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Teaching Case

Pembrolizumab After Carbon Ion Radiation Therapy for Alveolar Soft Part Sarcoma Shows a Remarkable Abscopal Effect: A Case Report

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Introduction

Alveolar soft part sarcoma (ASPS) is a rare soft tissue sarcoma (STS) mainly affecting adolescents and young adults. Its occurrence rate is approximately 0.5% to 0.9% of all STS cases.[1,2] In children, the tumor most commonly occurs at the head and neck regions, especially in the orbit and tongue.[3] Conversely, the lower extremities are the most common site of origin in adult patients.[4] Although ASPS usually increases gradually, early metastasis is one of the tumor characteristics, which leads to decreased survival rate. Indeed, recent analysis reported that the 5-year overall survival was 27% for patients with distant metastasis but 82% for patients with locoregional disease.[5] Histopathologically, an organoid or uniform nesting pattern is the most common characteristic feature of ASPS. The nests are separated through delicate partitions of connective tissues lined by flattened endothelium that form the pseudo-alveolar pattern, which is the source of the name of "alveolar" in ASPS. The tumor has high vascularity; therefore, contrast-enhanced computed tomography (CT) image or magnetic resonance imaging (MRI) is very useful for the diagnosis. Radical resection is the standard treatment for ASPS. There has been no evidence that chemotherapy, radiation therapy, or immune checkpoint inhibitor improves the prognosis.[6,7]

Recently, we encountered a case that showed remarkable response to the combination of carbon ion radiation therapy and immune checkpoint inhibitor. Herein, we report the case with some literature consideration.

Case

A 24-year-old woman had a thicker right lower leg than the left, without pain or abnormal skin findings in 2010. The leg mass was clinically diagnosed as hemangioma in a local hospital at that time. In the same year, she received polidocanol injection thrice and took the same treatment once a year until 2016 (2011-2016, for a total of 5 times). In 2012, electrochemotherapy/radiofrequency ablation was administered for the leg tumor in another hospital. In June 2017, the right lower leg became thicker than before. Contrast-enhanced MRI showed an enlarged mass and a new right pelvic lesion. In June 2017, pathological biopsy from both right lower leg and right pelvic lesion showed ASPS. As the pelvic tumor gradually increased and considered to be difficult to surgically resect, the patient was referred to our hospital in October 2017 for carbon ion radiation therapy. At pretreatment, the pelvic tumor diameter was 11.9 cm and that of the leg tumor was 11.0 cm (Fig 1). She did not show any symptoms such as pain or numbness.

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Fig. 1 Magnetic resonance imaging pre-CIRT of pelvis and leg. The pelvic tumor diameter was 11.9 cm and that of the leg tumor was 11.0 cm.
Abbreviations: Ax = axial image; CIRT = carbon ion radiation therapy; Cor = coronal image; Sag = sagittal image.

Medical history

The patient was previously healthy without history of infective diseases, operation or trauma, and drug allergies.

Family history

The patient reported that she had no family history of malignancies or other significant diseases.

Treatment

Carbon ion radiation therapy

Pelvic tumor was treated using carbon ion (C-ion) radiation therapy (CIRT). C-ion beams were generated using synchrotron at Gunma University Heavy-ion Medical Center, Japan. Passive scattering technique and layer stacking technique were applied for the treatment, and the beam energy was 290, 380, and 400 MeV/u. At our facility, radiation dose was calculated as XiO-N, which is

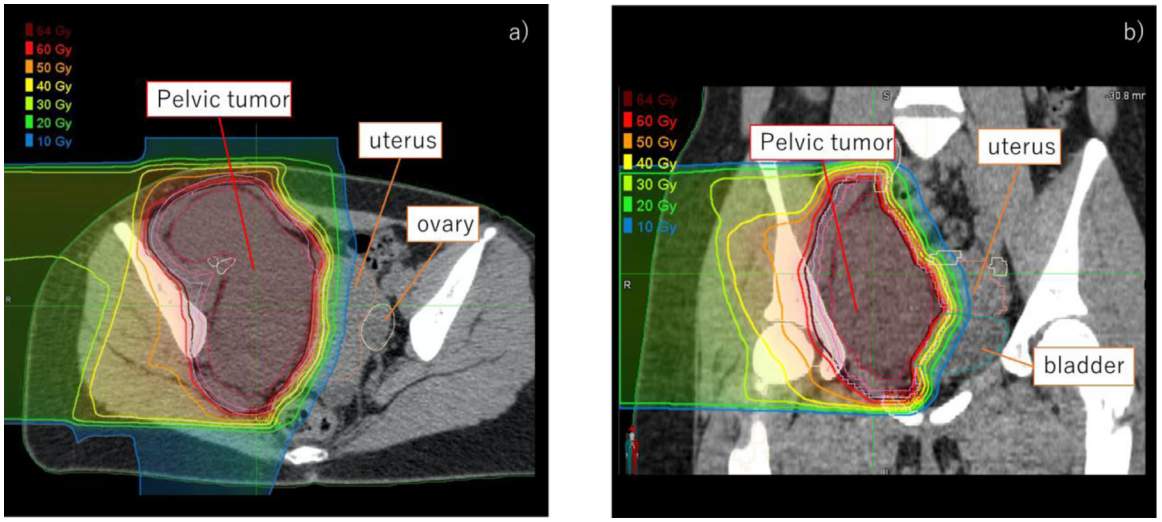

Fig. 2 Dose distribution of carbon ion radiation therapy for pelvic tumor. **(a)** Axial image of the dose distribution. **(b)** Coronal image of the dose distribution. All irradiation doses are shown in units of Gy (RBE). *Abbreviation:* RBE = relative biological effectiveness.

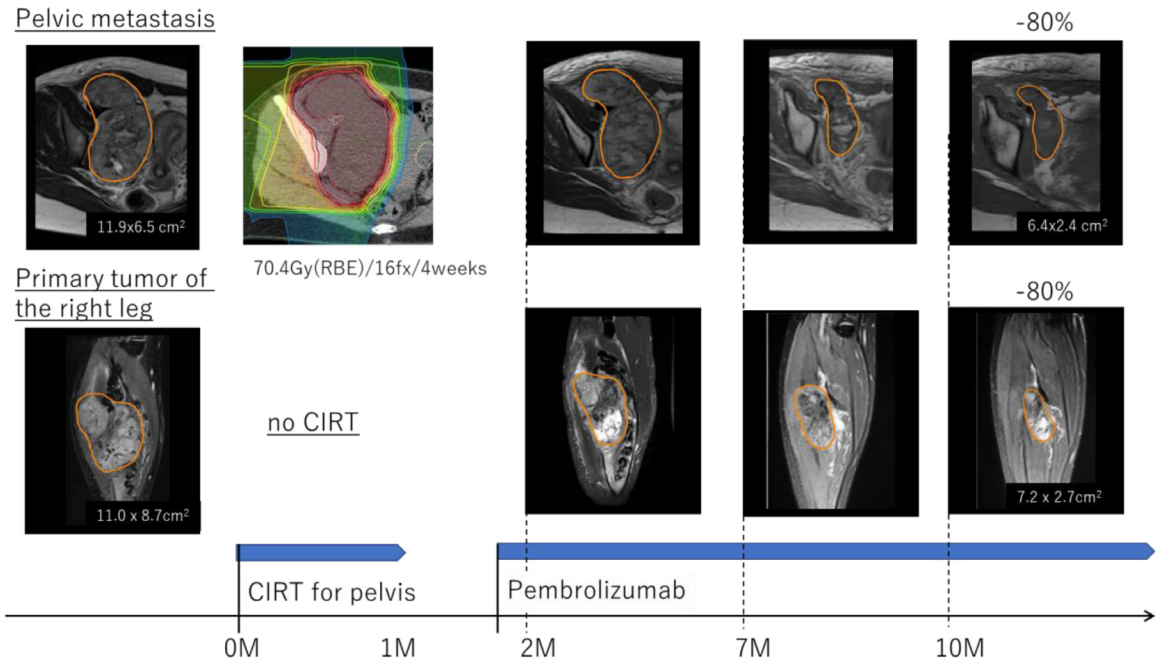

Fig. 3 The time course after CIRT. Both tumors showed 80% decrease from baseline on the magnetic resonance imaging taken at 10 months after CIRT. *Abbreviations:* CIRT = carbon ion radiation therapy; M = month; RBE = relative biological effectiveness.

XiO (Elekta)-based software incorporating a dose engine for ion beam radiation therapy (K2 dose) developed by National Institutes for Quantum Science and Technology, Japan,[8] with interfaces from Mitsubishi Electric. The CIRT dose was expressed in Gy (relative biological effectiveness [RBE]), which was defined as the physical dose multiplied by RBE of carbon ions.[9] Before the CIRT, the patient was immobilized with tailor-made fixation cushions and thermoplastic shells for acquiring treatment planning CT images, and then respiratory-gated CT (expiratory phase) and 4-dimensional CT images were obtained after immobilization. Images from the expiratory phase were used for treatment planning. The patient received CIRT once daily, 4 days a week.

The treatment period was 29 days from November 2017 to December 2017. The total irradiate dose was 67.2 Gy (RBE) in 16 fractions (4.2 Gy [RBE] for each fraction). The dose distribution of CIRT is shown in Figure 2. Irradiated volume parameters were V20 Gy (RBE) = 30% and V10 Gy (RBE) = 80% in the right ovary and V15 Gy (RBE) = 12% and V10 Gy (RBE) = 4% in the left ovary. D_{2cc} and D_{1cc} were 37.9 Gy (RBE) and 40.8 Gy (RBE) in the small intestine, 24.4 Gy (RBE) and 28.0 Gy (RBE) in the rectum, and 57.8 Gy (RBE) and 61.3 Gy (RBE) in the uterus, respectively.

Although radical resection of the leg tumor was suggested after completing CIRT for pelvic tumors, the patient refused the surgery due to high invasiveness. Therefore, an immune checkpoint inhibitor was selected as adjuvant therapy.

Immune checkpoint inhibitor

The anti-PD-1 antibody (pembrolizumab) was administered at 20 days after CIRT. According to the standard protocol, 2 mg/kg of a pembrolizumab drip was infused intravenously at 3-week intervals. A total of 3 courses of pembrolizumab were administered.

After the CIRT and pembrolizumab treatment, both the irradiated pelvic tumor and nonirradiated leg tumor remarkably shrunk (Fig 3). Both tumors showed 80% decrease from baseline on the MRI taken at 10 months after CIRT. Although the patient had menstrual irregularity as a side effect, no motor dysfunction or gastrointestinal tract disorder has occurred to date. Side effects specific to immune checkpoint inhibitor such as liver and endocrine disorders were not observed, except for menstrual irregularity. Both CIRT and immune checkpoint inhibitors can possibly affect the menstrual cycle.

Discussion

This is the first report that mentions the effect of CIRT for ASPS. C-ion is a charged heavy particle, and the charged particle beam has a special profile with Bragg peak that allows very sharp dose distribution. The Bragg peak of the C-ion is very narrow, and the linear energy transfer is exponentially higher at its tail. Thus, by using a ridge filter and adjusting the physical dose according to the flying distance, we created a spread-out Bragg peak

having a uniform biological effect and a wide range for treatment. C-ion beam has another feature of high linear energy transfer, a greater number of DNA double-strand breaks and more cell damage even for x-ray radiation-resistant tumors, such as sarcoma and hypoxic cancer. Therefore, CIRT is now considered a useful treatment option for unresectable STS. In fact, Imai et al[10] reported the 5-year local control rate and overall survival after CIRT for unresectable localized axial STS as 65% and 46%, respectively, a remarkably better result than standard x-ray irradiation. In their report, local recurrence or metastases, large target volume (>500 cm^3), and chemotherapy before CIRT were risk factors affecting the overall survival. According to their report, this patient is classified into a high-risk group of worse survival due to metastasis and 570 cm^3 clinical target volume. However, the patient showed remarkable response to therapy. Although there had been no mention before, high sensitivity to CIRT would be a significant characteristic of ASPS.

Recently, immunotherapy has become one of the standard treatments for many types of cancer. Among them, immune checkpoint inhibitors such as anti-PD-1/PD-L1 antibody have been shown to achieve remarkable response in several types of cancer. Some reports mentioned the effectiveness of the immune checkpoint inhibitor for STS. The SARC028 trial, a phase 2 single-arm trial to evaluate the effectiveness of pembrolizumab on advanced STS and bone sarcoma, showed 18% objective response among 40 patients with STS.[11] However, no patients had ASPS in the SARC028 trial. In 2018, Conley et al[12] reported a patient with ASPS who showed positive tumor response to combined checkpoint inhibitors, including anti-PD-1 and anti-cytotoxic T-lymphocyte antigen-4 antibodies. Metastatic tumors showed a 69% decrease from baseline after 2 cycles of nivolumab plus ipilimumab followed by 7 cycles of nivolumab. In 2019, Wilkey et al[13] reported the results of a phase II trial of axitinib and pembrolizumab for STS, including ASPS. Six of the 11 evaluable patients with ASPS achieved partial response, and 2 showed stable disease. A relative high sensitivity of ASPS to immune checkpoint inhibitors among STS was suggested.

The importance of this case is that the abscopal effect was observed after the combination therapy. The abscopal effect is a cytoreductive effect on distant metastatic lesions outside the irradiated field induced by a systemic immune response. Although the abscopal effect is rare, several clinical studies suggest that the combination of radiation therapy and immune checkpoint inhibitors can potentially induce it.[14-16] Supporting this notion, accumulating evidence has revealed that radiation therapy activates the host immune response, including immunogenic cell death, which releases or expresses damage-associated molecular patterns, for example, adenosine triphosphate, calreticulin, heat shock proteins, and high-mobility group box 1, leading to the effective presentation of tumor antigens and priming of antigen-specific T cells.[17,18] In addition, recent preclinical studies revealed that CIRT can induce a greater immune activation than x-ray radiation therapy.[19-21] Furthermore, case reports of metastatic recurrent colorectal cancer had shown the abscopal effect after CIRT.[22]

Anti-PD-1/PD-L1 antibodies may be appropriate as adjuvant therapy after CIRT because radiation therapy induces PD-L1[23] and anti-PD-1/PD-L1 antibodies are particularly effective for tumors with high PD-L1 expression.[24] The present case implies that PD-L1 upregulation by CIRT may enhance the effect of anti-PD-1 antibody, resulting in a remarkable local control and abscopal effect, although PD-L1 status could not be evaluated.

As a limitation of this study, because the case was from overseas, it was difficult for the patient to come to the hospital continuously and the follow-up period was not long enough. Moreover, in this case, all tumors could have disappeared with only pembrolizumab treatment without CIRT at the pelvis. However, the tumor-shrinking effect seemed to be stronger than the usual case, and CIRT and pembrolizumab are considered to have enhanced the treatment effects.

Conclusion

CIRT was a safe and effective treatment for localized ASPS. Combination of CIRT and anti-PD-1 antibody can potentially achieve better tumor control even in metastatic ASPS.

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