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Teaching Case

Young Adult Secondary Cancer After Proton Beam Therapy: A Case Study

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Introduction

Proton beam therapy (PBT) is an essential radiation therapy for pediatric cancers.[1] It is a conformal radiation therapy that can significantly reduce radiation-related long-term side effects and low-dose exposure to areas beyond the targeted irradiated field.[2,3] Dosimetry results revealed that protons could be used to block the irradiation to normal tissues and reduce the accumulated dose outside the irradiation range.[1] However, the risk of therapy-related secondary cancers persists.[2]

As cancer genomic analysis using next-generation sequencing technology has developed remarkably, cancer genome profiling (CGP) panel tests, such as the FoundationOne CDx Cancer Genomic Profile and OncoGuide NCC Oncopanel System, have been covered by medical insurance plans in Japan since 2019.[4,5] The Foundation One Liquid was insured starting in 2021 to test blood samples of patients who cannot undergo biopsy.[6] These tests are optimized to detect genetic abnormalities in adult cancers, but the detection rate of targetable genes in pediatric cancers is low.[7]

Here, we report a case of a young adult patient with secondary cancer from the irradiation field after PBT for Ewing sarcoma who underwent the FoundationOne CDx test.

Case Report

At 14 years of age, the patient visited a hospital for chest pain. X-ray and computed tomography (CT) scan showed a solid tumor adhering to his left lung, and it partially ruptured with bloody pleural effusion (Fig. 1A, B). Ewing sarcoma with *EWS-Fli1* translocation was diagnosed. An urgent operation was performed, but the tumor gradually increased in size. After receiving vincristine monotherapy and 4 courses of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide therapy, he was transferred to our hospital for PBT. He received 56 GyE PBT in 28 divided doses and 2 courses of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide therapy (Fig. 2). Proton irradiation was difficult to plan because 26 patterns had to be superimposed to irradiate only the tumor on the dorsal thoracic region. There was a site where 120% of the planned dose was irradiated in a localized area. Subsequently, he underwent autologous peripheral blood stem cell transplantation with myeloablative conditioning regimen (carboplatin 1600 mg/m^2 and melphalan 180 mg/m^2) at the age of 15 years. He was discharged while on remission.

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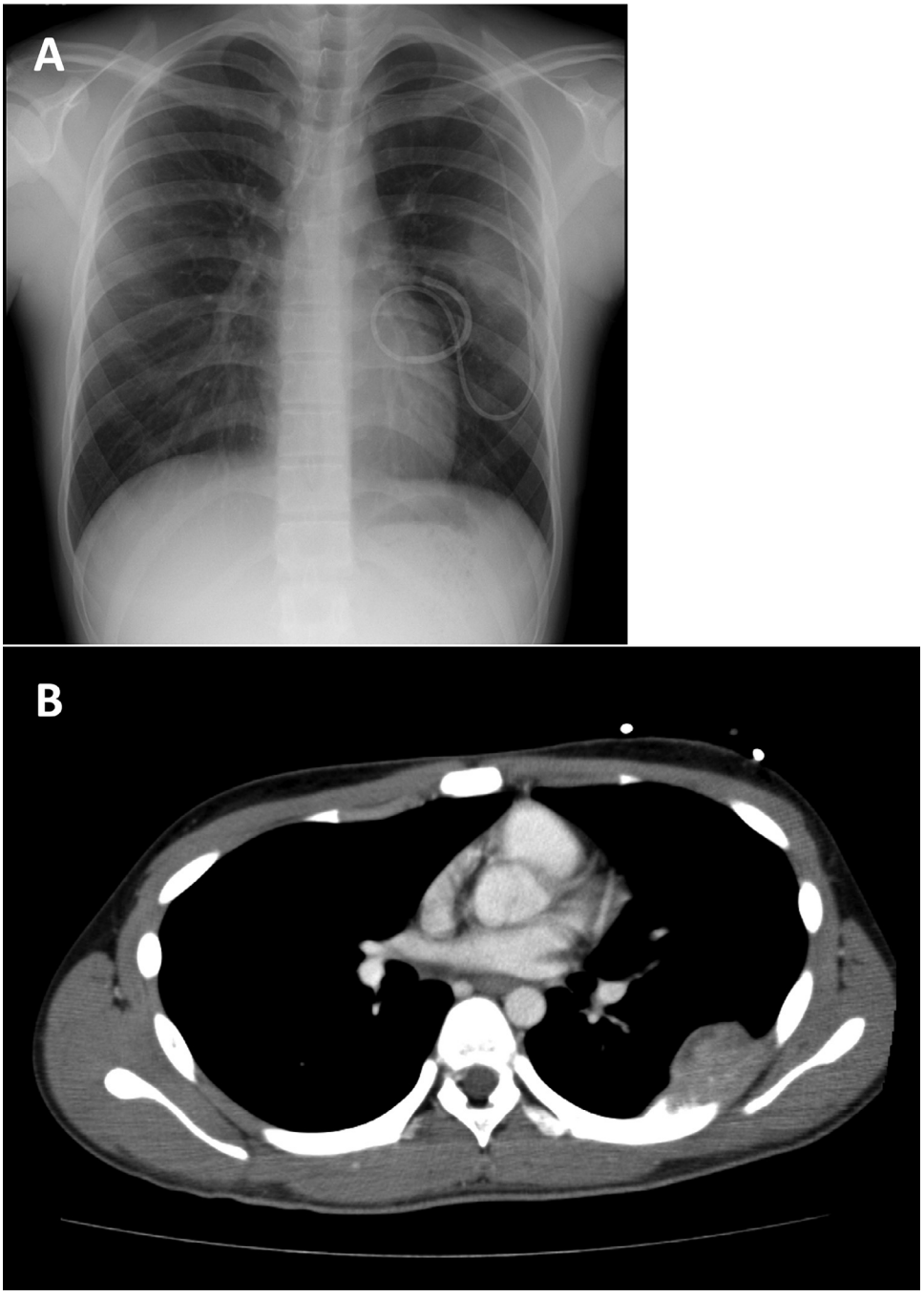

Figure 1 (A) X-ray image of Ewing sarcoma. The primary tumor was adhering to the left lung. (B) Computed tomography scan image corresponding to the mass in the area of reduced permeability on the left chest side in x-ray image (A).

Eight years later, CT scan revealed a posterior mediastinal mass. The mass emerged from the irradiated area (Fig. 3A, B). CT-guided biopsy was done, and he was pathologically diagnosed with pleomorphic and spindle cell sarcoma with no specific differentiation. It was focally positive in desmin and antismooth muscle antibodies and slightly positive in CD99, but it was negative in epithelial membrane antigen, S-100, MUC4, MDM2, NKX2.2, and MyoD1. The Ki-67 index was 35%.

After the diagnosis, he received 2 cycles of trabectedin and 10 cycles of eribulin, but the tumor grew, so he was switched to pazopanib. Pazopanib was effective for 4 months, but the tumor grew slowly. FoundationOne CDx test was performed, but it did not reveal any targetable variants other than the *TERT* 5'UTR missense variant (c.−124C > T), *TP53* in-frame deletion variant (c.383-391CTGCCCTCA > TCC, p.128_N131delinsLH), and 11 variants of uncertain significance (*APC, CBL, FANCA,*

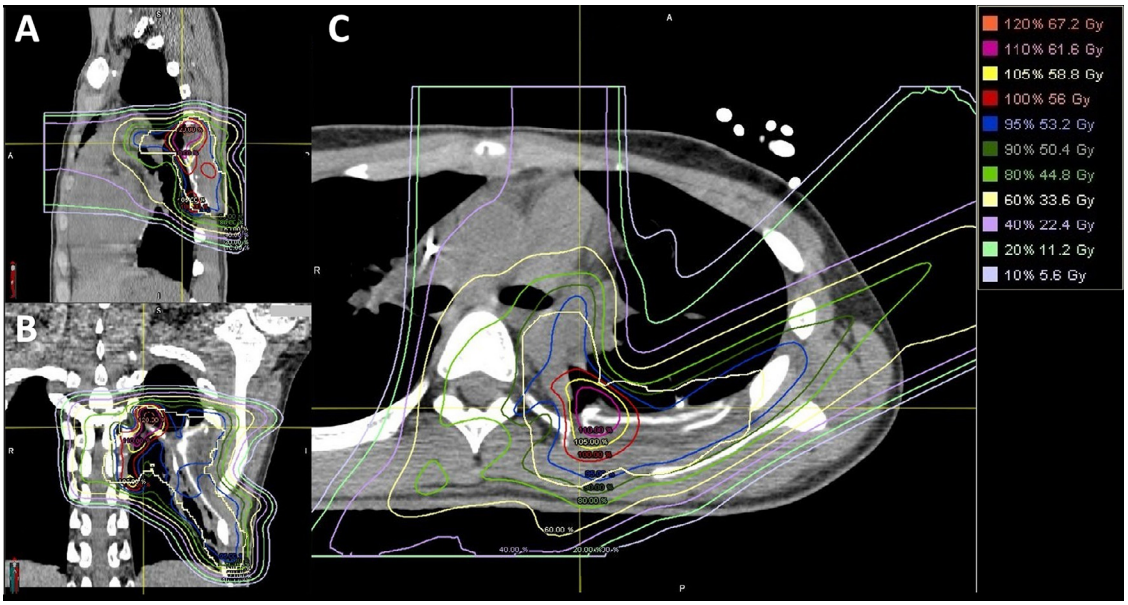

Figure 2 Dose distribution diagrams for proton irradiation of primary Ewing sarcoma. (A) Sagittal section, (B) coronal section, (C) axial section. To avoid irradiation of normal tissues, especially the lungs, as much as possible, while delivering the necessary dose to the tumor spreading to the mediastinum and chest wall, multiple proton beam irradiation from a broad-beam machine was used. A complex plan was implemented to integrate a total of 26 coplanar proton beams from 5 different angles using the patch technique. Eight years later, a second undifferentiated pleomorphic sarcoma is observed in the proton irradiated field.

FACNL, POLE, SDHC, SETD2, TSC2, BRCA2, STK11, and *TBX3*). Although the CGP test result did not prove the candidate drugs recommended for him, ifosfamide, carboplatin, and etoposide (ICE) therapy improved his fever and cancer pain. Although it did not significantly reduce the tumor size, a monthly ICE therapy allowed him to be temporarily discharged during the blood cell recovery period and stay at home, maintaining a stable disease status without cancer pain or fever for more than 6 months (Fig. 3C, D).

This study was approved by the ethics committee of Shizuoka Cancer Center. Written informed consent was obtained from patient and his parents before the genetic tests were conducted.

Discussion

PBT is one of the important treatments in radiation therapy. It is required to reduce the radiation dose to critical organs of children with cancer as much as possible.[2] PBT can reduce radiation-related late-onset side effects and secondary cancer incidence by managing the proton beam distribution accurately.[3] Secondary cancers are more likely to arise from tissues with low-dose irradiation lower than 2.5 Gy.[8,9] In recent years, Galloway et al[10] suggested that secondary cancers are most commonly located in tissues exposed to a moderate dose (20-36 Gy). These findings suggest that reducing the irradiated area with low or moderate doses could decrease the secondary cancer rates. A high-dose spot (120% of the prescribed dose, 67.2 GyE) occurred within the target volume of this case. We speculate that this was due in part to the rather complex irradiation technique used in the treatment plan for this case, which involved the use of a patch irradiation technique. It is not clear whether or not this was related to the development of a second cancer.

In studies on the susceptibility of secondary cancers to PBT and photon beam therapy, no significant difference was found.[11,12] Indelicato et al[13] reported that the incidence of secondary cancers among 1173 pediatric patients with cancer treated with PBT at their institution between 2006 and 2019 was 0.8% (5-year cumulative incidence) and 3.1% (10-year cumulative incidence). In a cohort study on pediatric and young adult patients aged older than 20 years with malignant tumors who received PBT in Japan between 1983 and 2014, 6 (1.6%) of 343 irradiated patients developed a secondary cancer within 3.1 years from PBT (median observation period).[14] Two of these 6 patients had secondary cancers outside the gross tumor volume calculated in the irradiation plan. The remaining patients had hematologic malignancies that were considered unlikely to have been caused by PBT alone. On the other hand, a childhood cancer survivor study reported that any radiation exposure was correlated with the risk of developing a secondary cancer, and the risk increased significantly from 10 GyE. An increased risk was documented in patients receiving PBT at doses

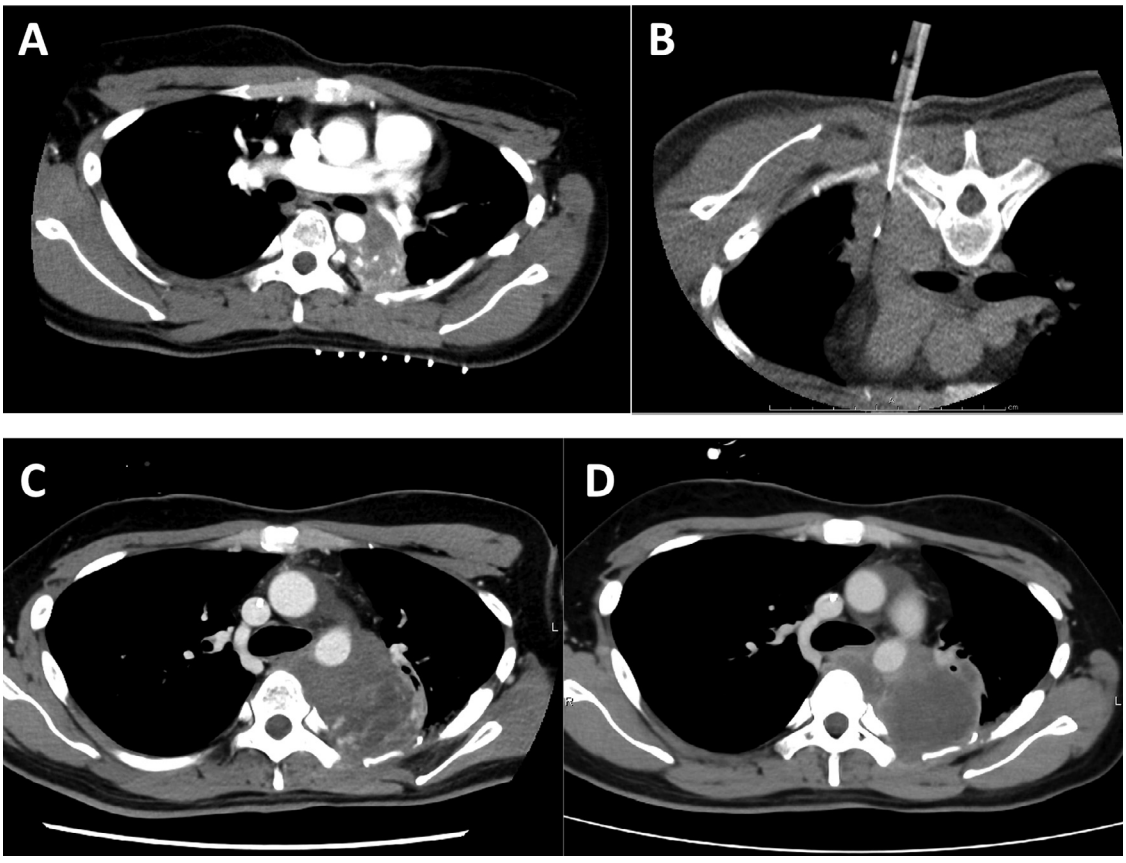

Figure 3 (A) CT scan image of the secondary UPS. (B) CT scan image of fluoroscopic biopsy procedure by interventional radiologists. (C) CT scan image of the secondary UPS at the beginning of ifosfamide, carboplatin, and etoposide therapy. (D) CT scan image of the secondary UPS 6 months after starting ifosfamide, carboplatin, and etoposide therapy.
Abbreviations: CT = computed tomography; UPS = undifferentiated pleomorphic sarcoma.

higher than 50 GyE.[15] Although radiation therapy is a risk factor for developing secondary cancers, no prospective data have examined the radiation sources. Thus, a large observational cohort study has been analyzing the radiation cytotoxity and secondary cancer development in 10,000 children who underwent proton therapy and 10,000 children who underwent photon therapy in 2007 to 2022 in the United States and Canada.[16]

Kuttesch et al[17] reported that 16 patients developed secondary malignancies, including 10 sarcomas in 266 survivors with primary Ewing sarcoma, during a median follow-up of 9.5 years (range, 3-30 years). A cancer predisposition syndrome was not suspected, and it was considered that the combination of PBT and chemotherapy was strongly linked to the development of his secondary cancer. Therefore, this was the first radiation-related secondary cancer case that developed within the irradiation field reported in Japan.

The patient underwent a Foundation One CDx test, which has been insured in Japan since 2019.[4,5] He had a *TERT* promoter variant, which is the most encountered mutation among patients with cancer, but it is not presently targetable.The results using a data set of 10,945 tumors revealed that G > A substitutions at the base-pair positions −124 and −146 relative to the *TERT* transcription start site were the most common alterations (96.3%), and they were observed in 43 principal tumor types.[18] Patients with a *TERT* promoter variant have a worse prognosis than those without it. The probability of finding meaningful variants after the Foundation One CDx test is 30%, and it is even lower in pediatric cancers.[18] Given the small number of genes reported for variants and copy number alterations in pediatric patients, special attention should be paid to genes associated with cancer predisposition syndromes. A study on CGP testing specialized for pediatric, adolescent, and young adult patients with cancers aims to have these tests covered by insurance as soon as possible. Recent studies using whole genome sequencing analysis of radiation-induced secondary cancers reported that the burden of small deletion mutations and chromosomal aneuploidy,[19] rearrangement,[20] and chromothripsis[21] significantly increased due to irradiation, but no studies mentioned the difference in carcinogenesis between PBT and photon beam therapy.

Few reports have stated that ICE therapy is effective for undifferentiated pleomorphic sarcoma.[22] According to a

report, ICE therapy is effective in patients with neurofibromatosis with undifferentiated pleomorphic sarcoma.[23] He did not have any clinical symptoms or family history of neurofibromatosis, but ICE therapy was proven to be effective in this case. There are few reports on CGP testing using secondary cancer specimens from pediatric, adolescent, and young adult patients. One study limitation is that CGP testing could not be compared between primary Ewing sarcoma and secondary cancer. At present, the insurance coverage for CGP testing is only allowed once in a lifetime, but comparing primary and secondary cancers may provide drug target variant information for pediatric cancer survivors with secondary cancers.

In summary, this is the first case report of a young adult patient in Japan who developed a secondary cancer in irradiated field after PBT for Ewing sarcoma diagnosed during childhood. Therefore, accurate epidemiologic studies on secondary cancer development within irradiated fields after PBT and gene analysis about its mechanism in a large cohort are desirable.

Disclosures

All 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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