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Case report

Neoadjuvant chemotherapy for Ewing's sarcoma family tumors of the uterine cervix: A case report

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ABSTRACT

Ewing's sarcoma family tumors of the uterine cervix are extremely rare and, thus, an optimal treatment strategy has not yet been established. To the best of our knowledge, 28 cases were reported in the English literature between 1996 and 2020, and treatments involved surgery, neoadjuvant chemotherapy, adjuvant chemotherapy, and radiotherapy. The vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VDC-IE) protocol increased the survival rate of patients with non-metastatic Ewing's sarcoma family tumors. We herein present a case of a Ewing's sarcoma family tumor of the cervix in a one-month postpartum woman treated with neoadjuvant chemotherapy using the VDC-IE protocol and radical hysterectomy followed by adjuvant chemotherapy, and discussed the diagnosis and treatment of this tumor through a literature review.

1. Introduction

Ewing's sarcoma family tumors (ESFT) include primitive neuroectodermal tumors, Askin tumors, skeletal Ewing's sarcoma, and extraskeletal Ewing's sarcoma. Patients with ESFT are primarily adolescents or young adults, with the majority being younger than 30 years, and the incidence of ESFT is significantly higher in Caucasians than in Africans or Asians (Cash et al., 2016; Pappo and Dirksen, 2018). The most common primary sites for ESFT are along the central axis of the chest wall, head, and neck; however, ESFT may also arise in any soft tissue (Gaona-Luviano et al., 2003). Case reports of ESFT of the uterus, ovaries, vagina, and vulva have been published, whereas those of ESFT of the cervix are extremely rare.

ESFT is a small round cell tumor that is often difficult to differentiate from neuroblastoma, rhabdomyosarcoma, and small cell carcinoma by hematoxylin and eosin staining only. The positive immunohistochemical staining of CD99 suggests ESFT. However, CD99 is also positive in synovial sarcoma and non-Hodgkin's lymphoma. In addition to CD99, vimentin, neuron-specific enolase (NSE), S-100 protein, CD57, and synaptophysin are often positive in ESFT (Banerjee et al., 1997).

Approximately 85% of ESFT cases exhibit the genetic change of translocation (11;22) (q24;q12), which generates the chimeric fusion of the EWS-FLI1 gene (Cetiner et al., 2009). Molecular methods, such as fluorescence *in situ* hybridization (FISH), a reverse-transcriptase polymerase chain reaction (RT-PCR), and next-generation sequencing, are essential for the detection of these translocations and, thus, the diagnosis of ESFT.

ESFT of the cervix is rare and, to the best of our knowledge, only 28 cases were reported in the English literature between 1996 and 2020 (Ahmad et al., 2017; Hu et al., 2017; Murthy et al., 2020; Kyriazoglou et al., 2019; Wang et al., 2017). We herein present a case of ESFT of the cervix and describe diagnostic and treatment procedures.

2. Case report

A 37-year-old, gravida 1, para 0, woman underwent a cesarean section due to obstructed labor. At one-month postpartum, the patient presented to the hospital with major uterine bleeding. The doctor in charge detected a bulky tumor in the vaginal area and referred the patient to our previous hospital for uterine artery embolization due to hemostasis.

At our previous hospital, the doctor in charge decided that uterine artery embolization was unnecessary for hemostasis. The results of a pathological examination of a biopsy specimen indicated a

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neuroendocrine tumor of the uterine cervix and the patient was diagnosed with cervical cancer with a clinical stage of IB2 according to the International Federation of Gynecology and Obstetrics 2008 staging system. She was referred to our hospital for treatment.

Pelvic magnetic resonance imaging performed at the previous hospital showed a 10-cm bulky tumor arising from the cervix (Fig. 1A, B), while no findings of lymph node or distant metastasis were detected on computed tomography.

Carcinoembryonic antigen, carbohydrate antigen 19–9 (CA19–9), and CA125 levels were within normal limits; however, squamous cell carcinoma-related antigen and NSE levels were slightly elevated at 2.2 and 20.2 ng/mL, respectively.

A pathological examination was conducted at our hospital. A histopathological examination revealed small darkly stained tumor cells with a scant cytoplasm that were arranged in dense sheets without rosette formation (Fig. 1C, D). An immunohistochemical examination showed that CD99 (MIC2) and CD56 were strongly positive (Fig. 1E), whereas cytokeratin OSCAR, synaptophysin, desmin, MyoD1, myogenin, melan-A, MITF, chromogranin A, and INSM1 were negative. The Ki-67 labeling index was 50%. We detected the ESWR1 gene rearrangement using the Vysis LSI EWSR1 (22q12) Dual Color Break Apart Rearrangement FISH Probe Kit (Abbott), confirming the diagnosis of ESFT (Fig. 1F).

The patient received four cycles of neoadjuvant chemotherapy with the vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VDC-IE) protocol; vincristine (1.5 mg/m^2 on day 1), doxorubicin (37.5 mg/m^2 on days 1 and 2), and cyclophosphamide (1,200 mg/m^2 on day 1), alternating with ifosfamide (1,800 mg/m^2 on days 1–5) and etoposide (100 mg/m^2 on days 1–5) every 3 weeks. As a supplementary explanation, four cycles of the VDC-IE protocol involved two VDC and two IE treatments.

A gynecological examination after four cycles of neoadjuvant chemotherapy revealed a necrotic cervical tumor measuring 3 cm at its greatest dimension (Fig. 2C, D). The lesion at the uterine cervix was not detected on MRI (Fig. 2A, B).

The patient underwent radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. The surgical time was 5 h 52 min and the blood loss volume was 590 g. No perioperative complications occurred. The patient began receiving estrogen replacement therapy one month after surgery.

In a postoperative histopathological examination, cervical lesions showed a wide range of foam cells, which were evaluated as post-treatment changes (Fig. 2E). There were no viable atypical cells suggestive of ESFT in cervical lesions, no viable cells in the removed lymph nodes, and no metastases; however, foam cells were present in some lymph nodes, which was suggestive of the chemotherapy-induced regression of metastases. These findings showed that the patient achieved a pathological complete response.

The patient received six cycles of adjuvant chemotherapy with the VDC-IE protocol and five cycles of the VAC-IE protocol; vincristine (1.5 mg/m^2 on day 1), actinomycin D (1.25 mg/m^2 on day 1), and cyclophosphamide (1200 mg/m^2 on day 1), alternating with ifosfamide (1800 mg/m^2 on days 1–5) and etoposide (100 mg/m^2 on days 1–5) every 3 weeks. The patient received a total of fifteen cycles of chemotherapy. Pegfilgrastim was subcutaneously injected on day 3 of VDC

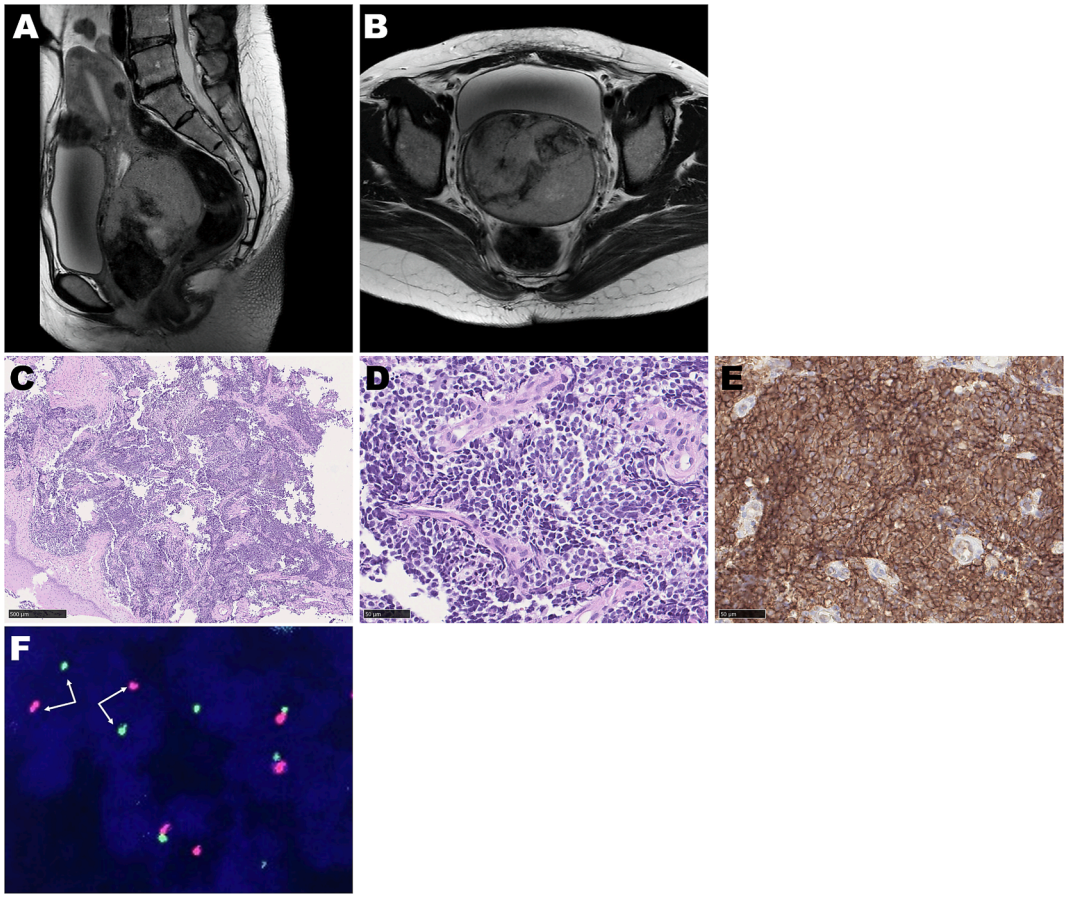

Fig. 1. Pelvic MRI before neoadjuvant chemotherapy and histopathological examination. MRI findings suggest the tumor originated from the uterine cervix. A: T2-emphasized sagittal imaging, B: T2-emphasized horizontal imaging. Hematoxylin and eosin staining: small darkly stained tumor cells with a scant cytoplasm were arranged in alveolar dense sheets without rosette formation (C: Scale bar = 500 μm, D: Scale bar = 50 μm). Immunohistochemistry showed that tumor cells were positive for CD99 (Scale bar = 50 μm) (E). A fluorescence *in situ* hybridization (FISH) analysis revealed chromosome rearrangements involving the EWSR1 gene region on chromosome 22q12 (arrows: dual color break-apart rearrangement) (F).

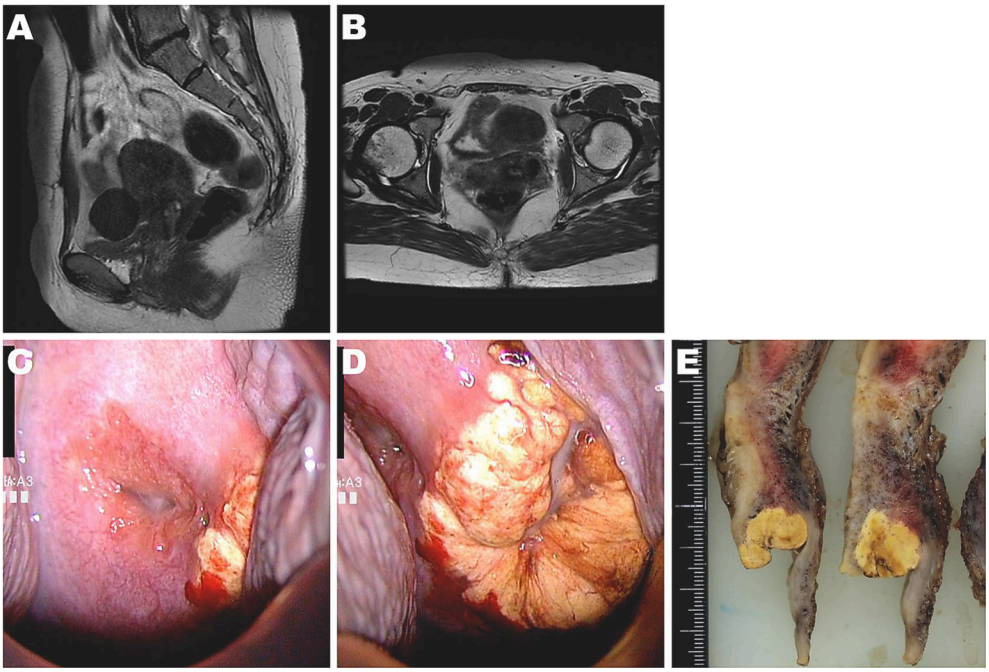

Fig. 2. The lesion of the uterine cervix was not detected on MRI after neoadjuvant chemotherapy (A: T2-emphasized sagittal imaging, B: T2-emphasized horizontal imaging). An image of the cervix during colposcopy showed a necrotic tumor on the left of the external os, measuring 3 cm at its greatest dimension (C, D). Sections of the formalin-fixed uterine cervix after surgery (E).

therapy, day 2 of VAC therapy, and day 6 of IE therapy to prevent neutropenia. No grade 3 or 4 adverse events were observed, and none of the doses of the drugs administered were reduced.

After surgery and adjuvant chemotherapy, the clinical course was favorable. Regular follow-ups were performed at our hospital every 3 months. The patient undergoes blood examination and computed tomography every 3 months, and gynecologic examination every 6 months. Twenty-four months after initial neoadjuvant chemotherapy, the patient is asymptomatic with no evidence of disease.

3. Discussion

In the fourth edition of the WHO Classification of Tumors of Soft Tissue and Bone, ESFT are defined as small round cell sarcoma with distinctive molecular features and a variable degree of neuroectodermal differentiation. Most cases are characterized by translocations between the EWSR1 gene on chromosome 22 and genes belonging to the ETS family of transcription factors (Pappo and Dirksen, 2018). The diagnosis of ESFT is difficult based on hematoxylin and eosin staining alone, and, thus, requires a combination of morphological and immunohistochemical findings. CD99, an immunohistochemical marker specific for the diagnosis of ESFT, is detected in more than 97% of cases (Wang et al., 2017; Akazawa et al., 2018; Bose et al., 2012). A molecular genetic analysis may identify chromosomal translocations that may be useful for differentiating ESFT from other types of round cell tumors. Approximately 85% of ESFT have a balanced t(11;22)(q24;q12) translocation, forming the chimeric fusion of the EWS-FLI1 gene(Akazawa et al., 2018). The fusion of the EWS gene with ERG, the second member of the ETS family, was observed in the majority of the remaining cases (10–15%). The EWS-ERG fusion arises as a result of the chromosomal translocation t(21;22)(q22;q12) (Li et al., 2013). The ability to detect these translocations using molecular methods, such as FISH, RT-PCR, and next-generation sequencing, is increasingly critical to the diagnosis and management of ESFT. In the present case, difficulties were associated with diagnosing ESFT based solely on hematoxylin and eosin staining. Immunohistochemistry was positive for CD99 and the FISH analysis revealed chromosome rearrangements involving the EWSR1 gene region, leading to the diagnosis of ESFT.

Treatment strategies for ES include neoadjuvant chemotherapy, surgery, adjuvant chemotherapy, and radiation therapy. Kyriazoglou et al. reported a case of Ewing's sarcoma of the cervix treated with surgery, adjuvant VIDE therapy (Vincristine 1.5 mg/m^2 day 1, Ifosfamide 3 g/m^2 day 1-3, Doxorubicin 20 mg/m^2 day 1-3, Etoposide 150 mg/m^2 day 1-3), and radiotherapy (Kyriazoglou et al., 2019). The patient in this case report is still living at 42 months following the diagnosis of her tumor after primary surgery followed by chemotherapy and radiation. In Europe, VIDE therapy has been used instead of VDC-IE therapy, however the latest reports indicate that VDC-IE therapy is superior to VIDE therapy (EE2012 study) (Brennan et al., 2020). Also, Kyriazoglou et al. did not address the reason for adding radiation therapy after chemotherapy. Adjuvant chemotherapy plays an important role in the management of ESFT because the relapse rate of these tumors is 80–90% with surgical resection alone (Bose et al., 2012). The prognosis of ESFT has improved due to systemic combination chemotherapy.

Radiation therapy has been used for patients with inoperable tumors, positive surgical margins, and a poor histological response (Carvajal and Meyers, 2005). Ozaki et al. retrospectively reviewed 244 localized cases of Ewing's sarcoma and reported that the local recurrence rate was significantly lower in 10 (4%) of 241 patients who underwent surgery compared to 15 (15%) of 102 patients who underwent radiotherapy alone (Ozaki et al., 1996). Therefore, we performed neoadjuvant chemotherapy, followed by radical hysterectomy, with no postoperative radiation therapy because of the negative margins and good response to chemotherapy.

Neoadjuvant chemotherapy was performed in the present case due to the bulky tumor. Ahmad et al. discussed that all patients of ESFT of the cervix who received neoadjuvant chemotherapy (followed by either surgery or radiation therapy) were disease-free at the last follow-up, suggesting that neoadjuvant chemotherapy followed by local treatment (and adjuvant chemotherapy) may be the most effective protocol in the management of this tumor (Ahmad et al., 2017). To the best of our knowledge, nine cases of neoadjuvant chemotherapy have been reported, and postoperative pathological findings showed complete response in three cases. The chemotherapy regimens were different: DIE

(doxorubicin, ifosfamide and etoposide) in Snijders et al, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) in Benbrahim et al, and pirarubicin, cisplatin and ifosfamide in Wang et al, respectively (Snijders-Keilholz et al., 2005; Benbrahim et al., 2012; Wang et al., 2017). Primary chemotherapeutic approaches include vincristine, doxorubicin, cyclophosphamide, actinomycin D, ifosfamide, and etoposide, and several combinations, such as VDCA-IE and VAC, have been compared. Based on the findings of several trials, the current standard treatment in the United States is the VDC-IE regimen (Grier et al., 2003). In AEWS0031, the Children's Oncology Group conducted a randomized controlled trial comparing VDC-IE therapy with a shorter treatment period (every 2 weeks) and standard treatment period (every 3 weeks), and the findings obtained showed significantly better 5-year progression-free survival with the shorter treatment period, but similar toxicity. (Womer et al., 2012) In Japan, a phase 2 trial of multimodal treatment based on VDC-IE with an interval-compressed schedule using G-CSF for patients with non-metastatic ESFT (JESS14) is ongoing for patients younger than 50 years, and the efficacy and safety of a shorter treatment period (every 2 weeks) in Japanese patients are being evaluated. Therefore, this dosing regimen was not used in the present case.

In AEWS0031, chemotherapy cycles were administered every three or two weeks for a total of 14 cycles. In the National Cancer Institute protocol INT-0091 (CCG-7881 and POG-8850), chemotherapy cycles were administered every three weeks for a total of 17 cycles. The duration of chemotherapy was planned to be 49 weeks (Grier et al., 2003). In the present case, the patient was administered chemotherapy every three weeks for a total of 15 cycles, and since the dose of doxorubicin approached 500 mg/m^2, the protocol was changed from VDC to VAC. In AEWS0031 and the National Cancer Institute protocol INT-0091 (CCG-7881 and POG-8850), chemotherapy cycles were administered every two or three weeks for a total of from 14 to 17 cycles. Therefore, we did not reduce the total number of chemotherapy cycles in this present case, which showed pathological complete response on post-operative pathological examination.

After four cycles of neoadjuvant chemotherapy, the tumor appeared to have decreased in size; therefore, we performed radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy as the standard surgery for stage IB2 cervical cancer. We considered the tumor to have been sufficiently reduced to perform surgery without any perioperative complications or the need for blood transfusions.

4. Conclusion

ESFT of the uterine cervix is rare. The immunohistochemical marker CD99 and EWS-FLI1 gene translocations by FISH or RT-PCR are important for an accurate diagnosis, which is crucial before the initiation of primary therapy to increase the survival rate of these patients. Furthermore, VDC-IE therapy is considered to be an effective regimen for ESFT of the uterine cervix.

5. Ethic approval

This case report has been approved by the Institutional Review Board.

6. Consent

Informed consent has been obtained from the patient and assent has been given.

The patient consented to report this case and the attached images.

CRediT authorship contribution statement

Masahiko Mori: Conceptualization, Writing – original draft. **Kazunori Honda:** Conceptualization, Writing – original draft. **Hirofumi Tsubouchi:** Writing – original draft. **Jun Sakata:** Writing – original draft. **Seiichi Kato:** Writing – original draft, Investigation. **Shiro Suzuki:** Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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