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Case report

Peripheral primitive neuroectodermal tumor of the ovary with torsion

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ABSTRACT

Peripheral primitive neuroectodermal tumors (pPNETs) of the ovary are rare monophasic teratomas, and fewer than 100 cases have been reported in the literature. pPNETs mainly involve young women during their reproductive age, therefore, accurate diagnosis followed by multimodal treatment should be taken into consideration for fertility preservation. We report a patient with stage IA pPNET of the ovary presenting with acute abdominal pain secondary to torsion that was successfully managed by fertility-sparing surgery and six courses of combination chemotherapy with vincristine, Adriamycin, and cyclophosphamide. She has had a disease-free survival of >3 years. This brief review demonstrates the clinical course of pPNET and summarizes the literature to show that clinical stage at the time of diagnosis is the most important prognostic factor and that the vast majority of recurrences are observed within 10 years.

Clinical presentation

A 28-year-old woman, G0P0, presented with sudden onset of lower abdominal pain. Prior to this, neither family history nor other medical or surgical illnesses were remarkable. Past menstruation history was regular. Physical examination revealed an acutely ill-looking woman with a palpable firm and smooth-surfaced mass without rebounding pain or muscle guarding. Further physical examination showed a normal female pattern, without other positive findings, except the those mentioned above. Computed tomography (CT) demonstrated a 12-cm complex mass at the left adnexa (Fig. 1). The tumor markers, including cancer antigen (CA) 125, CA 19-9, and α-fetoprotein, were all within normal limits. Exploratory laparotomy showed torsion of the left ovarian tumor (Fig. 2). Left salpingo-oophorectomy was performed, and immediate frozen pathology favored a diagnosis of granulosa cell tumor, based on the presence of small round cells with prominent necrosis (Figs. 3 and 4). Fertility-preserving staging surgery then followed, and included appendectomy, left pelvic lymph node dissection, partial omentectomy, and peritoneal washing cytology. The patient recovered well and was discharged from the hospital on post-operative day 7.

Diagnosis and management

Immunohistochemistry was reactive for CD-99 (the glycoprotein cluster of differentiation molecule 99 (MIC2)), Friend leukemia virus integration (FLI)-1 and glial fibrillary acidic protein, and lacking for Melan A, α-inhibin, calretinin, cytokeratin, epithelial membrane antigen (EMA), synaptophysin, chromogranin, myogenic regulatory factor 1 (myoD1), vimentin, and desmin (Fig. 5). The final pathology was peripheral primitive

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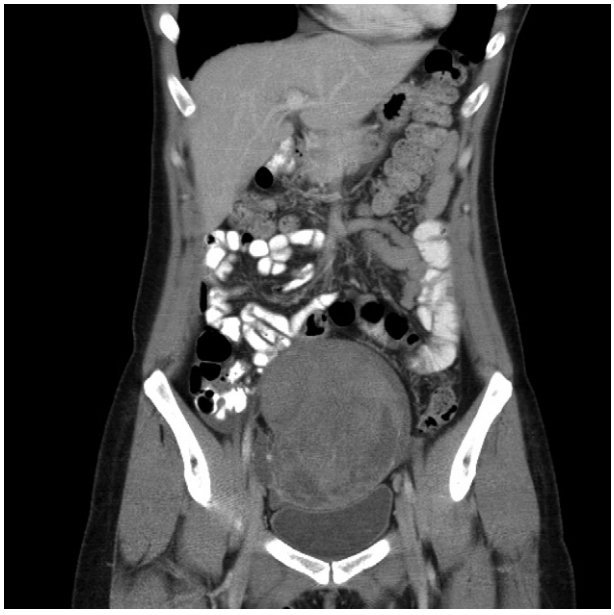

Fig. 1. Pelvic computed tomography revealed a round-shaped heterogeneous mass, with a solid and cystic multilobulated pattern, about 8.4 cm × 11.2 cm × 12.7 cm, in the midline anterior pelvis, favoring a left ovarian tumor.

neuroectodermal tumor (pPNET) of the left ovary. Extraskeletal Ewing sarcoma (ES) gene translocation was positive using the Vysis EWS Dual Color Break Apart Probe: 30-190059 (Vysis, Downer's Grove, IL, USA).

Bone marrow examination showed a normal 46,XX karyotype and there was no evidence of tumor involvement. The patient received six courses of combination chemotherapy, including vincristine, Adriamycin, and cyclophosphamide as adjuvant therapy, without further radiotherapy. In the last follow-up at 3 years post-operative, a series of examinations, including bone scan and positron emission tomography/CT, showed the patient was free of tumor.

Discussion

pPNET, classified as part of the Ewing family of tumors (EFTs), are a group of highly malignant tumors composed of small round cells of neuroectodermal origin that affect soft tissue and bone, for the most part.[1] The EFTs present a spectrum of neoplastic diseases, which include undifferentiated ES, atypical poorly differentiated ES, Askin tumor, and pPNET.[2,3] Although there are differences in tumor characteristics and clinical manifestations of EFTs, they are known to share the same reciprocal balance translocations, t(11,22)(q24;q12), which fuse the 5′ portion of the EWSR1 gene on chromosome 22 to the 3′ portion of the FLI-1 gene on chromosome 11 in 85–90% of cases.[4,5] The EFTs often arose from the long bones of the extremities and pelvis, and 20–30% of patients have a soft tissue origin.[6]

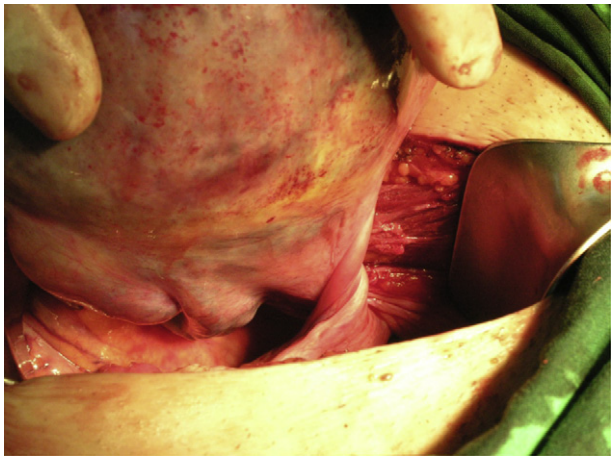

Fig. 2. Left ovarian tumor with torsion was noted during the operation.

pPNET of the ovary is extremely rare, and is not considered a common differential diagnosis of an ovarian tumor with torsion. Preoperative CT imaging and magnetic resonance imaging are nonspecific and variable.[7] With regard to the clinicopathological features of the reported cases of pPNET of the ovary, all the patients were young (13–29 years, mean: 23.5 years) (Table 1).[8–12] pPNET of the ovary in some reported cases was associated with teratomas, and the cases were therefore considered to be PNETs of the central nervous system arising as components of such teratomas.[13,14]

In our case, initial frozen pathology revealed small round cells with prominent necrosis, suggesting a diagnosis of granulosa cell tumor.[15] The permanent histological report was pPNET of the ovary, and this was validated by immunostaining, reverse transcriptase polymerase chain reaction, and karyotyping. The differential diagnosis of small round cell tumors of the ovary includes pPNET/ES, granulosa cell tumor, small cell tumor of a hypercalcemic type, and intra-abdominal desmoplastic small cell tumor.[16]

Immunohistochemistry can be used to detect FLI-1 in the gene fusion product of pPNET/ES. The expression of the MIC2 gene produces an antigen, MIC2, which consistently identifies both ES and pPNETs. By contrast, central nervous system PNETs and neuroblastomas uniformly lack expression of MIC2. Furthermore, pPNETs typically coexpress CD99 and vimentin. Other nonspecific markers include S-100, neuron-specific enolase, CD75, and synaptophysin.[9,17] Granulosa cell tumors are constantly positive with α-inhibin and calretinin and partially reactive with CD56, CD99, CD2-40, and low-molecular-weight keratin. Melan-A, CD10, and EMA are negative.[18]

Ovarian small cell carcinomas of the hypercalcemic type are positive for EMA, cytokeratin antibodies, N terminus of Wilms' tumor suppressor protein 1 (WT1), calretinin, and CD1. Parathyroid hormone-related protein is partially reactive and may be the explanation for the hypercalcemia in these cases. Desmin, S100, and α-inhibin are constantly negative.[16] Ovarian small cell tumors of a pulmonary type are positive for cytokeratin antibodies, EMA, and neuroendocrine markers.[19]

Intra-abdominal desmoplastic small round cell tumors are characterized by immunoreactivity with a variety of epithelial neural and mesenchymal markers. Desmin positivity is especially common, usually with a globular paranuclear pattern, and many cases exhibit nuclear positivity with the C terminus of WT1, in contrast to ovarian small cell tumors of the hypercalcemic type, which exhibit nuclear positivity with antibodies against the N terminus. Intra-abdominal desmoplastic small round cell tumors are usually positive for cytokeratin antibodies; other markers that are commonly positive include EMA, vimentin, neuron-specific enolase, CD57 (B3GAT1 (CD57) beta-1,3-glucuronyltransferase 1 (glucuronosyltransferase P), CD15 (FUT4 (CD15) fucosyltransferase 4 (alpha (1,3) fucosyltransferase, myeloid-specific), MOC-31 (a cell-membrane glycoprotein present on the surface of epithelial cells), and Ber-EP4 (a Mr 34,000 human epithelium-specific surface glycoprotein: a

Table 1
Peripheral primitive neuroectodermal tumor of the ovary.

Authors	Age (y)	FIGO stage	Treatment	C/T regimen	Complications	Follow-up
Kawauchi et al[9]	29	II[a]	TAH + BSO + omentectomy + PALA C/T	NDA[b]	NDA	11 mo DOD
Chow et al[10]	13	IV	Debulking C/T 2nd debulking surgery C/T + R/T	BEP VIP EPDC	NDA	17 mo DOD
Demirtas et al[8,c]	25	IC	LSO + omentectomy + PLA 2nd look laparotomy	BEP VIP	Pelvic abscess after 2nd look laparotomy + VIP	2 y NED 2 successive pregnancies
Kim et al[11]	18	IIIC	RSO + omentectomy + PLA + PALA R/T	TP VACA	Bowel obstruction	10 mo DOD
Ateser et al[12]	28	IV	TAH + LSO + omentectomy R/T	VDC at GA 30 wk DAC EIP	Neutropenia, placental metastasis	13 mo DOD
Huang et al[d]	28	IA	LSO + omentectomy + left PLA + appendectomy)	VDC		28 mo NED

A = actinomycin-D; B = bleomycin; BEP = bleomycin, etoposide, cisplatin; BSO = bilateral salpingo-oophorectomy; C = cyclophosphamide; C/T = chemotherapy; D = doxorubicin; DAC = doxorubicin, cyclophosphamide, docetaxel; DOD = died of disease; E = etoposide; EIP = ifosfamide, vinblastine, cisplatinum; EPDC = etoposide, cisplatin, doxorubicin, cyclophosphamide; FIGO = International Federation of Obstetrics and Gynecology; GA = gestational age; I = ifosfamide; IC = in FIGO stage IC; LSO = left salpingo-oophorectomy; NDA = no data available; NED = no evidence of disease; P = cisplatin; PALA = para-aortic lymphadenectomy; PLA = pelvic lymphadenectomy; RSO = right salpingo-oophorectomy; R/T = radiotherapy; T = paclitaxel; TAH = total abdominal hysterectomy; TP = paclitaxel, cisplatin; V = vinblastine; VACA = vincristine, actinomycin, cyclophosphamide, doxorubicin; VDC = vincristine, doxorubicin, cyclophosphamide; VIP = vincristine, ifosfamide, cisplatin.

[a] Tumor nodules on pelvic floor.

[b] Regimens for common ovarian carcinoma, malignant germ cell tumor, or small cell carcinoma.

[c] No available immunostaining or karyotype report.

[d] Current case: ovarian tumor with torsion.

monoclonal antibody that recognizes 34-kDa and 39-kDa non-covalently linked glycopolypeptides expressed by most human epithelial cells and carcinomas).[20]

In addition to their cytogenetic and immunohistochemical similarities, the pPNET/ESs share important clinical features and should be treated similarly.[21] Fewer than 25% of patients have overt metastasis at the time of diagnosis, therefore, the relapse rate could be 80–90% in patients undergoing local therapy alone. It is suggested that the majority of patients have subclinical metastatic disease at the time of diagnosis, even in the absence of overt metastases.

pPNET/ESs are characterized by rapid growth and a high potential to recur, most commonly in the lungs, bones, and bone marrow.[22] Despite multimodal treatment involving surgery, chemotherapy, or radiotherapy, patients with advanced disease show rapid dissemination (Table 1). Out of concern for the future fertility of our patient, fertility-sparing surgery was performed and adjuvant chemotherapy given, which has been accepted in the management of many kinds of gynecological tract neoplasms and cancers.[23–26] Demirtas et al[8] have reported a patient that had two successive pregnancies after treatment of International Federation of Obstetrics and Gynecology (FIGO) stage IC pPNET of the ovary; the patient's reproductive function was preserved after fertility-sparing surgery and adjuvant chemotherapy. However, the follow-up time after treatment in these patients is short (only 2–3 years), including our current patient; therefore, the feasibility of fertility-sparing surgery in these pPNET/ES survivors needs confirmation, because this situation is similar to other conservative treatment for other gynecological tract cancers.[24,27] Current standard chemotherapy for nonmetastatic pPNET/ES includes vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide.[28] Some chemotherapeutic agents, including trabectedin (ecteinascidin 743, or ET-743) and palifosfamide (ZIO-201) for the treatment of sarcoma[29] might also be useful in cases of pPNET/ES; especially for those patients who have failed or are not candidates for anthracycline-based or ifosfamide-based chemotherapy.[30] Trabectedin, a chemotherapeutic agent originally derived from a marine tunicate, binds to the minor groove of DNA affecting transcription and inducing the formation of DNA double-strand breaks, and cells in the G1 phase of the cell cycle are particularly sensitive to trabectedin.[29] Trabectedin is generally well tolerated, but some patients after treatment may develop severe myelosuppression, with prolonged and severe neutropenia and thrombocytopenia, and hepatic toxicity.[29] Palifosfamide is a stabilized formation of isophosphoramide mustard (the active metabolite of ifosfamide) that appears to be active in sarcomas and better tolerated than ifosfamide, because palifosfamide has antitumor activity comparable or superior to that of ifosfamide, and does not display the nephrotoxic effects associated with ifosfamide.[31]

Adjuvant radiotherapy is indicated for patients undergoing surgery if the surgical margins are inadequate, although effective chemotherapy also reduces the risk of local failure in such patients.[32]

Although the majority of pPNET/ES survivors have some late effects of therapy, in terms of employment, marital status, fertility, and functional status, secondary myelodysplasia and

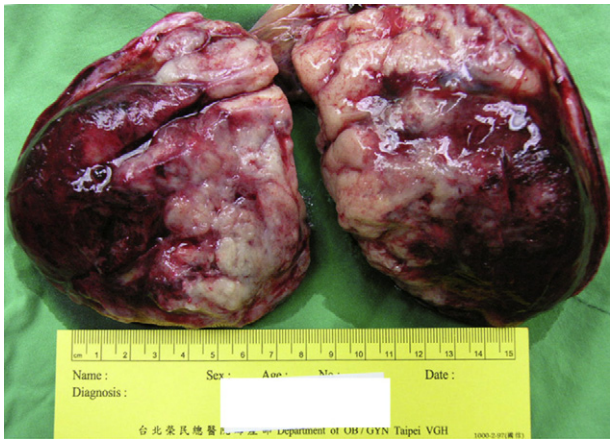

Fig. 3. The ovarian tumor was well demarcated and well encapsulated. The cut surface was solid with focal necrosis, hemorrhage, and cystic change.

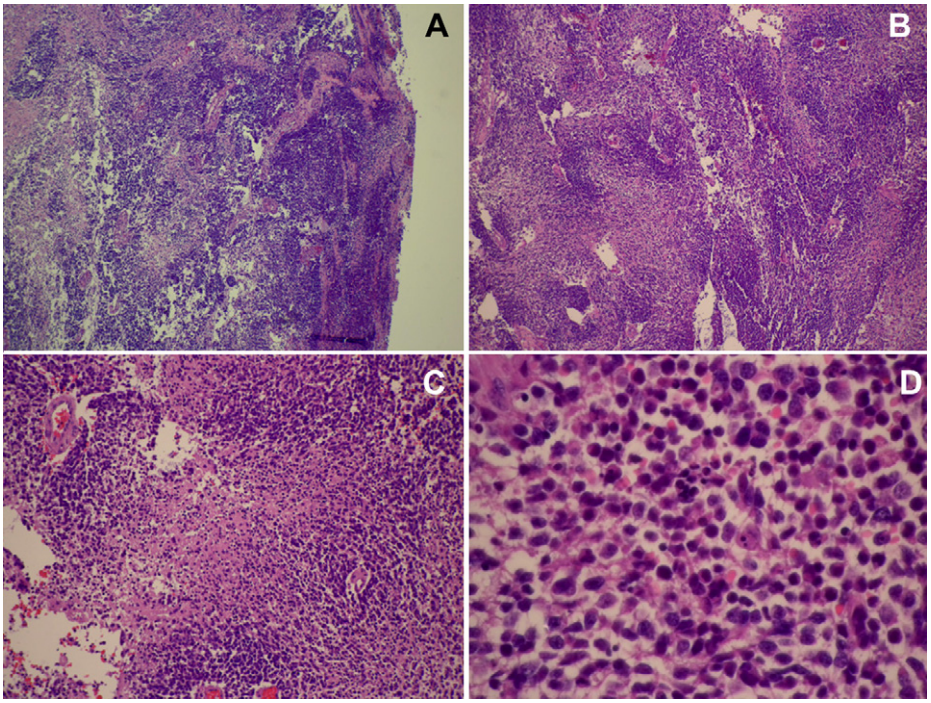

Fig. 4. Tumor cells grew in a solid sheet pattern with intervening edematous stroma and showed vascular invasion and focal necrosis (A–C). Tumor cells were small, round and with less cytoplasm with indistinct cell boundaries; rosettoid features are present (D). (A, 100×; B and C, 200×; D, 400×; hematoxylin and eosin stain).

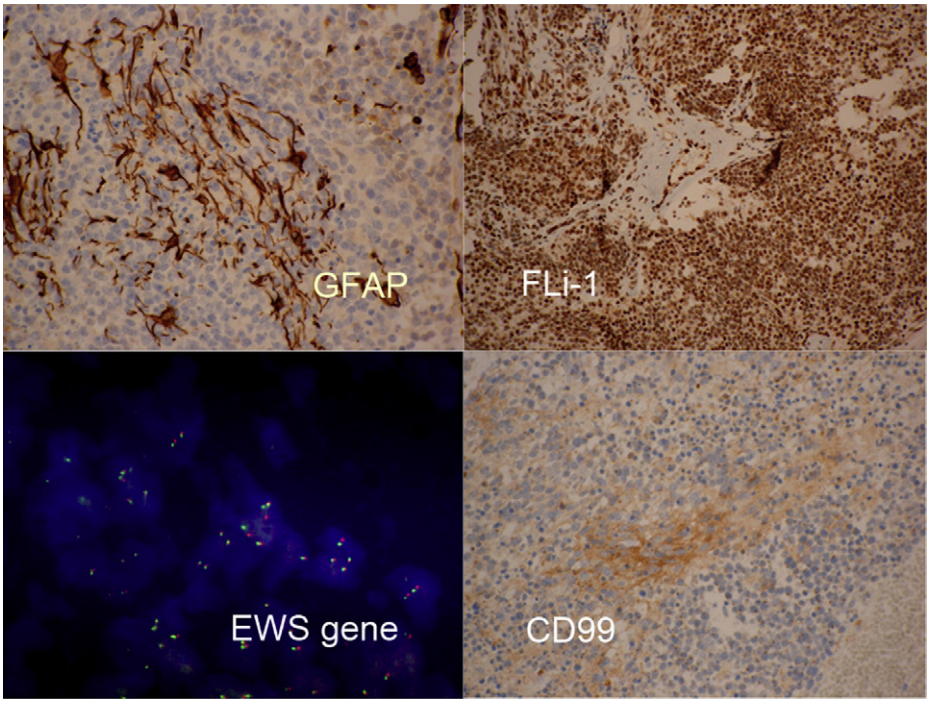

Fig. 5. Immunohistochemical staining. Positive glial fibrillary acidic protein expression revealed more differentiation from small primitive cells. Positive CD-99 (MIC-2) was expressed in the cytoplasm. Friend leukemia integration (FLI)-1 is expressed within the nuclei of the tumor cells. EWS gene translocation was demonstrated by fluorescence *in situ* hybridization, but not frequently.

acute myeloblastic leukemia occur in only 1–2% of survivors.[33,34] Furthermore, Kuttesch et al[35] have reported that 20% of patients who received radiotherapy doses >60 Gy developed secondary malignancies, compared with only 5% of those who received 48–60 Gy. Those treated with <48 Gy had no additional risk of second malignancies. Although the appropriate duration of follow-up is unknown, the vast majority of recurrences are observed within 10 years. It is suggested that positron emission tomography/CT may have great utility in monitoring the response to chemotherapy and/or radiotherapy, and in the postoperative evaluation of recurrence.[36]

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