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Tumor Discovery

CASE REPORT

Desmoplastic small round cell tumor: A case report

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Abstract

Desmoplastic small round cell tumors are extremely rare, occurring primarily in young males. This disease is characterized by the reciprocal translocation of the *EWS-WT1* fusion gene. Treatment for this tumor is multidisciplinary, including surgery, chemotherapy, and radiation therapy. The disease progresses rapidly and even with complete resection, local recurrence, and distant metastasis is likely to occur and the prognosis is poor. This report describes a case of primary ovarian cancer in a 33-year-old woman. The pre-operative test showed elevated CA125, CA19-9 and carcinoembryonic antigen, and hypercalcemia. Staging laparotomy was performed without residual tumor. The clinical stage was IIB, and adjuvant chemotherapy was performed. Immediately after the end of chemotherapy, multiple lymph node metastases, and the patient subsequently experienced repeated recurrences and died 10 months after surgery. In the future, it is desirable to establish standard treatment for desmoplastic small round cell tumors by analyzing more cases.

Keywords: Case report; Desmoplastic small round cell tumor; Ovarian cancer; Chemotherapy; Multikinase inhibitor; Immune checkpoint inhibitor

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1. Introduction

Desmoplastic small round cell tumor (DSRCT) is an extremely rare malignant tumor. DSRCT is more prevalent in men than in women, with a male-to-female ratio of 4:1. DSRCT rarely occurs in the ovaries; it mainly occurs in adolescents and young adults, and tends to cause peritoneal dissemination, lymph-node metastasis, and distant metastasis to the liver and lungs. A molecular biological feature of DSRCT is the reciprocal translocation of the *EWS-WT1* fusion gene. Treatment for DSRCT includes multidisciplinary treatments such as surgery, chemotherapy, and radiation therapy, and may include radiofrequency ablation, gamma knife, cryoablation, and vascular embolization in cases of recurrence. In the present case, despite complete resection, lymph node and distant organ metastases occurred early. Recently, molecular-targeted drug treatment has also been expected, and there have been reports of long-term growth inhibitory effects of the multikinase inhibitor sunitinib.[1] However, in the case reported herein, no response was obtained despite treatment with a protocol that included lenvatinib.

2. Case presentation

Here, we report the case of a 33-year-old woman with three pregnancies and three births. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The patient gave birth in November 2020, and no abnormalities were found during pregnancy or post-partum examination. In October 2021, the patient experienced frequent lower abdominal pain. She visited a nearby obstetrics and gynecology clinic. Ultrasonography revealed a 10 cm solid pelvic tumor. Therefore, she was referred to our hospital with suspected ovarian cancer.

The examinations conducted at our hospital, including computed tomography (CT) (Figure 1) and magnetic resonance imaging (MRI) (Figure 2), revealed a large ovarian tumor measuring approximately 12 × 10 × 10 cm, with no evident lymph node or distant metastases. Blood test results were as follows: No anemia – hemoglobin, 12.1 g/dL; cancer antigen 125 (CA125), 119.2 IU/mL; cancer antigen 19-9 (CA19-9), 163 IU/mL; carcinoembryonic antigen (CEA), 7.8 ng/mL; neuron-specific enolase (NSE), 10.0 ng/mL; and alpha-fetoprotein <2.0 ng/mL. Although she was asymptomatic, her serum calcium level was significantly high (15.0 mg/dL). She was hospitalized on October 8, 2021, for ovarian cancer treatment, and elcatonin was pre-operatively administered.

The operation was performed on October 11. Upon laparotomy, a solid tumor of approximately 10 cm in the left ovary was found (Figure 3), without any ascites or minor adhesions between the tumor surface and the rectum. No significant lymph node swelling was observed. Rapid intraoperative histopathological examination indicated malignancy; however, the specific type was indeterminate. We performed abdominal total hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, and pelvic and para-aortic lymph node dissection. The surgery lasted for 4 h and 14 min, with a total blood loss of 891 mL.

The degree of surgical completion was satisfactory. The patient's post-operative course was uneventful, and she was discharged from the hospital on October 18 without any perioperative complications. In addition, histopathological examination revealed highly atypical small round cells with swollen nuclei and a high nucleus-to-cytoplasm ratio, which proliferated densely and clustered to form alveolar nests. Various degrees of hyaline stroma were also observed between alveolar nests (Figure 4A and B). Immunostaining was positive for WT-1 (Figure 4C), CD99 (Figure 4D), CD56 (Figure 4E), and EMA (Figure 4F). Based on these results, the histopathological diagnosis was DSRCT, clinical stage IIB, and pT2bN0M0.

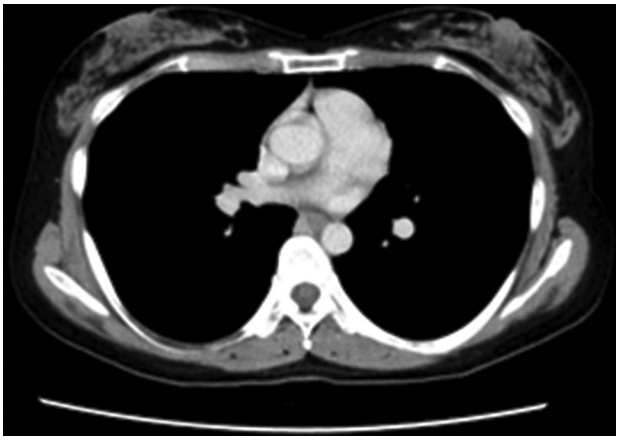


Figure 1. Computed tomography result (contrast computed tomography)

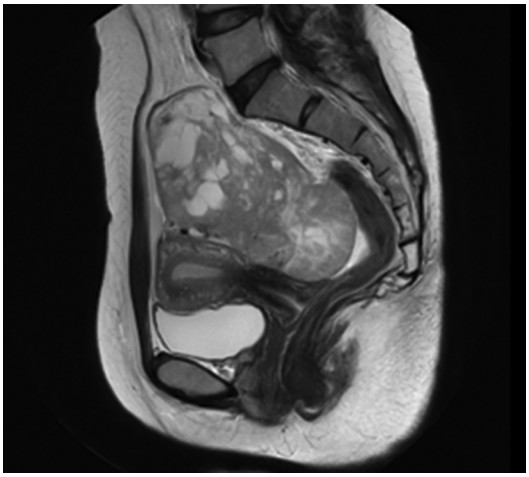


Figure 2. Magnetic resonance imaging result (T2)

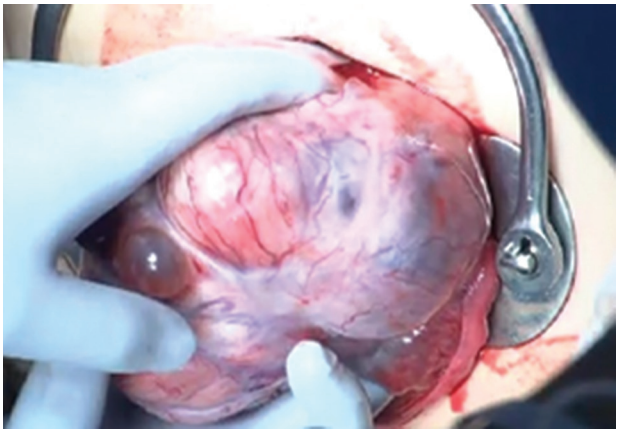


Figure 3. The tumor intraoperatively

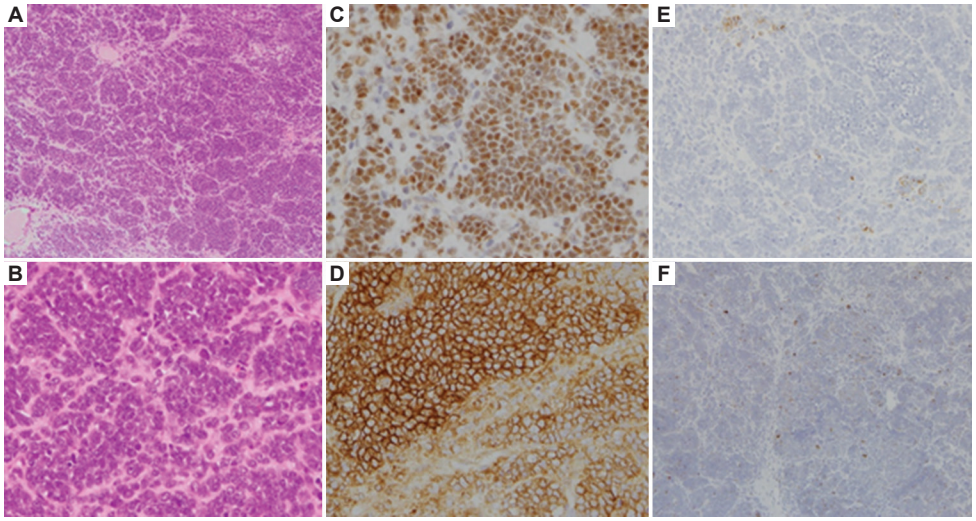


Figure 4. Histopathological findings. (A and B) Hematoxylin & eosin (HE) staining; magnification: ×100 (a), ×400 (b). (C-F) Immunohistochemistry staining for WT-1 (c; ×400), CD99 (d; ×200), CD56 (e; ×200) and EMA (f; ×100).

Consequently, six cycles of paclitaxel, carboplatin, and bevacizumab were initiated on October 27 as adjuvant chemotherapy. During this period, the tumor marker levels did not increase, and a CT scan performed on December 1 showed no evidence of recurrence. The patient continued outpatient follow-ups; however, positron emission tomography (PET) on March 11, 2022, revealed multiple lymph-node metastases in the mediastinum (Figure 5A), para-aortic lymph nodes (Figure 5B), and right obturator nodes (Figure 5C).

Nonetheless, the tumor marker levels were negative. Therefore, radiation therapy (right obturator node, para-aortic lymph node, and mediastinum; total dose: 54 Gy) was administered between March 23 and May 11. Subsequently, CT scans taken on May 17 (Figure 6) revealed multiple liver metastases and left subclavian lymph node metastasis; thus, we started administering lenvatinib + pembrolizumab as second-line chemotherapy on June 1, with informed consent.

A CT scan on July 27, 8 weeks post-treatment, revealed increased liver metastasis (Figure 7); hence, docetaxel + gemcitabine were initiated as third-line chemotherapy on August 3. On August 14, the patient presented to our emergency department with difficulty in breathing and coughing. Upon admission, she was in shock, with a blood pressure of 70/45 mmHg, requiring oxygen at 7 L/min and SatO2 (arterial blood oxygen saturation) at 70%, and exhibited mild consciousness disturbance. Blood tests indicated a hemoglobin level of 7.1 g/dL, platelet count of 18,000/μL, and C-reactive protein level of 33 mg/mL. Subsequent CT images (Figure 8) showed accelerated progression of the liver and multiple lung metastases, with

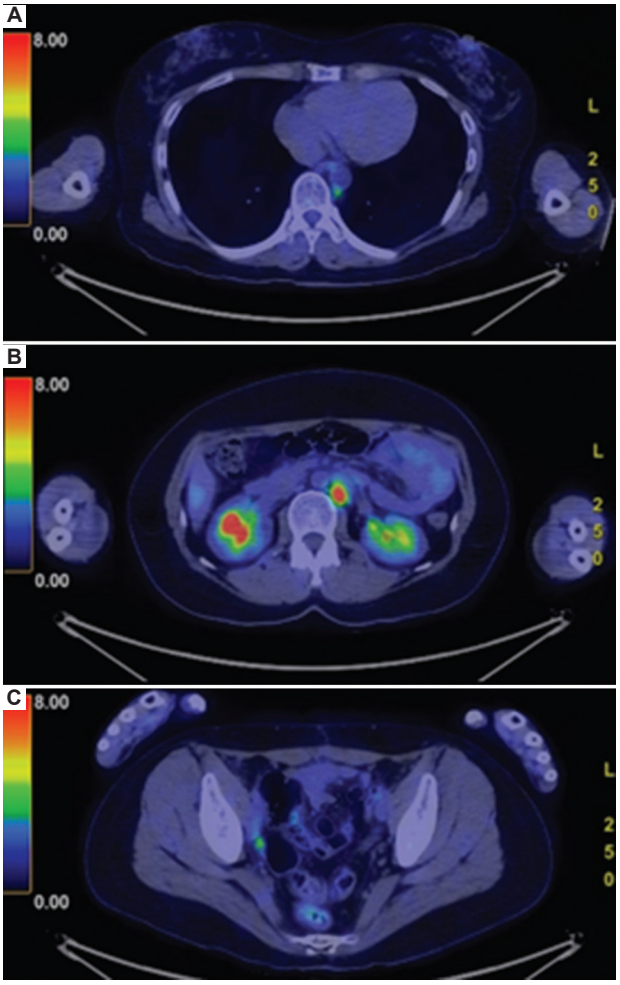


Figure 5. Positron emission tomography. (A) Mediastinal lymph node metastasis. (B) Para-aortic lymph node metastasis. (C) Right obturator lymph node metastasis.

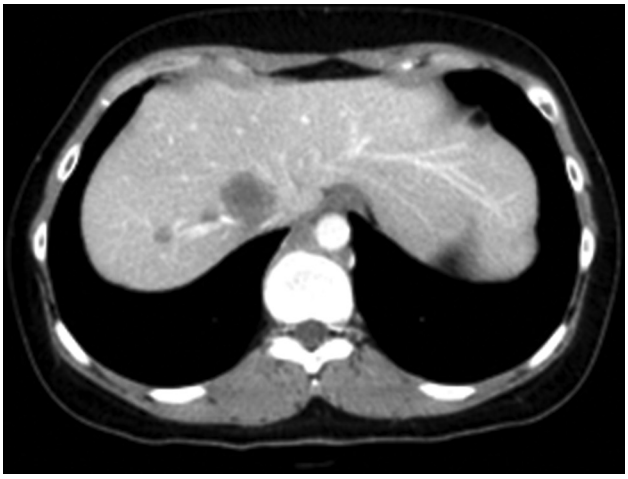


Figure 6. Multiple liver metastases after irradiation (contrast computed tomography)

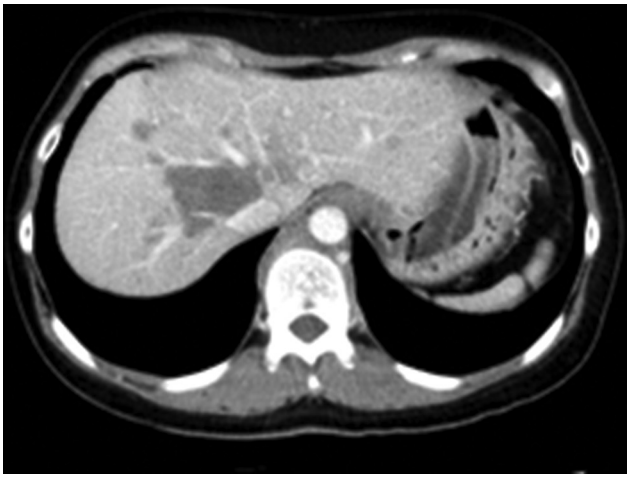


Figure 7. Increased liver metastasis after administration of lenvatinib and pembrolizumab (contrast computed tomography)

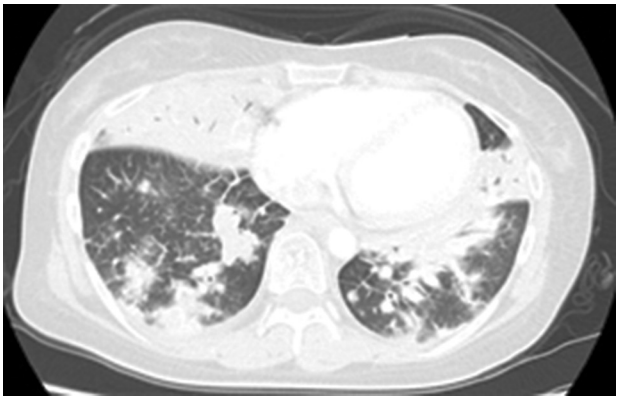


Figure 8. Computed tomography scan of the patient before death

no signs of pulmonary embolism. Her condition quickly worsened, leading to cardiopulmonary arrest, and she died 3 h after admission. No autopsy was conducted according to the wishes of the patient's family.

3. Discussion

DSRCTs were first reported by Gerald and Rosai in 1989.[2] This condition occurs most frequently in young people, and its peak incidence has been reported in people in their 30s. It predominantly affects men and is exceedingly rare in women. While it most frequently presents in the peritoneum and omentum, occurrences at other sites, including the pleura, ethmoid sinus, scalp, hands, posterior cranial fossa, pancreas, ovaries, paratesticular region, and kidneys, have been documented.[3-5]

Clinical symptoms of primary gynecological disease are abdominal distension with abdominal pain and ascites, mass palpation, constipation, anorexia, and weight loss.[6,7] More than 40% of patients have distant metastases at the time of the initial diagnosis, mostly to the liver, lungs, bones, and lymph nodes. Most cases develop as intra-abdominal masses, which have an average size of 11 cm by the time that they are diagnosed.[3] Although diagnostic imaging is useful, it often shows non-specific findings.[8] The patient had previously presented with asymptomatic lower abdominal pain. The patient was diagnosed as having asymptomatic hypercalcemia; post-surgery, their serum calcium levels decreased to 9.3 – 9.9 mg/dL, and during the period from recurrence to death, it stabilized at 9.1 – 9.7 mg/dL without an upward trend.

Examination findings are often recognized as large tumors with internal heterogeneity on CT scans. Moreover, MRI often shows high signal intensity on T2-weighted images and equal signal intensity on T1-weighted images.[8] PET is often used to accurately detect early post-treatment recurrence.[9] In this case, the imaging was characteristic. The levels of the tumor marker CA125 are known to increase.[10] The tumor measured 10 cm, and pre-operative CT revealed no distant metastasis. In addition, the tumor markers CA125, CA19-9, and CEA values were elevated, NSE remained below the cut-off, and LDH levels were within normal ranges. However, post-recurrence, these markers did not increase, implying that they were not reliable indicators of disease status in later stages. This may reflect a variation in tumor cell populations between the initial treatment and recurrence.

According to the World Health Organization's 2020 classification, the condition is classified as a peritoneal tumor and is characterized by gene translocation, including that of the *EWSR-WT1* fusion gene.[11] Macroscopically, it appears as a solid mass, and the cut surface is white and solid, which is sometimes accompanied by necrosis. Histological features include epithelial-like tumor cells

that exhibit large and small solid alveoli with high connectivity, cord-like structures, tubular structures, and rosette-like arrangements, which proliferate in an invasive manner and are accompanied by desmoplastic stroma.[11] Immunohistologically, the tumor was positive for cytokeratin and was stained with desmin in dots around the nucleus.[11]

These tumors are believed to originate from undifferentiated, multipotent cells. During chemotherapy, tumor cells differentiate into rhabdomyoblast-like cells and express the muscle lineage markers Myo-D and myogenin.[12]

The molecular biological feature of DSRCTs is the reciprocal translocation of the *EWS-WT1* fusion gene. *EWS* is located on chromosome 22q12 and encodes a member of the TET family of RNA-binding proteins. Furthermore, the TET family proteins are thought to be involved in transcription and splicing. The *EWS* gene is also related to other sarcomas, such as *EWS-FLI1* and *EWS-ERG* fusion genes in Ewing's sarcoma. Furthermore, *WT1* is located on 11p13, and the WT1 protein contains a zinc finger DNA-binding region that is responsible for the transcription and post-transcriptional regulation of many target genes. The reciprocal translocation t (22:11) (q12: p13) fuses the N-terminal region of WS with the C-terminal DNA-binding region of WT1. The resulting chimeric protein acts as an abnormal transcription factor that causes desmoplastic small-cell tumors. In addition, the EWS-WT1 fusion protein is thought to regulate the expression of various genes involved in carcinogenesis, such as *IGF-1* receptor, *PDGFα*, *PAX2-2*, *WT-1*, *ENT4*, *TALLA-1*, and *IL2/15Rβ*.[13-16] Although atypical, this mechanism may also be involved in the development of Wilms tumor, hypercalcemic small cell carcinoma of the ovary, gonadal cell tumor, and undifferentiated small round cell tumor, in addition to DSRCT.

Primary treatments include surgery, radiation therapy, chemotherapy, and molecular-targeted drugs. However, no standard treatment exists. Techniques, such as radiofrequency ablation, gamma knife, cryoablation, and vascular embolization, are used to treat metastatic lesions. Surgical therapy, often entailing omentectomy, splenectomy, or lymph node dissection, is commonly performed. Achieving negative margins is typically impractical because of the tumor invasiveness. In this case, although the lymph node and liver metastases recurred, there was no intraperitoneal recurrence, such as peritoneal dissemination or ascites. Despite slight rectal adhesions, no visible residual disease or local pelvic recurrence was detected during surgery, suggesting completeness of the procedure.

Chemotherapy is often performed using the P6 protocol that combines cyclophosphamide, doxorubicin, vincristine, ifosfamide, and etoposide. Other drugs included cisplatin, carboplatin, topotecan, temozolomide, vinorelbine, and irinotecan. High-dose chemotherapy and autologous hematopoietic stem cell transplantation are sometimes performed, but these have not been shown to improve the long-term prognosis.[17] Although DSRCTs are chemotherapy-sensitive, they are prone to local recurrence and chemotherapy alone is not effective enough to cure them. This potentially reflects the diversity of tumor cells. Furthermore, rapamycin, an mTOR inhibitor, reduced EWS-WT1 expression and triggered apoptosis in DSRCT cell lines. However, no clinical benefit has been reported in patients with DSRCTs treated with rapamycin alone.[18] In addition, the tumor progression was reported to be suppressed for 56 weeks when sunitinib, a multikinase inhibitor that targets *VEGFR1*, *2*, *3*, *PDGFR-α*, *PDGFR-β*, *KIT*, *FLT-3*, *RET*, and *CSF-1*, was administered.[1,19] In this instance, due to the delay between surgery and pathological diagnosis, we initiated adjuvant chemotherapy with paclitaxel, carboplatin, and bevacizumab with no evidence of recurrence during treatment, suggesting potential efficacy. After recurrence, lenvatinib plus pembrolizumab was administered because lenvatinib has effects comparable to those of sunitinib; however, the patient showed no response. In addition, the effects of immune checkpoint inhibitors are uncertain.

A report summarizing the treatment results of 66 cases of DSRCTs from the Memorial Sloan Kettering Cancer Center found that while there were no survivors in cases without surgery, the 3-year survival rate of patients who underwent tumor resection was 58%.[20] However, in this case, distant metastasis occurred relatively early, despite a complete surgical procedure, and although it appeared to be localized within the peritoneal cavity, micro-distant metastasis may have already occurred. Thus, the present case appears to highlight a case-specific discrepancy regarding the effect of complete surgical resection on prognosis. Furthermore, if possible, a more precise diagnosis using PET is desirable when formulating a treatment strategy. However, prediction of this disease is impossible, and may not be realistic.

4. Conclusion

Herein, we report a case of primary desmoplastic small round cell ovarian tumor. We hope that, by accumulating such cases, standard treatment can be established.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: Masaru Kanasugi
Investigation: Masaru Kanasugi
Writing – original draft: Masaru Kanasugi
Writing – review & editing: Tsuyoshi Honda, Shigeyuki Asano

Ethics approval and consent to participate

The patient and her family were given an oral explanation and written consent was obtained.

Consent for publication

The patient and her family gave consent to publish their data.

Availability of data

Not applicable.

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