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Teaching Cases

Cytokine Release Syndrome in a Patient With Metastatic Triple-Negative Breast Cancer Treated With Hypofractionated Radiation Therapy, Who Had Previously Undergone Immunotherapy: A Case Report

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Introduction

Radiation therapy (RT) serves a crucial role in several aspects, ranging from curative intentions to alleviating symptoms associated with metastatic lesions. With the emergence of immunotherapy as an effective cancer treatment, patients increasingly receive RT before, during, or after immunotherapy administration, either in hope of achieving an immune synergistic effect or as an incidental combination.[1] Despite its growing prevalence in routine clinical practice, the combination of RT with modern systemic drugs, such as immunotherapy, remains poorly understood due to limited safety data and a lack of comprehensive, high-level evidence to inform clinical management.[2] Furthermore, given the inherent connection between possible immune-related adverse events (irAEs) and immunotherapy drugs, discerning whether RT might increase irAEs, either directly or indirectly, is challenging.[3]

Cytokine release syndrome (CRS) is a cluster of immune response symptoms that can occur as an irAEs of immunotherapy, particularly in treatments involving T-cells and in patients with hematologic malignancies.[4,5] Clinical manifestations range from mild symptoms, such as fever, fatigue, and body aches, to severe complications such as organ failure and potentially life-threatening medical conditions.[6] Prompt intervention is paramount, with some patients necessitating intensive care and immunosuppressive drugs to mitigate the immune response.[5]

Although a recent case report highlighted the occurrence of grade 3 CRS after RT in a patient with leukemia and Merkel cell carcinoma undergoing anti-programmed cell death protein 1 (PD1) immunotherapy,[7] a fatal CRS after RT in a patient has not been previously described in the literature. We report a case of grade 4 CRS that occurred after hypofractionated RT in a patient with metastatic triple-negative breast cancer, who had previously undergone immunotherapy.

Case and Clinical History

Chronology of previous cancer treatment

We present the case of a 49-year-old female patient diagnosed with stage IIIA triple-negative breast cancer.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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She underwent anthracycline, taxane-based neoadjuvant chemotherapy followed by a mastectomy and axillary lymph node dissection, with direct implant-based breast reconstruction. Immediately after completing the fourth cycle of postoperative adjuvant chemotherapy, she experienced a recurrence in the skin of the reconstructed breast. An excisional biopsy was performed for this recurrence, after which she was referred to our hospital for postoperative RT. Before starting RT, a PET-CT scan was conducted, revealing metastases in the chest wall, lungs, and lymph nodes in the internal mammary, supraclavicular, and axillary regions. Consequently, the planned postoperative RT was canceled based on these findings.

The patient began palliative second-line eribulin cytotoxic chemotherapy treatment. Unfortunately, 3 months later, a chest computer tomography (CT) scan revealed disease progression in the bilateral lungs and bilateral hilar and interlobar lymph nodes. A biopsy of the metastatic chest wall lesion revealed PD-L1 positivity (Combined Positive Score, 20) based on the 22C3 antibody, with triple-negative characteristics. She was started on efineptakin alfa in combination with anti-PD-1 inhibitor pembrolizumab after enrolling in a major immunotherapy clinical trial. After 5 cycles, the patient made an unscheduled visit to the clinic due to a growing mass in the chest wall and increasing pain. Because of the refractory nature of her disease and its rapid progression off therapy, she was referred to us for RT to alleviate symptoms and control the protruding tumor, while concurrently starting the next line of systemic therapy with paclitaxel and carboplatin. Figure 1 shows the extent of the progressed tumor, involving the anterior chest wall, sternum, and bilateral internal mammary chains at the time of RT.

CRS occurrence with radiation

One week after the first cycle of chemotherapy, which was 34 days after the last administration of pembrolizumab, the patient was scheduled to receive 5 fractions of 30 Gy over 5 consecutive days, targeting the chest wall mass originating from the sternum. The high gradient was achieved by prescribing 40 Gy to a partial volume at the core of the tumor. This dose prescription was selected to provide symptom palliation and also achieve durable local control of the bulky, oligo-progressive mass. The planning target volume and gross tumor volume was 252.65 cc and 121.2 cc, respectively. RT contours and isodose lines are shown in a representative CT axial image (Fig. 2). Dosimetric parameters and the dose-volume histogram are summarized in Fig. E1. When she returned after her second fraction in the late afternoon, she was experiencing fever, chills, and a skin rash with itching sensations. The skin rash spread to her entire body, leading to her referral to emergency care.

In the emergency room (ER), with a suspected drug allergy to a nonsteroidal anti-inflammatory drug, specifically Stevens-Johnson syndrome, she received IV steroid therapy (0.4 g/kg for 5 days) and was discharged after her symptoms improved. The interleukin (IL)-6 level was tested to distinguish various types of drug hypersensitivity reactions or infections, and yet it indicated a value of 3.4 pg/mL. When she came back for her third fraction the next week, she was symptom-free and in good condition, so we decided to continue with the rest of the treatment. However, after the fourth fraction was delivered, she came back to ER again and was admitted for high sustained fever, general weakness, sore throat, and a facial and whole-body rash. Fluid resuscitation with crystalloids and empirical antibiotic therapy with intravenous piperacillin/tazobactam and teicoplanin were administered. Intravenous high dose steroid (methylprednisolone 2 mg/kg) was also quickly initiated. After being monitored for a couple of hours, she experienced dyspnea, desaturation, hypotension, and cardiac arrest with ventricular fibrillation. After the return of spontaneous circulation, she was admitted to the intensive care unit, where she required intubation, oxygenation, and ventilation, along with increasing doses of multiple vasopressors. After a differential diagnosis of septic shock, adrenal insufficiency/crisis, grade 4 CRS was diagnosed through a

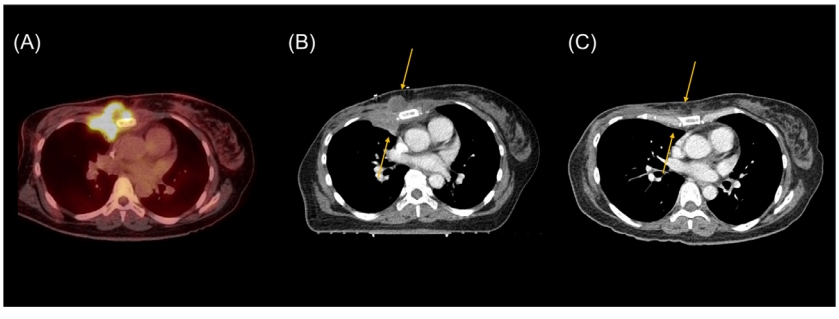

Figure 1 The extent of the progressed tumor involving the anterior chest wall, sternum, and bilateral internal mammary chains. (A) Axial PET-CT image prior to RT, (B) axial image from the simulation CT scan and (C) chest CT scan 34 days post-RT, revealing regression of the previously irradiated tumor.

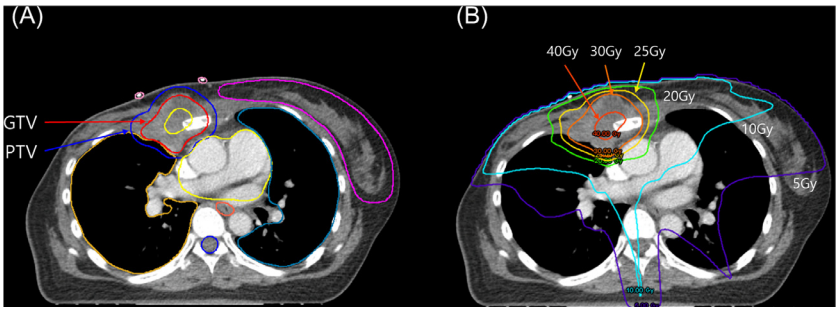

Figure 2 A high-gradient radiotherapy planning for 30 Gy in five fractions, with 40 Gy prescribed to the partial volume of the GTV core and 30 Gy to the PTV simultaneously. (A) Radiotherapy plan displaying RT contours of the gross tumor volume (GTV) with GTV core (yellow line) and the planning target volume (PTV). (B) Isodose lines from the radiation treatment plan in the axial view of the patient.

multidisciplinary tumor board discussion, and tocilizumab (anti-IL6 receptor antibody) was recommended along with the continuation of high-dose steroids. As this was the inaugural authorization for its use, necessitating time to secure its supply, 8 mg/kg tocilizumab was consequently administered on both the third and fourth days. After 17 days in intensive care with high-dose steroids and tocilizumab, her vitals normalized and symptoms improved, leading to her transfer to a general ward. The relevant laboratory results, as shown in Fig. 3, indicate that IL-6 levels spiked from 17.7 to 164.5 pg/mL 1 day after the fourth fraction of RT, then normalized to 8.9 pg/mL within 4 days after the administration of tocilizumab (Fig. 3A). After the initial increase after the first and second fractions of RT, the white blood cell count normalized, and then elevated again after the third and fourth fractions, but returned to normal after tocilizumab administration; concurrently, the lymphocyte count decreased after the first 2 fractions, normalized, and then sustained a decrease post the third and fourth fractions (Fig. 3B). Creatinine levels increased post the first and second fractions of RT, normalized, and then rose again after the third and fourth fractions but normalized with tocilizumab. Similarly, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels rose post the third and fourth fractions and decreased after tocilizumab administration (Fig. 3C). There were no occurrences of hyperkalemia, hyperphosphatemia, or hypocalcemia.

Disease course after CRS recovery

Despite a 2-month interruption of systemic therapy, follow-up chest CT scans revealed marked shrinkage of the irradiated chest wall lesion and overall stable disease in the lesions present before CRS. However, new lesions emerged in the brain and the left neck nodal area 4 months later. She was started on palliative third-line paclitaxel and carboplatin chemotherapy, along with stereotactic radiosurgery (SRS) for the brain metastasis. Despite undergoing 2 additional rounds of brain SRS for new brain metastases, her disease remained controlled for nearly 1 year under the same regimen. Unfortunately, the disease progressed to the leptomeningeal area, leading to the patient's demise approximately 32 months after the date of the first recurrence.

Discussion

Although CRS is a well-known irAE in hematologic malignancies, particularly after T-cell engaging therapies such as chimeric antigen receptor (CAR) T-cell therapy,[5] its occurrence due to RT is not widely known, despite potentially deadly toxicity. In this case, the administration of a PD-1 inhibitor and efineptakin alfa 1 month before RT, coupled with 1 cycle of cytotoxic chemotherapy a week before RT, likely created a hyperactivated immune environment, making RT the direct trigger for CRS's inflammatory cascades and the resultant release of large amounts of cytokines into the body. Hay et al reported that lymphodepletion chemotherapy is often associated with CRS, which occurs during CAR T-cell therapy.[8] Tay et al presented a case series of CRS in patients receiving immunotherapy and found that a longer time to fever onset, a lower platelet count, and higher urea levels at presentation were associated with severe CRS.[9] Considering several reports that the incidence and severity of CRS after adoptive T-cell therapy are greater in patients with large tumor burdens, the relatively large PTV (252 cc) and high dose per fraction (≥6 Gy) in our case might contribute to severe CRS.[10]

In this case, our patient's post-RT increase in serum IL-6 level and blood tests implying inflammation with typical clinical symptoms (eg, fever, hypoxia, and hypotension), which required ventilation and multiple vasopressors, met the definition of grade 4 RT-induced CRS.[11] The simultaneous rise in AST, ALT, and creatinine levels, followed by improvement after administering high-dose steroids and an anti-IL-6 receptor antibody, suggests multiorgan dysfunction associated with CRS in this case. The differential diagnoses included sepsis, tumor lysis

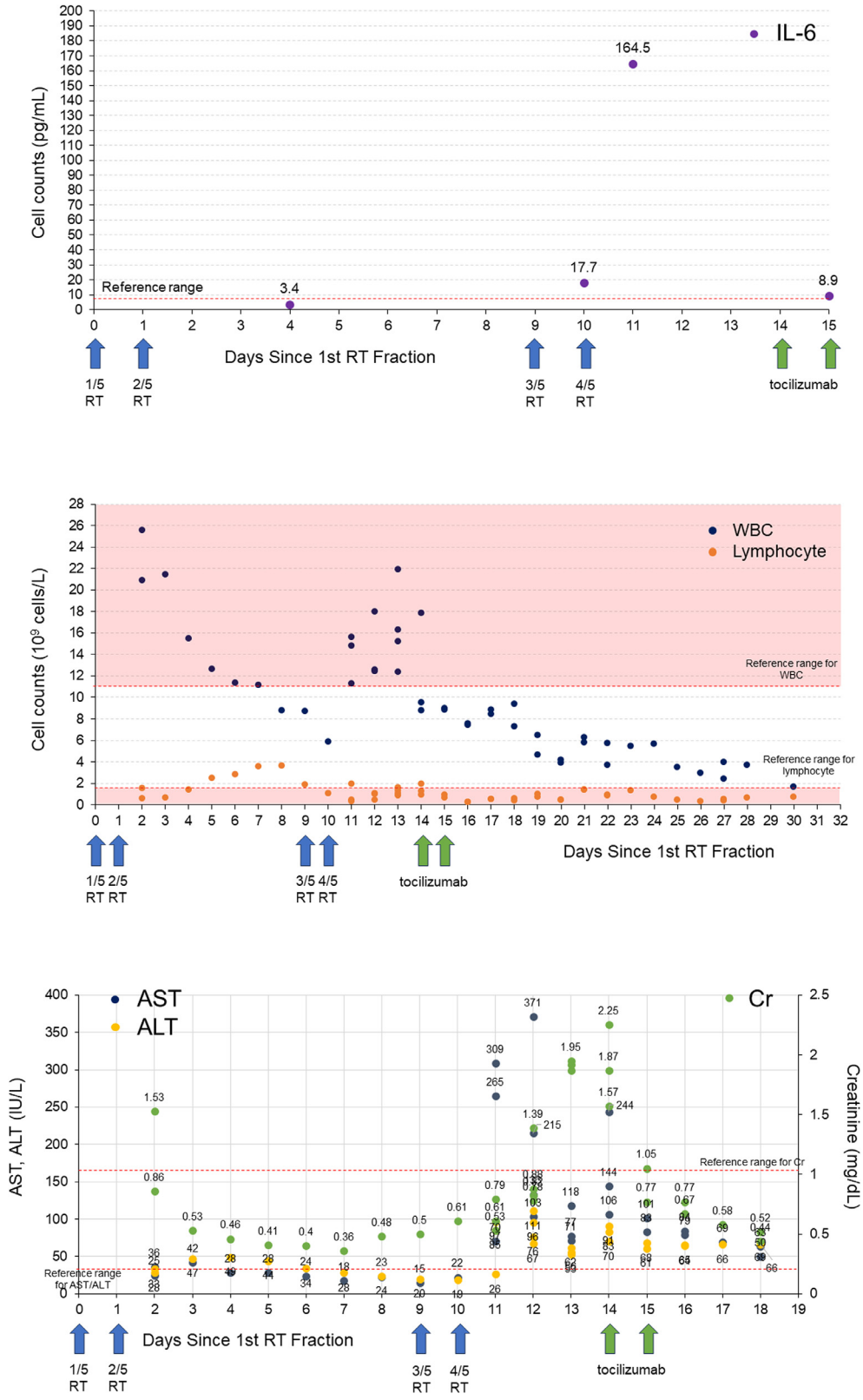

Figure 3 Absolute numbers of (A) interleukin-6 (IL-6) (B) white blood cells and lymphocytes, as well as the levels of (C) aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine, before and after radiotherapy and tocilizumab administration. Green arrows indicate tocilizumab administration, and blue arrows represent each fraction of RT. The x-axis represents days since the first fraction of RT. Red dotted lines indicate the reference ranges for each test.

syndrome, progression of the underlying malignancy, thromboembolism, and drug allergy.[5] Although these conditions have distinct causes, kinetics, and clinical features that can help distinguish them from CRS, they may also coexist with CRS. However, our practice was not aware of potential relationships of RT and CRS during the treatment, and this led to suboptimal decision-making to continue the third and fourth fractions of RT. If we had held the treatment after the patient's first recovery after the second fraction of RT, this may have been milder. To the best of our knowledge, there is 1 case of RT-induced grade 3 CRS with dose of 24 Gy in 3 fractions in a 65-year-old male patient with Merkel cell carcinoma and untreated chronic lymphocytic leukemia.[7] Before RT, the patient received 6 cycles of carboplatin and etoposide, alongside concurrent anti-PD1 immunotherapy. He experienced a precipitous lymphodepletion by the first day of RT. CRS symptoms occurred immediately after every RT fraction in a once-weekly schedule, accompanied by elevated levels of tumor necrosis factor α and IL-6. The patient was repeatedly admitted to the hospital after the first and second fractions of RT for supportive care for less than 24 hours, without a specific diagnosis explaining the condition. However, again, 1 hour after his last fraction, he experienced similar symptoms but was discharged 6 hours later in good condition. If RT was given with daily fractions, this may have been more fatal.

In CRS, IL-6 is well-known for playing a central role among a variety of cytokines released from T cells, B cells, natural killer cells, macrophages, and endothelial cells so that monitoring IL-6 levels is important for the monitoring of CRS.[10] A previous study reported that IL-6 overexpression, potentially affected by functional genetic variations in the IL-6 gene, is recognized as a key component in the development of CRS.[12] To counteract the immune response, a monoclonal antibody targeting the IL-6 receptor, tocilizumab, has been approved for the treatment of CRS.[13] Our patient benefited from this drug after multiple discussions at the multidisciplinary tumor board.

Notably, in our patient, CRS did not recur after multiple sessions of brain SRS, which can potentially be explained by 3 hypotheses. The first hypothesis concerns different RT treatment sites. McGee et al found that although stereotactic ablative RT to parenchymal sites induces a decrease in total and cytotoxic NK cells, an increase in TIM3+ NK cells, and an increase in activated memory CD4+ and CD8+ T cells, stereotactic ablative RT to nonparenchymal sites, such as the brain, does not induce these changes.[14] Building on this understanding, a recent study suggests that brain metastatic tumors are more immunosuppressed than primary lung tumors.[15] This is characterized by reduced TILs, a higher fraction of neutrophil infiltration, decreased scores of immune-related signatures, and a lower proportion of tumor microenvironment immune type I (high PD-L1/high CD8A) tumors. Therefore, the threshold required to activate the immune system sufficiently for CRS to occur might be significantly higher in an immune-privileged site such as the brain compared with other sites. Second, given the significant amount of time that has elapsed since the patient last received immunotherapy, local radiation alone might be insufficient to trigger systemic inflammation cascades, akin to the rare incidence of the abscopal effect. Third, the absence of chemotherapy-induced lymphodepletion, which could be a preconditioning factor, before brain SRS, could be another reason why CRS did not manifest after the brain SRS sessions. However, further investigations are necessary to identify the risk factors of RT-induced CRS.

The fact that hypofractionated RT can induce severe immune-related adverse events also implies its potential to enhance the immune response against cancer. Preliminary studies have demonstrated a significant modification of both the tumor immune environment and the peripheral immune cell landscape after hypofractionated and stereotactic regimens.[16] This is exemplified by a recent randomized phase 2 trial, where the combination of stereotactic ablative RT with immunotherapy showed a notable improvement in event-free survival in early-stage non-small-cell lung cancer.[17] Exploring the combination of hypofractionated or stereotactic ablative RT with immunotherapy holds promise, crucial for revealing RT's immunomodulatory impacts and enhancing our grasp of its therapeutic possibilities. Simultaneously, it is essential to rigorously investigate the occurrence of severe and unexpected adverse events, regardless of their rarity, to ensure patient safety and optimize treatment outcomes. Our observation of a favorable response in the irradiated lesion and the development of new metastases after CRS is similar to the case reported in Barker et al's study.[7] However, given the refractory nature of the disease to previous treatments, the relatively long disease-controlled interval after CRS in our case was encouraging, an aspect not described in Barker et al's study.

Conclusion

CRS is a cluster of immune response symptoms that can be triggered by various factors, such as infections and certain drugs, but it can also occur after just a few fractions of hypofractionated RT in the context of close chemotherapy and immunotherapy administration. This case report details an instance of grade 4 CRS in a patient with metastatic triple-negative breast cancer, occurring after receiving 24 Gy in 4 fractions out of a planned 30 Gy in 5 fractions of RT, with the initial CRS episode manifesting after just 12 Gy in 2 fractions. In the era of immunotherapy, clinicians are encouraged to recognize CRS, carefully monitor irAEs even after each fraction of RT, and be

mindful of RT's potential immunomodulatory effects, which can lead to potentially life-threatening CRS.

Disclosures

The 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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Supplementary materials

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