table during a C-section at term for a fetal indication, suggesting a small but invasive tumor.

Table 3

Fish results.

Gene	Result
EWS- FLI 1	Negative
EWS-ERG	Negative
EWS-ETV1	Negative
EWS-E1AF	Negative
EWS-FEV	Negative
CIC-DUX4	Negative
BCOR –CCNB3	Not tested
FUS-FEV	Not tested
EWSR1-WT1	Negative
SMARCA	Negative
SMARCB1	Negative

In our case, emergency laparotomy and caesarian section were performed in a pregnant woman at 25-weeks' gestation, and extensive 2-step debulking surgery, due to huge hemoperitoneum, abdominal pain, and a large pelvic mass. Our follow-up has lasted 24 months so far; the mean follow-up in the literature is 26.53 months. Among the 112 reported cases, including ours, there were 23 deaths with a mean interval before DOD, death of disease, of 12.7 months from diagnosis, and a median DOD of 9.5 months. The presentation stage, when reported or deducible from the information provided by the authors (94/112), was above all advanced (≥ III stage). We found 43 cases reported at stage III, including ours belonging to stage IIIC; 15 cases at stage IV and 36 at stages I-II, 18 cases at unknown stages. In 61.70% of cases, the presentation reaches advanced stages (III-IV stage), while in 38.29% cases, the presentation stops at the first stages (stage I-II). From the above data, the aggressiveness of the biological behavior of the uterine PNETs is very clear.

Treatment for PNETs can be surgery, radical, or conservative with or without lymphadenectomy because the role of radiation is unclear,[6] or chemotherapy alone or else a multimodal approach. At 2 years, survival of young people is 75%, versus 32% in the postmenopausal age group.[35]

Thanks to chemotherapy, the prognosis of Ewing sarcoma family of tumors reaches a 60% survival rate at 5 years: in more than 80% of cases, ESFTs are chemosensitive, with a good prognosis. Intensive chemotherapy schedules include alkylating agents (cyclophosphamide or ifosfamide), vincristine, actinomycin- D, and frequently doxorubicin.[36,37]

Recent studies suggest that doxorubicin, etoposide, and ifosfamide should be added to the standard cyclophosphamide-vincristine-actinomycin regimen.[38] More recently, in the literature, platinum-based chemotherapies have been reported to have similar survival rates compared with the much more toxic regimens commonly used for PNET. Case reports showed long disease-free intervals after treatment with platinum and etoposide therapy alone.[39,40] As there is no standard chemotherapy for PNET, the combination of carboplatin or cisplatin with etoposide can be considered a viable option. In the future, we may use monoclonal antibodies against a potential target, such as IGF-1, involved in PNET growth.[41] Other possible targets could be phospholipase D2 (PLD2) and protein tyrosine phosphatase I (PTPL1), both highly expressed in pPNET.[42,43]

4. Conclusion

PNETs are aggressive neoplasms, usually diagnosed at an advanced stage. Due to their low incidence, universally accepted guidelines are still unavailable. Nevertheless, they are not only known to be chemoresponsive but also characterized by local and metastatic growth. Radical surgery leaving no macroscopic residual disease is mandatory in advanced stages. A good fertility-sparing procedure can be performed only in young women at early stages of disease, when the wish for childbearing is not yet fulfilled.

It will become increasingly important to identify central PNETs and among them to subdifferentiate variants such as medulloblastoma, ependymoma, astrocytoma, glioblastoma, in order to select those patients who may benefit from commonly used therapies for CNS tumors.

Tailored combined chemotherapy could well be the best choice for the patient, as in our experience. On the basis of the biological pattern, it may be possible to design targeted therapy, improving survival and quality of life.

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