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, hypercaecal 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 caesarean 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.[4−8] 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 (DSRCTs), belonging to Ewing Sarcoma family of tumors, and small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT). SCCOHT is a very rare and aggressive
| Ref. | Age | c/p | Tumors associated | Clinical presentation | Serum Ca125 level before treatment | Pregrnancy, 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 + LND) | Adriamycin, IE, for total of 6 weeks(adjuvant + (RT)) | DFI 33 mo postsurgery |
| Venetsanous et al. [48] | 68 | NR | No | Vaginal bleeding | NR | No | Cervix and vaginal mass | NR | Not perfomed | | NR | Improvement in symptoms; mass markedly reduced in size |
| Goda et al. [19] | 19 | NR | No | Postmenopausal bleeding with polyposid mass emerging from endocervix | NR | No | Uterus, left parametrium and cervix | 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 polyposid mass emerging from endocervix | NR | No | Uterus | IIIA (one left external iliac lymph node) | TAH, BSO, OM and pelvic lymph node sampling | Vaginal vault relapse; 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 | NR | No | Uterus without endometrial involvement | IB (mass > 5 cm in particular 10 cm) | 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 infiltration 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 | BI (mass > 5 cm in particular 10 cm) | FSS (Diagnostic laparoscopy and local excision of the mass by laparotomy) | CT (MAR+CI) + RT (Protocol EPsOBORME2005) | Free of disease until now |
| Tsao et al. [13] | 24 | NR | No | Abnormal mass at routine gyn-ob evaluation | NR | Yes, 8 wks | CERVIX | ? | | | |
| Elizalde et al. [51] | 60 | C | EEC | Vaginal bleeding, abdominal pain, weight loss | NR | No | Uterus | IB | | | |
| Dizon et al. [39] | 50 | NR | No | Abdominopelvic pain and soreness | NR | No | Uterus without endometrial involvement | IB | | | |
| Dizon et al. [52] | 50 | NR | No | Abdominopelvic pain and soreness | NR | No | Uterus | IB | | | |
| Bartosch et al. [53] | 58 | C | ECC | Vaginal bleeding, abdominal pain, weight loss | NR | No | Uterus | IB | | | |
| Celik et al. [54] | 32 | NR | No | Abdominal pain, pelvic mass, intra-abdominal hemorrhage | NR | No | Uterus | IIA | | | |
| Karseladze et al. [55] | 16 | NR | No | Abdominal pain, AUB | NR | No | Cervix | IIC2 (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 systemic abdominal mass, retroperitoneal relapse. |
| Hendrickson and Scheithauer [56] | 12 | NR | No | Vaginal bleeding, pelvic mass | NR | No | Uterus | I | | | |
| Hendrickson and Scheithauer [57] | 57 | NR | No | Vaginal bleeding, uterine mass | NR | No | Uterus | IB | | | |

(continued)
| Ref. | Age | c/tp | Tumors associated | Clinical presentation | Serum Ca125 level before treatment | Site | Stage | Surgery/Adjuvant therapy | Survival and follow-up |
|------|-----|------|------------------|---------------------|-----------------------------------|------|-------|------------------------|-----------------------|
| Ward et al. [57] | 17 | NR | No | Vaginal bleeding, pelvic mass | NR | Uterus | IIIC | RH, PLND, bilateral ovarian wedge biopsy | NED, 10 y |
| Rose et al. [58] | 17 | NR | No | AUB, pelvic mass | NR | Uterus | II | TAH, BSO, PLND | NED, 5 y |
| Tarafdar Luna Laila et al. [44] | 20 | NR | No | Pelvic heaviness and abdominal pain, mid left and left adnexal mass at US | 22, 4 | Uterus | IV (liver metastasis) | TAH+BSO+ OM, line I: CAV +Dacarbazine (only 1 cycle) | Persistent with right upper quadrant relapse DOD, 6 mo |
| Daya et al. [46] | 67 | C (Gl) | NR | Vaginal bleeding, enlarged uterus with a huge polypoid mass extending from the fundus to the bitches | NR | Uterine corpus | IIA | TAH, BSO, right PLND | Persistent with supravacccular node relapse DOD, 12 mo |
| Daya et al. [46] | 68 | C (Gl) | NR | Vaginal bleeding, polypoid mass from posterior wall, pain in region of upper left labia, enlarged uterus | NR | Uterine corpus | IIA | Vincristine + Cyclophosphamide + Cisplatin | NED, 6 y |
| Daya et al. [46] | 69 | C (Gl) | ESS | Vaginal bleeding, polypoid mass from the fundus | NR | Uterine corpus | IIA | TAH, BSO | NED, 5 y |
| Molyneux et al. [59] | 72 | NR | No | Vaginal bleeding | NR | Uterus | II | TAH, BSO | NED, 9 mo |
| Frangatta et al. [60] | 78 | NR | No | Vaginal bleeding | NR | Uterus | III | TAH, BSO, PLND | DOD, 18 mo |
| Sørensen et al. [61] | 62 | NR | No | Vaginal bleeding | NR | Uterus | IIA | Cisplatin + RT to left upper labia | NED, 6 y |
| Taïeb et al. [62] | 36 | NR | No | Vaginal bleeding | NR | Uterus | IIA | TAH, BSO, PLND | NED, 6 mo |
| Akbay et al. [64] | 22 | NR | No | Vaginal bleeding, pelvic mass | NR | Uterus | IIA | TAH, BSO, PLND, PAUD, OM | NED, 10 mo |
| Peres et al. [57] | 15 | NR | No | Abdominal pain, pelvic mass | NR | Uterus | III | TAH, BSO, PLND | NED, 12 mo |
| Varghese et al. [11] | 43 | NR | No | Vaginal bleeding, uterine enlargement | NR | Uterine corpus | IIA | TAH, BSO | NED, 2 mo |
| Mittal et al. [63] | 24 | NR | No | Fever, abdominal pain, pelvic mass | NR | Uterus | IIA | TAH, BSO, PLND, PAUD, OM | NED, 6 mo |
| Nair et al. [31] | 48 | NR | No | Pelvic mass, fever | NR | Uterus | IIA | TAH, BSO, PLND | NED, 6 mo |
| Knoepke et al. [32] | 36 | NR | No | Vaginal bleeding, uterine enlargement | NR | Uterus | IIA | TAH, BSO, PLND | NED, 6 mo |
| Park, Jong-Yeol, et al. [20] | 30 | NR | No | Vaginal bleeding, uterine enlargement | NR | Uterus | IIA | CERAW | DOD, 16 |
| Mashig, Naiz, et al. [33] | 49 | P | No | Vaginal bleeding, lower abdominal pain | NR | Uterus | II B, right parametrium | None | Metastasizes to lumbar spine, pelvis, and bladder, distal colonic obstruction due to an extensive |
| Ref.          | Age | c/p | Tumors associated clinical presentation | Clinical presentation | Serum Ca125 level before treatment | Preoper. gestational age at diagnosis | Site                | Stage               | Surgery                          | Adjuvant therapy                  | Survival and follow-up |
|--------------|-----|-----|-----------------------------------------|------------------------|----------------------------------|-------------------------------------|----------------|----------------------|------------------------|----------------------------------|------------------------|
| Shah et al.  | 59  | NR  | Vaginal bleeding, pelvic mass           | NR                     | No                               | No Uterus                           | I              | NR                   | TAH, BSO, PLND           | Carboplatin                   | AWD, 12 mo              |
| Mijer et al. | 27  | NR  | Vaginal bleeding, uterine mass         | NR                     | No                               | No Uterus                           | NR             | NR                   | TAH/BSO                | Vinorelbite+Ifosfamide+Avastin | NED, 2 y                |
| Ren et al.   | 56  | NR  | Vaginal bleeding                        | NR                     | No                               | No Uterus                           | IB             | NR                   | TAH, BSO               | Cyclophosphamide+Glipotin | AWD, 41 mo              |
| Fukumaga et al. | 54 | NR  | Unknown                                 | NR                     | No                               | No Uterus                           | NR             | NR                   | TAH, BSO               | Cyclophosphamide           | AWD, 3 mo                |
| Venkatsal et al. | 68 | NR  | Vaginal bleeding                        | NR                     | No                               | No Uterus                           | Uterus         | I                    | TAH, BSO               | Cyclophosphamide+Glipotin | NED, 10 mo              |
| Euscher et al. | 58 | NR  | Vaginal bleeding with palpable mass    | NR                     | No                               | No Uterus                           | NR             | I                    | TAH, BSO               | Cyclophosphamide+Glipotin | NED, 10 mo              |
| Euscher et al. | 31 | NR  | Back pain from metastatic disease      | NR                     | No                               | No Uterus                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 12 mo              |
| Euscher et al. | 72 | NR  | Vaginal bleeding                        | NR                     | No                               | No Uterus                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 12 mo              |
| Euscher et al. | 48 | NR  | Vaginal bleeding                        | NR                     | No                               | No Uterus                           | I              | NR                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Euscher et al. | 81 | NR  | Vaginal bleeding, uterine mass         | NR                     | No                               | No Uterus                           | NR             | I                    | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Euscher et al. | 64 | NR  | Vaginal bleeding with pain              | NR                     | No                               | No Uterus                           | NR             | IV by imaging        | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Euscher et al. | 64 | NR  | Vaginal bleeding with pain              | NR                     | No                               | No Uterus                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Euscher et al. | 69 | NR  | Unknown                                 | NR                     | No                               | No Uterus                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Euscher et al. | 62 | NR  | Abdominal fibroid                       | NR                     | No                               | No Uterus                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Euscher et al. | 52 | NR  | Abdominal fibroid                       | NR                     | No                               | No Uteros                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Euscher et al. | 59 | NR  | Vaginal pressure with passage of tissue | NR                     | No                               | No Uteros                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Euscher et al. | 57 | NR  | Vaginal bleeding with passage of tissue | NR                     | No                               | No Uteros                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Strohm et al. | 12 | NR  | Vaginal bleeding with passage of tissue | NR                     | No                               | No Uteros                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Tate et al.   | 25 | NR  | Vaginal bleeding, uterine inversion and | NR                     | No                               | No Uteros                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Dizon et al.  | 53 | NR  | Abdominal pain                          | NR                     | No                               | No Uteros                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Yi et al.     | 29 | NR  | Abdominal bleeding and pain             | NR                     | No                               | No Uteros                           | NR             | IV                   | TAH/BSO               | Carboplatin, Etoposide     | NED, 10 mo              |
| Nivo et al. Gynecology [34,41] | 26 | C   | Vaginal bleeding, uterine mass          | 372                    | 10 at last follow-up              | No Uteros                           | NR             | IV                   | TAH/BSO, OM             | Carboplatin, Etoposide     | NED, 16 mo              |
| Shridha et al. | 63 | C   | No                                      | No Uteros              | No                               | No Uteros                           | NR             | IV                   | TAH/BSO, OM             | Carboplatin, Etoposide     | AWD, 18 mo              |
| Xiao et al.   | 52 | NR  | AUB and uterine enlargement             | 13.7                   | 64.5 (palpable)                  | 64.5                                | No Uteros     | No                   | TAH/BSO+PIND+Neoadjuvant      | Carboplatin, Etoposide     | NED, 57 mo              |
| Xiao et al.   | 59 | NR  | AUB, pelvic mass palpable from vagina   | 70.6                   | 64.5 (palpable)                  | 64.5                                | No Uteros     | No                   | TAH/BSO+PIND+Neoadjuvant      | Carboplatin, Etoposide     | NED, 57 mo              |
| Xiao et al.   | 43 | NR  | Incidental finding by other operation  | 37                     | No                               | Right round ligament                | NR             | IV                   | TAH/BSO+PIND+Neoadjuvant      | Carboplatin, Etoposide     | NED, 57 mo              |

(continued)
| Ref.                  | Age | c/p | Tumor associated          | Clinical presentation                      | Serum Ca125 level before treatment | Pregnancy, gestational age at diagnosis | Site                | Stage | Surgery                                | Adjacent therapy            | Survival and follow-up |
|----------------------|-----|-----|---------------------------|-------------------------------------------|-----------------------------------|--------------------------------------|---------------------|-------|----------------------------------------|---------------------------|------------------------|
| Xiao et al[14]       | 31  | NR  | No                        | Abdominal pain and pelvic mass            | 96                                | No                                   | Right broad ligament | III   | wedge resection + PLND                 | Pelvic + pelvic tumorectomy | Lost to follow-up       |
| Xiao et al[14]       | 37  | NR  | No                        | Pelvic mass + AUB                        | 18-44                              | No                                   | Uterine corpus       | III   | RH                                     | VDC + IE, 1 course        | DOD, 6 mo               |
| Xiao et al[14]       | 31  | NR  | No                        | AUB + uterine enlargement                | 44                                | No                                   | Unresectable         | III   | RH                                     | Pelvic recurrence, 62 mo | Alive at 16 mo, NED    |
| Xiao et al[14]       | 18  | NR  | No                        | Abdominal pain + AUB                     | 71                                | No                                   | Uterine corpus       | III   | RH                                     | PAC + RT                  | Alive, 6 mo             |
| Russian et al[15]    | 63  | NR  | No                        | Vaginal bleeding                         | NR                                | No                                   | Uterus               | II    | TAH + BSO + VAC, second look after 6 mo | Cisplatin, VP16, cyclophosphamide + Adriamycin | Under treatment          |
| Sato et al[16]       | 37  | NR  | No                        | Pelvic mass + AUB                        | 184.4                              | No                                   | Uterine corpus       | III   | RH                                     | Pelvic recurrence, 62 mo | Alive, 6 mo             |
| Horn et al[17]       | 26  | NR  | No                        | Suspect cervical smear                   | NR                                | No                                   | Cervix               | II    | TAH + BSO                              | No                        | Died 42 y after diagnosis |
| Cencic et al[18]     | 36  | NR  | No                        | Irregular vaginal bleeding               | NR                                | No                                   | Cervix               | III   | TAH without BSO                        | No                        | Alive 18 mo, NED       |
| Matyska and Mihatsch | 35  | NR  | No                        | Vaginal bleeding                         | NR                                | No                                   | Cervix               | III   | TAH                                     | Pelvic RT                | Alive 5 mo, NED         |
| Matryka and Mihatsch | 51  | NR  | No                        | Vaginal bleeding                         | NR                                | No                                   | Cervix               | III   | TAH                                     | Adjunct chemotherapy, regimen not reported | Alive 18 mo, NED       |
| Sleijfer-Kelkhuiz and Ewing[19] | 21 | NR  | No                        | Intermenstrual bleeding                  | NR                                | No                                   | Cervix               | III   | TAH                                     | Six courses of DME, noreadjuvant + VAC | Alive 27 mo, NED       |
| Farzaneh et al[20]   | 43  | NR  | No                        | Persistent vaginal discharge             | NR                                | No                                   | Cervix               | III   | TAH + BSO + VAC / VACalternating with E/adjunct 12 weeks of VAT alternating with E/adjunct | No                        | Alive 4 y NED          |
| Berntzen et al[21]   | 25  | NR  | No                        | Irregular vaginal bleeding               | NR                                | No                                   | Cervix               | III   | Cisplatin + Adriamycin + IF + RT | Four cycles of Adriamycin + Cisplatin/neoadjuvant + RT | Alive 8 y NED          |
| Ann et al[22]        | 23  | NR  | No                        | Irregular bleeding, dysuria              | NR                                | No                                   | Cervix               | III   | TAH + BSO + VAC, second look after 3 y | One cycle of CAV followed by 2 cycles of cyclophosphamide + Adriamycin + RT | Alive 4 y NED          |
| Monsen et al[23]     | 23  | NR  | No                        | Irregular bleeding, abdominal pain       | NR                                | No                                   | Cervix               | III   | TAH + BSO                              | Cisplatin + Adriamycin + IF + RT | Died, 12 mo, NED       |
| Eklöf et al[24]      | 63  | NR  | No                        | Fibroid-like submucosal degenerated myoma nodule in the uterine cavity on ultrasonographic examination | NR                                | No                                   | Miometrium           | III   | TL + BSO + VAC | After severe renal failure and granulocytic fever QVAC-E combination | NED, not reported time of follow up |
| Eklöf et al[24]      | 17  | P   | No                        | Uterine masses like myoma                | NR                                | No                                   | Miometrium           | III   | TL + BSO + VAC | VAC and diuretic depleting for 52 weeks | NED, 61 mo           |
| Chuang[25]           | 66  | C M | No                        | Vaginal bleeding                         | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | Multigene agent, regimen not known | DOD, 6 m               |
| Chuang[25]           | 51  | C M | No                        | Vaginal bleeding                         | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NED                    |
| Chuang[25]           | 50  | C M | No                        | Vaginal bleeding                         | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chuang[25]           | 31  | C M | No                        | Vaginal bleeding                         | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chuang[25]           | 26  | P   | No                        | Vaginal bleeding                         | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chuang[25]           | 68  | C M | No                        | NA                                       | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chuang[25]           | 64  | C M | No                        | NA                                       | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chuang[25]           | 70  | C M | No                        | NA                                       | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chuang[25]           | 63  | C M | No                        | NA                                       | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chiang[26]           | 66  | C M | No                        | Vaginal bleeding                         | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | Multigene agent, regimen not known | DOD, 6 m               |
| Chiang[26]           | 51  | C M | No                        | Vaginal bleeding                         | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NED                    |
| Chiang[26]           | 50  | C M | No                        | Vaginal bleeding                         | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chiang[26]           | 31  | C M | No                        | Vaginal bleeding                         | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chiang[26]           | 26  | P   | No                        | Vaginal bleeding                         | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chiang[26]           | 68  | C M | No                        | NA                                       | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chiang[26]           | 64  | C M | No                        | NA                                       | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chiang[26]           | 70  | C M | No                        | NA                                       | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chiang[26]           | 63  | C M | No                        | NA                                       | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chiang[26]           | 63  | C M | No                        | NA                                       | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chiang[26]           | 63  | C M | No                        | NA                                       | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| Chiang[26]           | 63  | C M | No                        | NA                                       | NR                                | No                                   | Uterus               | III   | Th + 480 mg                               | No                        | NA                     |
| 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 |
|--------------|-----|-----|-------------------|-----------------------|-----------------------------------|-------------------------------------|------|-------|---------|------------------|------------------------|
| Dundr et al. | 80  | C   | EEC               | Abdominal pain        | NR                                | No                                  | Uterine corpus IB | Abdominal RH+BSO+ RUND | RT (60Gy)          | DOD 7 mo after diagnosis (pelvic, mesenteric, and peritoneal metastases) AWD 6 mo after diagnosis (intrabdominal metastases), then lost to follow up |
| Dundr et al. | 79  | C   | EEC               | Vaginal bleeding      | NR                                | No                                  | Uterine corpus IB | Abdominal RH+BSO+ RUND | None              | NED 29 mo            |
| Dundr et al. | 78  | C   | No                | Vaginal bleeding      | NR                                | No                                  | Uterine corpus IIA | None              | None              | NED 11 mo            |
| Gersel et al.| 66  | G   | MMMT              | Pelvic mass prolapsed from vagina | NR                                | No                                  | Uterus IC (Para-aortic firm nodes noted but not biopsied) | Abdominal RH+BSO+ RUND | RT (60Gy)          | 18 mo after surgery pulmonary metastases, abdominal pain, ascites Reduced pulmonary nodules after CT, but new nodal metastases (left paracaval and right hilar nodes). DOD, 2 years |
| Oudides et al.| 67 | Mostly P | 5 ESO cases + 7 EEs cases | NR | Yes, 25th week | Uterus, parametrium, periaortic lesions, colic and peritoneal dissemination (epigastric, ileal, pelvic, omental, ovarian, pouch, hepatic flexure, paracolic, para-aortic, and para-caval lymph nodes) | All the cases presented at IC stage | NR | NR | NR | Free of disease until now (34 mo) |

Our case 39 C No Shock state with severe anemia, hypovolemia, and abundant hemoperitoneum with an abdominal mass 166, 5 (after 1st emergent surgery) Paracaval including a large lymph node infiltrating the left renal vein and pelvic lymph nodes, First surgery emergency carcinoma section and type B RH + pelvic peritonectomy + vena cava + appendectomy. 2nd surgery, after staging CT scan PALND , gynecologic surgery until NED Cisplatin 25/m² days 1–3+, Etoposide 100 mg/m² days 1–3 q 21 for 6 courses

Table 1 (continued).

STAGE: RGO defined according to primitive lesion. Adit = 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, D/R = disease-free interval, DOD = died of disease, EDC = endometrial endometrial carcinoma, ESS = endometrial stromal sarcoma, EVA/A= ifosfamide, dacarbazine, Adriamycin, etoposide, vincristine, uracilten, and G-CSF, FSS = fertility sparing surgery, GI = Glioblastoma, NADO = Rosai–Dorfman, vinci, 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, OMA = aminopterin, PAC = cisplatin, epirubicin, and cyclophosphamide, PAUND = pelvic and para-aortic lymph node dissection, PEI = cisplatin, epirubicin, and ifosfamide, PLND = pelvic lymph node dissection, RH = radical hysterectomy, RGO = metasomyosarcoma, RF = radiotherapy, TAH = total abdominal hysterectomy, Termination of pregnancy (TOP), TLM = total laparoscopic hysterectomy, VOICE = vincristine, doxorubicin, cyclophosphamide, and etoposide+ ifosfamide/ mesna, MOCA = vincristine, actinomycin D, and doxorubicin

1 We also dissected a large lymph node infiltrating the left renal vein, by interruption and reconstruction.
2 Chiang et al. wrote that 2 of the 8 patients had lymph node dissection, but did not specify which patients underwent the procedure.
3 PNETs that arise from the myometrium, without involvement of the endometrium, are classified by RGO 2009 sarcoma staging; PNETs of the endometrium are staged as endometrial cancer, while PNETs of the cervix are classified as cervical cancer, according to RGO 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.[6,11] In the case series of uterine PNETs collected by Euscher et al,[9] CD99 was positive in 7 of 9 cases with the peripheral types. 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 400mL 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 400g, 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,[8,14,16] associated with pelvic peritoneectomy, 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.

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 1.33mg/dL (n.v. 0.51–0.95mg/dL), eGFR 50 mL/min (n.v. >90 mL/min)] and severe hypocalcemia [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-obturator, peri-aortic, intercavo-aortic regions, the largest measuring 6x5 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 peritoneectomy 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
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 0.78mg/dL and eGFR 96ml/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 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 ascendent 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 5mm, 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 25mg/m2 days 1–3 + Etoposide 100mg/m2 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: 100×, 200×). The neoplastic cells showed mild and focal immunoreactivity for (C) WT1 and (D) CD99.

Table 2

| 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%                                    |
| Pgf                           | 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                         | Negative                    | Negative                                        |
| Synaptophysin                 | Negative                    | Negative                                        |
| Protein S100                  | Not tested                  | Negative                                        |
| EMA                           | Negative                    | Negative                                        |
| GCDFP15                       | Not tested                  | Negative (CD 56 not tested)                     |
| CD2; CD10; CD20; CD54; CD 56; CD138 | Negative (CD 56 not tested) | Negative (CD 3; CD 20; CD 138 not tested)       |
| TTF1                          | Negative                    | Not tested                                      |
| HMB45                         | Negative                    | Not tested                                      |
| Myeloperoxidase               | Negative                    | Not tested                                      |
| BCL1                          | Not tested                  | Negative                                        |
| SF1                           | Not tested                  | Negative                                        |
| SALL4                         | Not tested                  | Negative                                        |
| MiB-1 (proliferation index)   | Not tested                  | Mild                                            |
myoma\textsuperscript{15–17} and one of a severe placenta percreta precluding ordinary LSCS.\textsuperscript{19}

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 extrasosseous Ewing sarcoma is composed entirely by sheets of small round cells and sometimes rosettes without a CNS-like architecture.\textsuperscript{19} 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).\textsuperscript{8,19,20}

In our case, the tumoral cells were undifferentiated, round, small, and monomorphic with a tendency to form nets; immunochemistry 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 transscripts, 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, E1A1, or FEV; in other cases, there is no translocation involving EWSR1, such as CIC-DUX4 or BCR –CCNB3.\textsuperscript{14,17,20–22}

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.\textsuperscript{81} Desmoplastic small round cell tumors (DSRCTs), 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 (11; 22) (p13; q12).\textsuperscript{12,22,23}

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.\textsuperscript{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).\textsuperscript{12,25,26} 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

\textbf{Table 3}

\textbf{Fish results.}

| Gene              | Result  |
|-------------------|---------|
| EWS-FLI1          | Negative|
| EWS-ERG           | Negative|
| EWS-ETV1          | Negative|
| EWS-E1A1          | Negative|
| EWS-FEV           | Negative|
| OC-DUX4           | Negative|
| BCR –CCNB3        | Not tested|
| FUS-FEV           | Not tested|
| EWSR1-WT1         | Negative|
| SMARCA            | Negative|
| SMARCB1           | Negative|

In the 150 cases of SCCOHT described by Young et al in 1994,\textsuperscript{131} 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.\textsuperscript{134} In literature, SCCOHT at surgery was unilateral in 148 cases (99\%), and extraventral 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.\textsuperscript{133} 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.\textsuperscript{131}

According to Young et al,\textsuperscript{133} 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.\textsuperscript{131} 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 43.64 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\textsuperscript{11}), PNET was found incidentally at the operating table during a C-section at term for a fetal indication, suggesting a small but invasive tumor.
In our case, emergency laparotomy and caesarian section were performed in a pregnant woman at 23-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 IICC; 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,[3] or chemotherapy alone or else a multimodal approach. At 2 years, survival of young people is 75%, versus 32% in the postmenopausal age group.[33]

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 (PTP11), 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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