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Case Report

Primary uterine Ewing sarcoma – A case report

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ABSTRACT

Objective: Ewing sarcoma is a type of neuroectodermal tumors (Ewing family of tumors-EFT) that mostly affect the bone or soft tissue. Primary uterine Ewing sarcoma is extremely rare.
Case report: We report a case of a primary uterine Ewing sarcoma in a 46-year-old patient, treated with total abdominal hysterectomy, and bilateral salpingo-oophorectomy and following adjuvant chemotherapy with 6 cycles of vincristine, doxorubicin, and cyclophosphamide, achieving complete remission for one year.
Conclusion: Complete resection for EFT is the first choice of treatment, regardless of their origins. Adjuvant chemotherapy or radiotherapy is mandatory if needed. Due to rarity of the disease, this report re-emphasizes the accurate diagnosis and appropriate treatment for these unusual tumor types occurred in female genital organs.

Introduction

Ewing sarcoma (ES) is a type of neuroectodermal tumors (Ewing family of tumors: EFT) that mostly affect the bone or soft tissue, contributing to extreme rarity of primary ES occurred in the female genital organs [1–10]. The diagnosis of this extra osseous ES needs a special attention, not only based on the typical findings of small blue round cells in the routine hematoxylin & eosin (H&E) examination, but also assisted by immunohistochemical (IHC) staining or genomic examination, such as positive immunostainings of NKX2.2, CD99 and the finding of chromosomal translocation of t(11; 22)(q24; q12) [4,10].

Due to its rarity in the female genital tract, there are only a few cases reported in the literature [1–10]. Therefore, we are now presenting a case of a primary uterine ES in a 46-year-old woman, and also discuss the further treatment of primary uterine ES.

Case

A 46-year-old woman did not have any underlying diseases. She visited our outpatient clinic due to an accidental finding of the pelvic mass accompanied with endometrial hyperplasia in routine health examination. A series of examination were done. Laboratory data showed unremarkable findings, including tumor markers, such as (carbohydrate antigen (CA) 125 at 31 U/ml, CA199 at 12.01 U/ml and carcinoembryonic antigen (CEA) at 2.26 ng/ml. Transvaginal sonography revealed a pelvic mass around 21 × 13 × 14 cm with presence of blood flow and accumulated fluid within the cul-de-sac (Figs. 1 and 2). Pelvic computed tomography (CT) suspected a cystic neoplasm of the uterus (Fig. 3). The results of the upper and lower gastrointestinal tract, and breast were negative. Dilation and curettage was also negative for malignancy. Finally, the patient underwent exploratory laparotomy due to the pelvic mass.

During operation, a 20-cm pedunculated mass on the right fundus was found. Total abdominal hysterectomy and bilateral salpingo-oophorectomy was done. The external surface of the lesion was smooth and glistening generally. On cut, the tumor was well-encapsulated, tan to gray, and soft solid tumor, showing necrotic change and bloody fluid (hemorrhage). Frozen pathology revealed a small round cell tumor. Then the entire abdominal cavity and retroperitoneal space was checked up in detail. No significant abnormality was found.

Microscopically, the tumor showed a small blue round cell tumor with features of round to oval nuclei, fine chromatin, and small nucleoli, growing in sheets or nodular pattern. Diffuse hemorrhage and cystic change were noted. Under IHC staining, the tumor was positive for NKX2.2 (Fig. 4), CD99 (Fig. 5), and cyclin D1, but negative for CD10, estrogen receptor, progesterone receptor,

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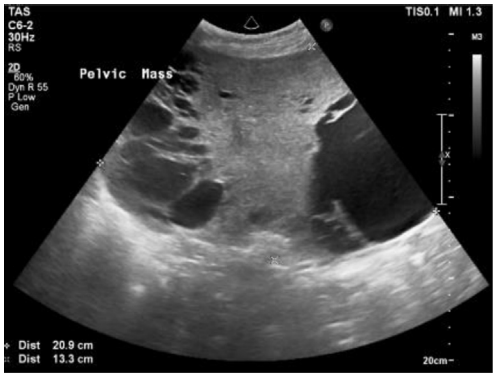

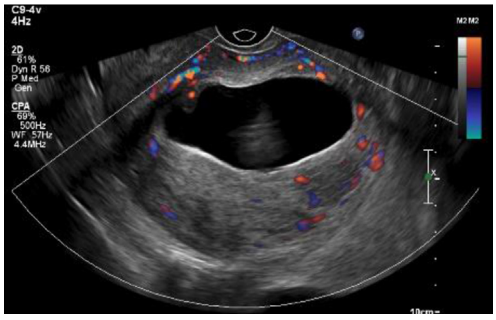

Figures 1 and 2. Transvaginal sonography revealed a pelvic mass around 21 × 13 × 14 cm with presence of blood flow and accumulated fluid within the cul-de-sac.

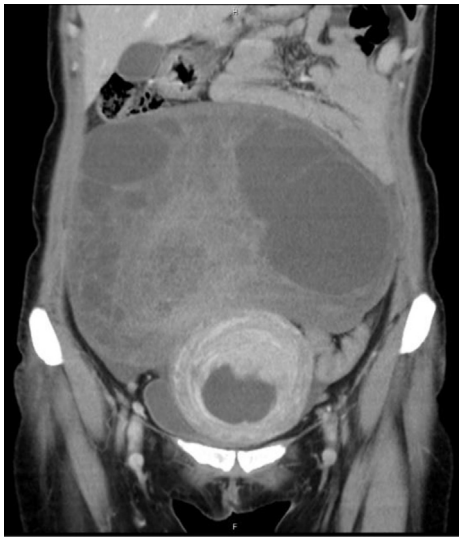

Fig. 3. Pelvis computed tomography showing a cystic mass lesion from the pelvic cavity to the abdominal cavity (the coronal view).

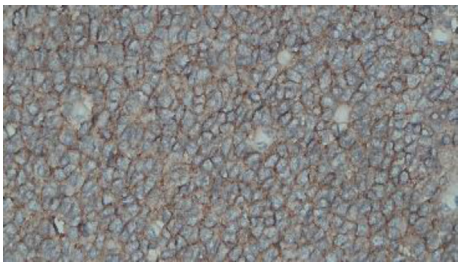

Fig. 5. IHC staining with strong immunoreactivity for CD99.

cytokeratin, desmin, myogenin, S100, synaptophysin, chromogranin A, alpha-inhibin and TLE1. Fluorescence *in situ* hybridization (FISH) showed rearrangements of *EWSR1* and *FLI1* genes, confirming the diagnosis of ES (see Fig. 6).

The final staging was pT4N0M0, Stage IIIB. Further bone evaluation excluded the primary bone lesion. Adjuvant chemotherapy was administered using 6 cycles of vincristine, doxorubicin, and cyclophosphamide. She is free of disease for one year.

Discussion

ES is a bone malignancy mostly seen in children and adolescents, but extremely uncommon in the female genital systems, such as ovary, uterus, vagina or cervix [1–10]. Among the organs of female genital systems, ovary is the most common site of primary ES [1,2,4,5]. Fertility might not be an issue because the female genital ES often occurs in the postmenopausal women; however, fertility-sparing surgery should always be considered if needed [1]. The commonest symptoms or signs of the female genital ES include abnormal vaginal bleeding, abdominal pain or a pelvic mass [7,8]. The mass lesion might extend up to 13–15 cm, which can be palpable in the routine physical examination [1]. Our presented case presented a typical symptom of sign, which is shown, including the age at the nearly menopausal age and a big pelvic mass lesion.

It is not easy to make an accurate diagnosis of primary uterine ES, partly because of their rarity, partly because of the needs of special IHC and genomic evaluations. According to literature review, IHC stains for diagnosis are highly recommended [1]. Recently, NKX2.2 has been identified as a useful marker in diagnosing ES to distinguish from other small round cell tumors [10]. It is a homeodomain-containing transcription factor, which is found to be a specific target of *EWS/FLI-1* fusion protein. NKX2.2 staining has a sensitivity of 93% and a specificity of 89% for ES [10]. Currently, CD99 is also useful for the assistance of diagnosis of EFT, which shows diffuse strong membranous expression [7]. Besides CD99, many primary neuroectodermal tumors (PNETs) also display nuclear FLI-1 expression [7]. Although CD99 and FLI-1 are the accepted IHC markers for ES, both markers are not specific for ES,

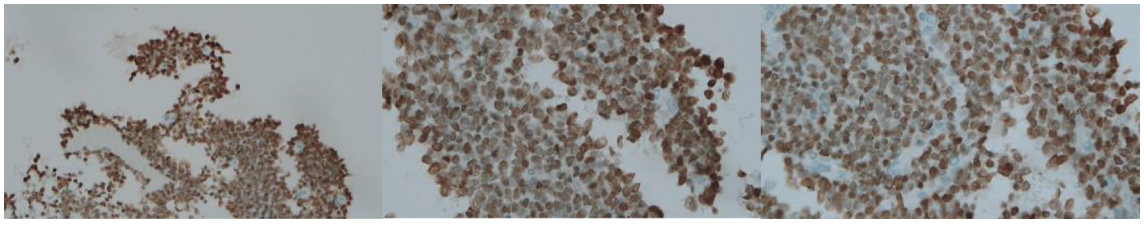

Fig. 4. IHC staining with strong immunoreactivity for NKX2.2.

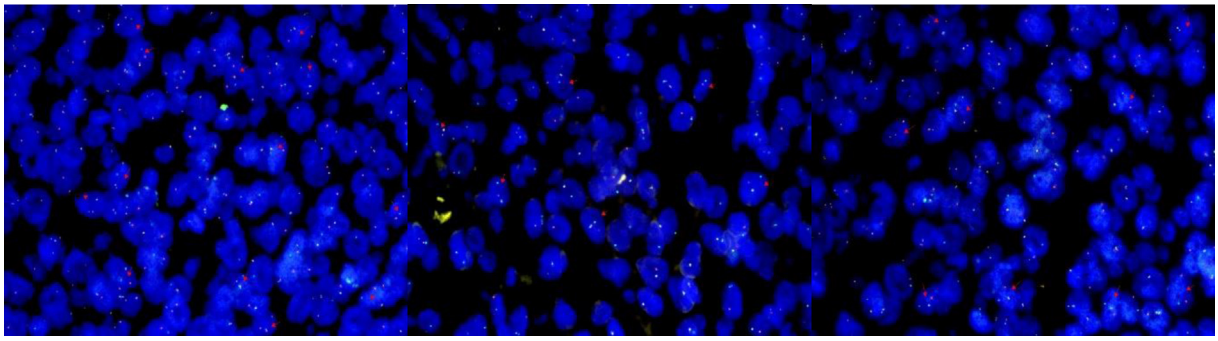

Fig. 6. Fluorescence in situ hybridization (FISH) showed rearrangements of *EWSR1* and *FLI1* genes.

leading to the questioning of accuracy of CD99 and FLI-1 for ES. Therefore, another marker, such as CD99, may be used in alternation, since most ES showed the diffuse positivity of CD99. Our patient also had a diffuse pattern of positivity for CD99. FISH is another important diagnostic tool that can provide an accurate specific genetic study. Up to 80%–95% of EFT patients harbor the chromosomal translocation of (11; 21)(q24; q12), resulting in the *EWSR1/FLI-1* fusion gene [9]. Therefore, positive *EWSR1/FLI-1* fusion gene is a powerful aid in confirming the diagnosis of primary uterine Ewing sarcoma [1–3].

In term of the treatment for primary uterine ES, there is no standard treatment. Surgery with complete resection is considered a best and well-documented therapy [4,7,9], although postoperative adjuvant therapy either by chemotherapy, radiation or combination of both might be needed in the certain conditions [4,7,9]. Additionally, it is also absent of agreement of the regimen of chemotherapy, although regimens used for the therapy of ovarian immature teratoma are often applicable to the primary gynecologic ES, including VDC (vincristine, doxorubicin, cyclophosphamide) with the additional combination of IE (ifosfamide, etoposide) [2]. Of most importance, the aforementioned regimen is also approved by the EWS family of tumor protocol [2]. Besides the above-mentioned chemotherapy regimen, some other combined chemotherapy regimens, such as carboplatin and paclitaxel combination is also accepted, similar to be used in the management of patients with uterine cancer [11]. The regimen, such a combination of bleomycin, etoposide, and cisplatin, which is often used for the treating germ cell tumors [12], is also reported before [2]. In our presented case, we used the VDC regimen with a satisfactory result.

The prognosis of stage IA disease was excellent [1], but the advanced (higher staging or distant metastasis) seemed to be worse in prognosis, since most patients will die of diseases within 10–18 months [2]. Therefore, there are many prognostic factors applicable to predict the outcome, including tumor size, age and staging at diagnosis [6]. Due to its rarity, the prognostic factors are not always reproducible.

Conclusion

Primary uterine ES is extremely rare with the similar clinical manifestations to other uterine cancers, which make the differential diagnosis difficult. Therefore, clinical specialists should always be alert of this unusual disease when encountering postmenopausal woman with abnormal vaginal bleeding, abdominal pain or undetermined pelvic mass. Accurate pathologic diagnoses rely on a combined evaluation of the histomorphology and ancillary tests, including IHCs and molecular testing if necessary, such as staining of NKX2.2, CD99 and detection of *EWSR1/FLI-1* fusion gene by FISH. Treatment for extra osseous ES of the female genital organs is still investigated. Surgery is needed for all patients, although fertility-sparing surgery might be applicable in the certain situations. Adjuvant therapy should be based on the risk after surgery, such as tumor size, age, and stage. Although it is uncertain whether regimen is appropriate for extra osseous ES of the female genital organs, our experience based on the current case report, VDC with or without IE can be considered a good treatment protocol.

Declaration of competing interest

All authors declare that there is no conflict of interests regarding the publication of this paper.

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