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【 CASE REPORT 】

Pembrolizumab-related Immune Thrombocytopenia in a Patient with Lung Adenocarcinoma Treated by Radiotherapy: Potential Immune-related Adverse Event Elicited by Radiation Therapy

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Abstract:

The effect of radiotherapy during immunotherapy on immune-related adverse events (irAEs) is not fully understood. We herein report a 74-year-old woman diagnosed with lung adenocarcinoma with programmed death ligand 1 expression ≥50% and treated with pembrolizumab. She developed fatal immune thrombocytopenia associated with pembrolizumab immediately following radiotherapy. A flow cytometry analysis of peripheral blood detected an increased expression of programmed death-1 (PD-1) and Ki-67 in $CD4^+$ and $CD8^+$ T cells after radiotherapy, compared with pre-irradiation measurements. This case suggests that radiotherapy may evoke irAEs during treatment with anti-PD-1 antibodies, which physicians should consider when using radiotherapy in patients treated with these drugs.

Key words: non-small-cell lung cancer, immunotherapy, PD-1, stereotactic radiotherapy, immune-related adverse effects

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Introduction

Immune checkpoint inhibitors (ICIs) inhibit the programmed death-1/programmed death ligand 1 (PD-1/PD-L1) pathway, demonstrate survival benefits for patients with non-small cell lung cancer (NSCLC), and are widely used in clinical practice (1). Pembrolizumab, an anti-PD-1 antibody, has shown survival benefits in treatment-naïve and pretreated NSCLC with a positive PD-L1 expression (1). However, ICIs cause immune-related adverse events (irAEs) affecting various organ systems, including the digestive tract, endocrine system, skin, liver, and lungs (2).

Radiotherapy is widely used to provide palliative relief of cancer-related symptoms associated with metastatic lesions (3). Radiation causes the release of tumor antigens by damaging cancer cells and enhancing the antigen-specific immune response (4). Recently, a combination of radiotherapy and ICIs was reported to have a synergistic effect on the antitumor immune response (4). However, the effect of radiotherapy during immunotherapy on irAEs is not fully understood.

We herein report a patient with lung adenocarcinoma who developed fatal pembrolizumab-related immune thrombocytopenia immediately following radiotherapy.

Case Report

A 74-year-old woman was diagnosed with pathological T 3N2M0 stage IIIA lung adenocarcinoma and underwent right upper lobectomy and mediastinal lymph node dissection in August 2016. She chose not to receive adjuvant che-

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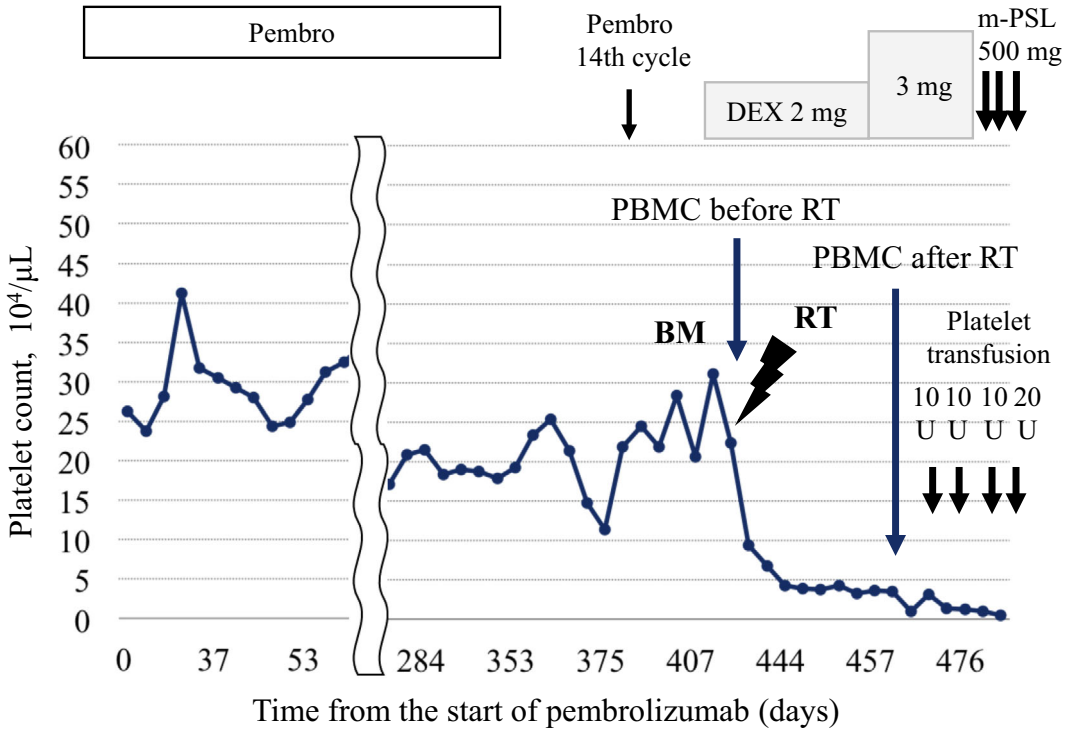

Figure 1. **Clinical course of the presented case. Pembro: pembrolizumab, BM: brain metastasis, RT: radiotherapy, DEX: dexamethasone, m-PSL: methylprednisolone, PBMC: peripheral blood mononuclear cells, U: units**

motherapy due to hypertrophic cardiomyopathy with an implanted cardioverter-defibrillator.

At seven months after surgical resection, computed tomography (CT) revealed an enlarged mediastinal lymph node and left pleural effusion with adenocarcinoma detected by thoracentesis. Since the primary tumor exhibited EGFR exon 20 insertion and a PD-L1 tumor proportion score of 90%, the patient was treated with pembrolizumab at 200 mg every 3 weeks, in addition to talc pleurodesis followed by drainage for management of the malignant pleural effusion.

CT performed after five cycles of pembrolizumab showed shrinkage of the mediastinal lymph node metastases, interpreted as a partial response. After the 13th cycle, the patient developed pericardial effusion with cardiac tamponade, and pericardiocentesis was successfully performed. Pembrolizumab treatment could be continued without any irAEs up to the 14th cycle for disease control, despite the presence of malignant pericarditis.

The patient became aware of increasing anorexia. Enhanced CT identified a solitary brain metastasis (3 cm in diameter) surrounded by edema in the right parietal lobe. The patient was prescribed oral dexamethasone 2 mg (prednisolone 0.5 mg/kg) and received stereotactic radiotherapy (33 Gy in 2 fractions) to this lesion. Eight days after intracranial radiotherapy, the platelet count rapidly decreased to 67,000/mm^3 (Fig. 1). The count continued to progressively decrease, after which the patient was admitted to our hospital with petechial rashes on the upper limbs and left lower limb 69 days after the last pembrolizumab cycle.

On admission, her platelet count was 10,000/mm^3 [Grade 4 on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0]. Positive antinuclear antibody test findings were determined by the chemiluminescent enzyme immunoassay (95.3 index, normal: <10 index) before the start of pembrolizumab treatment, but no symptoms associated with autoimmune activity were observed. Furthermore, she exhibited no signs of infection, nor was she receiving any medication associated with thrombocytopenia. A blood analysis revealed an elevated platelet-associated immunoglobulin G titer (PA-IgG; 56 ng/10^7 cells, normal: <46 ng/10^7 cells) and the absence of leukoerythroblastosis or disseminated intravascular coagulation. Bone marrow aspirate exhibited slight hypercellular age with normal trilineage hematopoiesis, a slight increase in megakaryocytes, poor platelet attachment to the megakaryocytes, and no findings suggestive of hematopoietic disorders. Based on these findings, the patient was diagnosed with severe immune thrombocytopenia associated with pembrolizumab.

After admission, the oral dexamethasone dose was increased to 3 mg/day (prednisolone 0.75 mg/kg), and platelet transfusion was performed. The platelet count did not increase, and corticosteroid pulse therapy (intravenous methylprednisolone 500 mg/day for 3 days) was subsequently started. However, the patient unfortunately developed alveolar hemorrhaging due to thrombocytopenia and died.

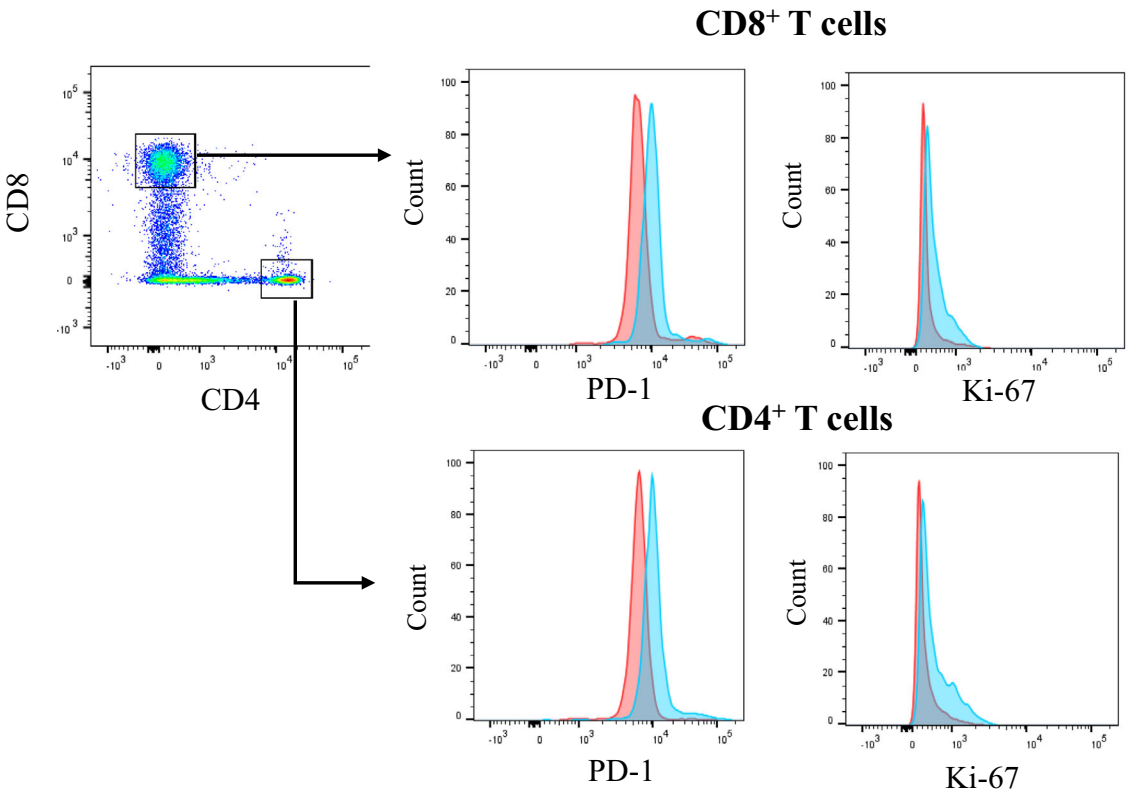

Figure 2. **A flow cytometry analysis of peripheral blood at 421 days (before radiotherapy) and 457 days (after radiotherapy) after the initiation of pembrolizumab treatment. The expression of PD-1 and Ki-67 in CD8$^+$ and CD4$^+$ T cells increased after radiotherapy. Red line: before radiotherapy, blue line: after radiotherapy.**

Discussion

Immune thrombocytopenia induced by ICIs is a rare and potentially life-threatening irAE. A 26-study meta-analysis showed that the incidence of all-grade anti-PD-1 antibody-related thrombocytopenia was only 2% (5). An observational study evaluating hematotoxicity of anti-PD-1/PD-L1 antibodies showed that the mean time from the initiation of immune therapy to the onset of grade ≥2 immune thrombocytopenia was 10.1 weeks. Severe adverse events were often observed, with 8 of 9 patients (89%) developing immune thrombocytopenia of grade ≥2 (6). Our patient developed severe immune thrombocytopenia more than 52 weeks following the initial pembrolizumab administration and experienced fatal alveolar hemorrhaging. Since anti-PD-1/PD-L1 antibody-related thrombocytopenia is often a life-threatening complication, regular monitoring of the platelet count is necessary during treatment.

The American Society of Clinical Oncology guidelines for the management of immune thrombocytopenia induced by ICIs recommend careful monitoring and continuation of ICI in case of grade 1 adverse events, discontinuation and administration of prednisolone (0.5-2.0 mg/kg/day) or intravenous immunoglobulin therapy (IVIG) in case of grade 2 adverse events, and withdrawal and administration of high-dose prednisolone (1-2 mg/kg/day) and IVIG in case of grade 3 or 4 adverse events (7). Furthermore, as in our case, patients with persistent thrombocytopenia despite high doses of steroids and IVIG are recommended to undergo additional treatments, such as splenectomy, rituximab, thrombopoietin receptor agonists, and immunosuppressants (7). In fact, successful treatment with romiplostim has been reported for steroid-resistant severe immune thrombocytopenia induced by anti-PD-1 antibody (8).

The mechanism underlying the association between radiotherapy during pembrolizumab treatment and the occurrence of immune thrombocytopenia remains unknown. In addition to its antitumor effects, radiotherapy can activate the host immune system (9). We performed a flow cytometry analysis of our patient's peripheral blood and found an upregulation of the expression of PD-1 and Ki-67 in both CD4$^+$ and CD8$^+$ T cells after radiotherapy compared with pre-treatment measurements (Fig. 2). Nie et al. reported that an aberrant PD-1/PD-L-negative co-stimulatory pathway potentially plays an important role in the pathogenesis of immune thrombocytopenia (10). Furthermore, Kim et al. showed that a higher percentage of Ki-67$^+$ among PD-1$^+$CD8$^+$ T cells after ICI treatment in NSCLC patients was significantly associated with the development of severe irAEs (11). Thus, changes induced in the immune system by radiotherapy and the blockade of the PD-1/PD-L1 pathway may have led to the development of pembrolizumab-induced immune thrombocytopenia in the present case. We propose that local radio-

therapy may affect the host's immune system and elicit irAEs in patients treated with anti-PD-1/PD-L1 antibody.

Conclusion

We herein report a patient with adenocarcinoma who developed fatal pembrolizumab-related immune thrombocytopenia immediately following radiotherapy. Considering the possibility of evoking irAEs by irradiation, physicians should keep in mind the potential occurrence of irAEs when using radiotherapy for patients treated with ICIs.

The authors state that they have no Conflict of Interest (COI).

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