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Teaching Case

Notable Response of SMARCA4-Deficient Undifferentiated Uterine Sarcoma to Palliative Radiation Therapy

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Introduction

The *SMARCA4* gene encodes the BRG1 protein, which, as one of the subunits of the SWI/SNF complex, functions as a tumor suppressor.[1] Recently, the SMARCA4-deficiency–related malignant tumor category was expanded to include several tumor types, including thoracic carcinomas and sarcomas, small cell carcinomas of the ovary, hypercalcemic type, and malignant ovarian rhabdoid tumors.[2-5] Those included in this category of tumor reportedly share some common clinicopathologic characteristics, such as (1) undifferentiated round cell or rhabdoid morphology and (2) highly aggressive, malignant behavior with a relatively poor clinical course.[2-5] Recent studies have proposed a novel entity, the SMARCA4-deficient undifferentiated uterine sarcoma, which is characterized by *SMARCA4* inactivation with a few alterations in other oncogenes, the presence of large atypical epithelioid cells with prominent rhabdoid morphology, extensive lymphovascular invasion, extrauterine spread, and marked infiltrative growth with a dismal clinical prognosis.[6,7] A previous case series of undifferentiated uterine sarcoma is thought to have described some cases of SMARCA4-deficient undifferentiated uterine sarcoma based on the presence of certain overlapping clinicopathologic features.[8] Malignant rhabdoid tumor, a well-established pediatric tumor entity, is characterized by the complete loss of SMARCB1, a member molecule of the SWI/SNF complex, to which SMARCA4 also belongs.[9] Because SMARCA4-deficient undifferentiated uterine sarcomas and malignant rhabdoid tumors commonly share an altered SWI/SNF complex as a fundamental pathologic abnormality, they have similar clinicopathologic features, such as histologically rhabdoid morphology and an aggressive clinical course.[6,9] However, the former is considered to be distinct from the latter because it never occurs in infants and completely lacks a *SMARCB1* gene abnormality.[6] Because of its rarity and rapid growth, no studies on specific treatments and outcomes have been done; thus, no standard treatment currently exists.

We described herein a case of SMARCA4-deficient undifferentiated uterine sarcoma, which progressed aggressively despite several courses of systemic therapy but showed a remarkable response to low-dose radiation therapy, especially in its diffuse liver metastases. Also

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presented is a hypothesis explaining the sensitivity of SMARCA4-deficient undifferentiated uterine sarcoma to radiation therapy.

Case Presentation

A 51-year-old female patient presented with massive irregular bleeding of several months' duration. An internal examination revealed a uterine mass protruding into the vagina. The initial laboratory assessment found hemoglobin 9.6 mg/dL (normal rage, 11.6-14.8 g/dL), lactate dehydrogenase 224 IU/L (normal range, 124- 222 U/L), and CA125 108.4 mg/dL (normal range, 0.0-35.0 U/mL). Other tumor markers, such as CA19-9, CEA, SCC, and NSE were negative, and a blood test revealed no other abnormal findings. She had a history of dyslipidemia and colorectal polyps and a family history of colorectal cancer.

Computed tomography revealed a large tumor (maximum diameter, 15 cm) occupying the uterine cervix to the corpus and a metastasis to the left common iliac lymph node (Fig 1A). The tumor appeared as an area of moderate intensity on T2-weighted magnetic resonance imaging (Fig 1B,C) and as an area of intermediate to high intensity on T1-weighted imaging, suggesting the presence of an intratumoral hemorrhage. Diffusion-weighted imaging revealed an area of high signal intensity with a very low diffusion coefficient value (0.766×10^{-3}), indicating malignant potential. A biopsy of the uterine lesion revealed a nonepithelial malignancy. Based on the diagnosis of advanced uterine sarcoma, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and low para-aortic lymph node dissection were performed with curative intent. The resected tumor was pathologically diagnosed as SMARCA4-deficient undifferentiated sarcoma based on the presence of a fairly monotonous proliferation of rhabdoid tumor cells resembling a malignant rhabdoid tumor with complete loss of SMARCA4 expression. The tumor had diffusely invaded the uterine cervix, where the surgical margin was positive due to diffuse intramural extension of the tumor and lymphatic invasion. The right external iliac and left common iliac nodes were positive for metastasis.

Six cycles of doxorubicin and ifosfamide were administrated as adjuvant chemotherapy. Radiation therapy was not administered as an adjuvant treatment due to the lack of supporting evidence. The tumor relapsed at the postoperative vaginal stump and right obturator lymph node at postoperative month 6. The patient received 1 cycle of gemcitabine and docetaxel as a second-line treatment, but the locally recurrent lesion and metastasis progressed to the iliac lymph nodes, causing bilateral hydronephrosis and renal dysfunction. The patient complained of pain and vaginal discharge; therefore, after considering the tumor's aggressiveness and the need for continued

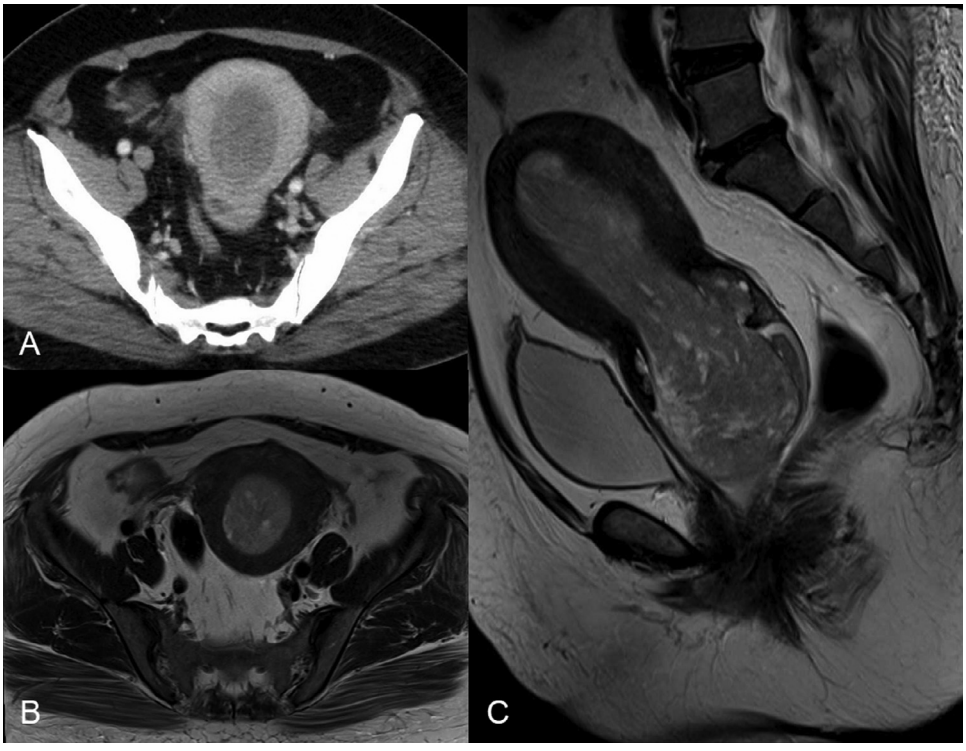

Fig. 1 Axial contrast-enhanced computed tomography (CT) imaging showing (A) the uterine mass and (B) the area of moderate intensity on T2-weighted magnetic resonance imaging (MRI). Sagittal T2-weighted MRI showing the (C) uterine mass protruding into the vagina.

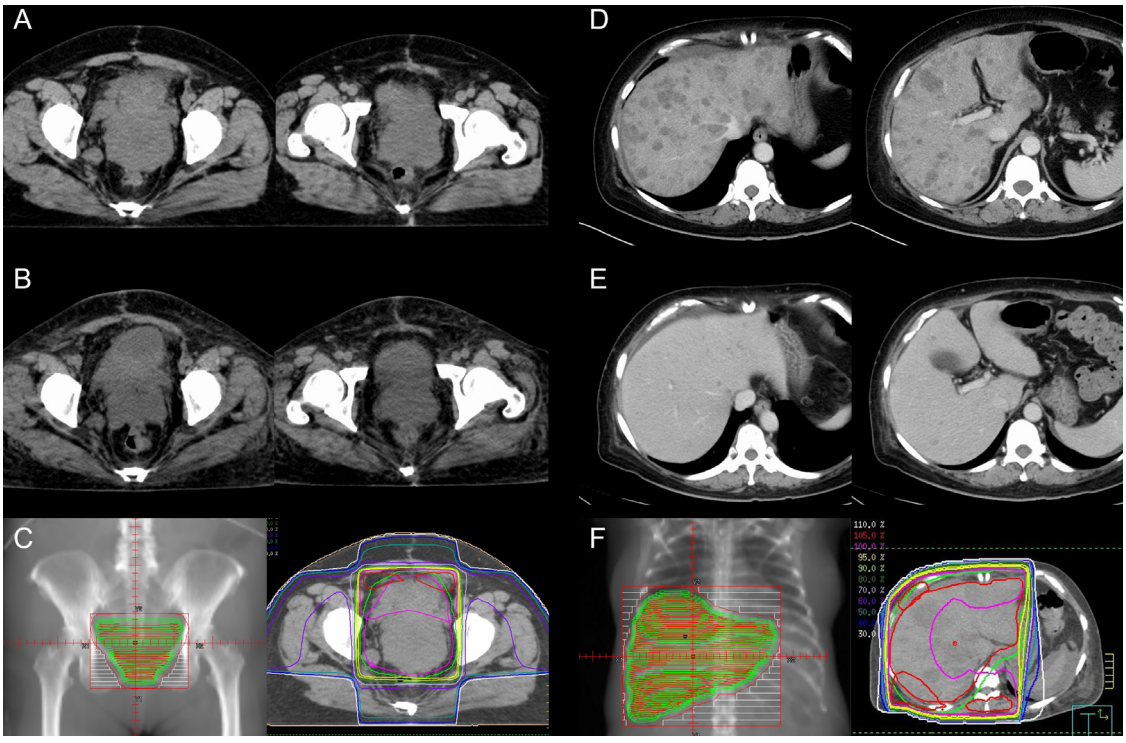

Fig. 2 Axial computed tomography (CT) of the locally recurrent lesion (A) before and (B) 2 months after radiation therapy. Axial CT of the liver (D) 3 weeks before and (E) 2 weeks after whole-liver radiation therapy. Radiation therapy plan for (C) the locally recurrent lesion and (F) the liver metastases.

systemic treatment, palliative radiation therapy at 8 Gy was administered in single fraction for the locally recurrent lesion. Radiation therapy led to symptom improvement and tumor shrinkage on computed tomography, with the diameter of the locally recurrent lesion decreasing from 8.3 × 8.1 cm to 6.1 × 6.8 cm at 2 months after the treatment (Fig 2A−C). Pazopanib hydrochloride and eribulin mesylate were administered as third- and fourth-line systemic treatments, but the tumor progressed rapidly via hematogenous and lymphatic spread. Because the patient complained of abdominal distension due to multiple diffuse liver metastases (Fig 2D) with elevated liver enzymes, whole-liver irradiation (8 Gy in a single fraction) was administered with palliative intent. After radiation therapy, the liver metastases decreased markedly, and the abdominal distension completely resolved (Fig 2E,F). Manual tumor delineation using a radiation therapy treatment planning system revealed a decrease in the total tumor volume from 45% (722/1718 mL) to 2% (32/1573 mL) of the total liver volume. Blood tests revealed an improvement in the values for aspartate aminotransferase (57-21 U/L), alanine aminotransferase (29-17 U/L), alkaline phosphatase (836-407 U/L), lactate dehydrogenase (974-638 U/L), and C-reactive protein (12.89-3.71 mg/dL) 2 weeks after radiation therapy. The patient received palliative care after treatment termination, and her general condition gradually deteriorated. Renal dysfunction resulted from hydronephrosis caused by the malignancies, and the patient died of the disease at postoperative 12 months.

Discussion

Because SMARCA4-deficient undifferentiated uterine sarcoma is a relatively new entity, to the best of our knowledge no study has yet described a treatment for the disease. The present case is unique in that it demonstrated aggressive tumor behavior with a remarkable response to radiation therapy.

Whole-liver irradiation is often used to ameliorate abdominal symptoms caused by a primary liver malignancy and liver metastasis and focuses on symptom management. Thus, a radiologic response to low-dose intensity is not necessarily expected.[10] Several small studies have evaluated the response of diffuse liver tumors to radiation therapy, and reports of whole-liver irradiation of primary and metastatic liver tumors at doses as low as 21.6 to 40 Gy have shown a predictably low objective response rate.[11,12] Furthermore, sarcomas are generally treated with doses of 50 Gy or more in a definitive or adjuvant setting, and the treatment effect at lower doses is not well understood.[13] In view of the findings in the present case, the remarkable response of the liver metastases to radiation therapy was noteworthy and

suggested that SMARCA4-deficient undifferentiated uterine sarcoma may be sensitive to radiation therapy.

The response of a locally recurrent tumor to radiation therapy at a dose of 8 Gy in a single fraction was minor compared with the response of the liver metastasis. Local oxygenation status may explain this discrepancy. Because surgery caused the pelvic lesions to become more hypoxic than in the original state, the recurrent tumors were possibly resistant to the radiation therapy. However, the abundant blood flow in the liver from the portal vein and the hepatic artery may have conferred some protection against ischemia.

Despite the absence of reports describing the treatment of SMARCA4-deficient undifferentiated uterine sarcoma, some previous studies have reported the treatment and response of SMARCA4-deficient malignancies.[14,15] Lower *SMARCA4* expression was associated with increased sensitivity to cisplatin-based chemotherapy despite the poor survival outcomes.[14] A case series of 47 cases of small cell carcinomas of the ovary, hypercalcemic type showed a trend toward lower recurrence rates in patients receiving radiation therapy as part of their primary adjuvant therapy.[15] Although generalizability across primary sites is an important issue, findings related to SMARCA4 expression in other malignancies might provide clues to the development of a treatment for SMARCA4-deficient undifferentiated uterine sarcomas. Although the proportion of SMARCA4-deficient undifferentiated uterine sarcoma cases among the malignancies formerly described as undifferentiated uterine sarcomas is uncertain, a previous report of 13 undifferentiated uterine sarcoma cases demonstrated the treatment benefits of radiation therapy; 8 patients with adjuvant radiation therapy did not experience a local relapse whereas 3 of 5 patients without adjuvant radiation therapy experienced a local recurrence.[8]

Palliative radiation therapy seems to be a good treatment option for metastatic SMARCA4-deficient undifferentiated uterine sarcoma, showing aggressive progression and a tumor response to radiation therapy as in the present case. Moreover, perioperative radiation therapy, including external beam pelvic radiation therapy and brachytherapy (which were not administered in the present case), may have the potential to improve the outcomes, given a favorable response to radiation therapy and local recurrence at the site of the initial recurrence.

Several basic studies of molecular cell biology have demonstrated that SWI/SNF function loss compromises DNA damage repair, leading to tumor radiosensitivity. A large-scale study examining cell survival after DNA damage reported that *SMARCA4* was one of 19 genes implicated in high radiation sensitivity after radiation exposure among a diverse array of 533 genetically annotated human tumor cell lines.[16] BRG1 and its combined protein modifications are the targets of research on radiosensitivity and sensitizing agents.[17,18] The suppression of ARID1A and ARID1B, which are also components of the SWI/SNF complex, as well as defects in these proteins, which have been found in several malignancies, inhibit the repair of DNA double-strand breaks and cause sensitivity to ionizing radiation.[19] Although these basic findings do not directly explain the remarkable response to radiation therapy observed in the liver metastases in the present case, future research might clarify the relationship between SMARCA4 deficiency and radiosensitivity. Malignant rhabdoid tumors are similarly characterized by SWI/SNF function loss. The treatments available for this disease, including perioperative radiation therapy and the multidisciplinary treatment approach, are well-established. Given the shared pathologic features between malignant rhabdoid tumors and SMARCA4-deficient undifferentiated uterine sarcoma, the treatment strategy for the former might be applied with good effect to the latter.[9]

Our study demonstrated rapid progression of the SMARCA4-deficient undifferentiated uterine sarcoma in the present case via both hematogenous and lymphatic spread. Because this disease entity is relatively new, only a few details on appropriate treatment are currently available. In the present case, low-dose radiation therapy not only ameliorated the symptoms but also resulted in a significant radiologic response, indicating the potential for radiation therapy as an effective treatment option for SMARCA4-deficient undifferentiated uterine sarcoma.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.adro.2021.100728.

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