Abscopal effect with unknown fever during radiotherapy: Two case reports

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Case Report

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Abstract

The abscopal effect is a rare phenomenon that is defined as regression of tumor lesions distant from irradiation targets. We have experienced two cases with an abscopal effect with unknown fever and an inflammatory response during radiotherapy. Radiotherapy is a local treatment, therefore, it rarely causes systemic side effects during radiotherapy, and if a patient develops a fever during radiotherapy, it is often considered tumor fever. We experienced 2 cases of unknown fever during irradiation followed by abscopal effect. The obvious relationship between the abscopal effect and the unknown fever is not clear. However, Unknown fever during radiotherapy may be a hint to the abscopal effect considering that immune response and cytokines closely related to the abscopal effect.

Introduction

Radiotherapy plays an important role of local treatment for malignancies. The mechanism of radiotherapy is mainly through the damage of deoxyribonucleic acid (DNA) inside the malignant cells in the irradiation field. However, rare phenomenon of spontaneous regression in lesions distant from an irradiation field has been reported, and is called “abscopal effect”. The abscopal effect was initially suggested by Mole in 1953 [1]. The biologic mechanism of this effect has not been completely dissolved, but immunologic mechanisms are considered to mediate this effect. In recent years, tumor immunity in combination with immune checkpoint inhibitors (ICIs) has become of increasing interest in the abscopal effect. However, this phenomenon is very rarely encountered in clinical practice, especially for an abscopal effect to manifest itself without pharmacologic immunomodulation (pure abscopal effect) [2]. Here, we report two cases with abscopal effects: one showed a pure abscopal effect and the other occurred after resistance to immunotherapy. Unknown fever was observed immediately after initiation of radiotherapy in both cases. The relationship between this fever and the abscopal effect was unclear, but radiotherapy does not normally induce systemic response. The symptoms at presentation, physical exams and laboratory results are given for each case in the following section. Written informed consent for this manuscript was obtained from each patient.

Cases

Case 1

A man aged 78 years was diagnosed pleomorphic sarcoma of iliac bone (size: 8.1×12.1×15.5 cm) with pelvic lymph node metastases and bilateral lung metastases, and referred to the department of palliative medicine. Palliative photon radiotherapy 36 Gy in 12 fractions over 16 days was indicated for iliac pain control and fracture prevention. The day after the start of radiotherapy, the patient complained of fever without respiratory or urinary tract symptoms. Fever up to 38°C was observed twice a day during the irradiation period. This fever broke spontaneously in 3 hours each time. Blood tests showed no characteristic findings other than a mild inflammatory reaction and thrombocytopenia. (C-reactive protein (CRP) of 7.07 mg/dl, Platelet 5.6×10^4/µl). Celecoxib was prescribed for antipyretic and analgesic therapy.
but was ineffective. The fever continued for 2 days after the finish of radiotherapy, but then spontaneously resolved. After radiotherapy, no additional treatment was given except for drugs for pain relief. Pain improved gradually and the patient started to be able to walk on his own 3 months after radiotherapy. Computed tomography (CT) showed significant shrinkage of the primary irradiated tumor and lung metastases. One year after radiotherapy, the primary tumor size was 3.6×6×5.5 cm. However, 14 months after radiotherapy, the patient complained of left coxalgia again and the iliac tumor had slightly increased. At this time, the tumor size was 4.4×8×6 cm, but lung metastases still maintained shrinkage and 18fluorodeoxyglucose-positron emission tomography (18FDG-PET) showed no accumulation except for the iliac tumor. Reirradiation with photon radiotherapy was impossible because the alimentary tract could not be avoided; therefore, proton therapy of 51 Gy(RBE) in 17 fractions over 27 days was used for the iliac tumor. During this course, there was no fever. Pain was relieved slightly, but the tumor did not shrink at all. The tumor then rapidly increased in size and lung metastases also progressed markedly. After proton therapy, palliative care was offered, and the patient died from lung lymphangitis. The timeline and imaging process, and the treatment fields of photon and proton radiotherapy are shown in Fig. 1.

Case 2

A 59-year-old man was diagnosed with renal cell cancer based on CT at the time he was admitted to hospital due to capsular hemorrhage. After recovering from this hemorrhage, a close examination for renal cell carcinoma (RCC) revealed metastasis to renal hilum lymph nodes and lung metastases, and the clinical stage was T3aN1M1. Nephrectomy was performed in 2016 and the pathological results showed clear cell carcinoma. Sunitinib was started one month after nephrectomy, and lung and lymph node metastases decreased. Sunitinib was continued for 10 months, then after the lung metastases increased and right adrenal metastasis appeared, treatment was switched to axitinib and the metastases shrank well again. However, severe chemical dehydration occurred 5 months after the start of axitinib; therefore, nivolumab was started thereafter and continued for 8 months, despite slight progression of lung and adrenal metastases 2 months after the start of nivolumab. However, nivolumab was then stopped due to a severe immune-related adverse events (IrAE) of pituitary insufficiency followed by infectious endocarditis and severe ischemic enteritis. Subsequently, no additional drug therapy was given, and in the 8 months after stopping nivolumab, right adrenal metastasis increased to 70×54 mm. Other metastases maintained a shrinkage. At that time, the size of the lung metastasis was 12.8×4.4 mm. Therefore, resection of the adrenal metastasis was attempted; however, this proved to be impossible due to strong adhesion. Radiotherapy was then considered, and photon radiotherapy of 50 Gy in 25 fractions over 36 days was delivered with palliative intent. On the first day of the radiotherapy, the patient had a fever of 37.5°C after returning home from radiotherapy. On the second, blood tests were performed because the fever persisted, and a high inflammatory response was observed: white blood cell 14,300 /µl and CRP 11.38 mg/dl. The fever was not broken with oral aspirin, and the inflammatory reaction rapidly elevated to a temperature of 39.2°C and CRP of 32.46 mg/dl. CT was performed to search for the cause of inflammation on the 6th day, but no cause could be identified. At this time, the adrenal metastasis increased to 97×69 mm and one of the lung metastases had slightly increased to 13.6×4.8 mm,
compared to 4 months earlier. Urine tests and blood and urine cultures were all negative. Therefore, we considered that the inflammation was caused by the tumor itself, and radiotherapy was continued despite the high inflammatory response. The inflammatory reaction gradually decreased spontaneously during the treatment period. The treatment course of Case 2 was shown in Fig. 2. After radiotherapy, the adrenal metastasis shrunk gradually and had reached a size of 35×25 mm by June 2022. The pulmonary metastases also slightly shrunk to 9.7×3.1 mm. The imaging processes for the lung and adrenal metastases are shown in Fig. 3.

Discussion

The abscopal effect has been reported in various carcinomas. Siva et al. suggested that this effect is transmitted by an acute inflammatory cytokine cascade and the immune system [3]. Ionizing radiation releases cytokines, which elicit augmented tumor surveillance, inhibit tumor growth, and have direct tumoricidal properties [4]. Also, ionizing radiation directly elicits innate immune recognition of a tumor: dendritic cells are activated by irradiated dying cells, and antitumor T cells are activated by the cross-presentation of tumor-derived antigens presented to T cells [5].

In practice, however, an abscopal effect of radiotherapy alone is extremely rare. A review of abscopal effects of radiotherapy found only 46 cases between 1969 and 2014 [6]. However, the number of reports of an abscopal effect in patients treated with a combination of radiotherapy and ICI has increased [7–15]. Only in one year of 2021, 21 case reports of abscopal effect promoted after radiotherapy were yielded [13, 16–35]. This is thought to be due to T-cell activation by a damage signal from irradiated dying cells and upregulation of Programed death receptor-1 (PD-1) and programmed cell death 1- Ligand 1 (PDL-1) [36, 37], and an ICI disarms immune escape mechanisms, and this may increase the effects of the innate immune response activated by radiotherapy. Gramaldi et al. reported an abscopal response in 52% of melanoma patients who received ipilimumab followed by radiotherapy [38].

In this report, we reported two cases of abscopal effects. The most characteristic feature of our two cases is that both patients had unknown fevers soon after the start of radiotherapy. Case 1 was a pure abscopal effect observed in the patient with pleomorphic sarcoma. In this case, a fever was observed during the initial irradiation period, but since it was mild and there were no signs of infection, we did not pay much attention to it. In contrast, the re-irradiation using proton therapy did not cause fever, and no abscopal effect was observed. Case 2 was an abscopal effect in a patient with RCC who received radiotherapy after ICI. RCC often has periods of disease quiescence, however, lung metastasis in this case showed increasing trend at the start of radiotherapy, therefore, it was expected to increase after radiotherapy to the adrenal metastasis. Generally, the prognosis of RCC after disease progression during treatment with an ICI is poor. In a retrospective analysis of 33 patients from 7 clinical trials, Barata et al. found a median progression-free survival (PFS) from initiation of molecular targeted therapy after progression on an ICI of 6.4 months (95% CI; 4.4–8.4 months) [39]. Roviello et al. obtained PFS of 5 months and 3 months (95% CI: 1–6 vs. 2–5; p = 0.6) for patients who received active treatment and best supportive care, respectively, after progression of metastatic RCC while on nivolumab and cabozantinib.
[40]. However, in our case, adrenal metastasis was well controlled with palliative dose and lung metastasis shrank over 3 years. This may be due to enhanced immune response by nivolumab, and strong inflammatory response observed during radiotherapy also related with immune response.

There was no evidence of relationship between the abscopal effect and fever during radiotherapy. However, the abscopal effect is known to involve activation of inflammatory cytokines, and these two phenomena are both so unusual that they may not be coincidental. The two cases in this study were treated palliatively and detailed data was missing. However, given that an inflammatory cytokine cascade is involved in the abscopal effect, it could be concluded that unknown fever during the radiotherapy may be a hint to the abscopal effect, not by coincidence, although it is often overlooked as tumor fever.

**Abbreviations**

ICI: immune checkpoint inhibitors
CT: Computed tomography
CRP: C-reactive protein
18FDG-PET: 18fluorodeoxyglucose-positron emission tomography
RCC: renal cell carcinoma
PFS: progression free survival
PD-1: programed death receptor-1
PDL-1: programed cell death 1- Ligand 1

**Declarations**

- Ethical Approval and Consent to participate

Since this is case report, ethical approval was not necessary in our institution

- Consent for publication

Written informed consent for writing and publish this manuscript was obtained from each patient.

- Availability of supporting data: Not applicable
- Competing interests: Not applicable
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• Authors’ contributions:

Y. Oshiro conducted photon radiotherapy of the 2 patients, and wrote a draft of the manuscript. M.Mizumoto and H.Sakurai conducted proton therapy of the case 1 patient. T. Hisanaga cared for the case 1 patient. M.Komine, K.Tanaka, and K.Kikuchi cared for the Case 2 patient. All authors contributed to manuscript revision, read, and agree to be accountable for the content of the work.

References


Figures

Figure 1

Clinical course and imaging process for iliac pleomorphic sarcoma (Case 1) and treatment planning for photon and proton radiotherapy.
Figure 2

Clinical course during radiotherapy (Case 2).
Figure 3

Imaging process for adrenal and lung metastases (Case 2). Lesions are indicated by yellow arrows.