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Case Report

Lung Adenocarcinoma Size Decrease after SARS-CoV-2 Vaccination during Long-Term Pembrolizumab Treatment: A Case Report

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Keywords
Immune checkpoint inhibitors · Lung neoplasms · Immunotherapy · Vaccination

Abstract
A man in his late 40s was diagnosed with clinical stage 4B lung adenocarcinoma with a PD-L1 tumor proportion score of 100% and high tumor mutational burden. A partial response was achieved after administration of pembrolizumab. The patient received two doses of a SARS-CoV-2 vaccine (BNT162b2) after 59 courses, and a chest computed tomography revealed consolidation in the peri-tumoral area, which subsequently disappeared, and the tumor continued to shrink in the next 4 months. This case provides indirect evidence for the persistence of cancer immunity during long-term treatment with immune checkpoint inhibitors and the potential for further activation.

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Introduction

In the context of the ongoing COVID-19 pandemic, mRNA vaccines have been administered worldwide as a means of mitigating SARS-CoV-2 infection and severe COVID-19 by eliciting an immune response [1]. Although these vaccines are reported to be safe for use in patients with cancer during treatment with immune checkpoint inhibitors (ICIs) [2] and are not expected to have much effect on disease status, accumulation of reports of rare events,

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responses, and data may be useful. We present a case of lung adenocarcinoma that decreased in size after a SARS-CoV-2 vaccination during prolonged administration of pembrolizumab. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533705).

Case Report

A man in his late 40s presented with bloody sputum and abnormal shadows in his right lung. The patient underwent computed tomography (CT)-guided biopsy and was diagnosed with clinical T3N0M1c (metastases in the mesenteric lymph nodes and small intestine) stage 4B right upper lobe lung adenocarcinoma and a PD-L1 tumor proportion score of 100% (Fig. 1a). Todai OncoPanel, which consists of DNA and RNA hybridization capture-based next-generation sequencing panels [3, 4], detected a tumor mutational burden of 13.4 muts/Mb and amplification of the *MET* gene. The patient had a 25-pack-year smoking history (from age 20–45 years) without other notable medical histories, medications, or allergies. Pembrolizumab monotherapy 200 mg every 3 weeks was initiated as the primary treatment, which achieved a partial response. After 35 treatment courses over approximately 2 years, the patient wished to continue treatment with pembrolizumab. CT showed that the tumor maintained a partial response between courses 8 and 59 (Fig. 1b). After 54 courses of treatment, the pembrolizumab dose was changed to 400 mg every 6 weeks. 5 courses and 30 weeks later, for a total of 59 treatment courses over approximately 4 years, the patient received two SARS-CoV-2 vaccine (BNT162b2) doses, and although he experienced mild fatigue, he had no fever or other respiratory symptoms such as cough or sputum. On routine follow-up CT performed several weeks after the second dose, no significant changes in the primary lesion were seen, but adjacent fluid retention and consolidation were observed (Fig. 1c). Blood tests showed a white blood cell count of 5,700/μL, and C-reactive protein was less than 0.02 mg/dL. Pembrolizumab treatment was continued, and CT images 6 weeks later showed a reduction in the fluid retention and consolidation. The primary lesion size (Fig. 1d), continued to decrease up to course 65 and then stabilized again. The patient received a third SARS-CoV-2 vaccine dose without notable changes on CT.

Discussion

We hypothesized that the vaccination had an effect on these changes on CT. The change in the pembrolizumab treatment schedule was likely inconsequential because 30 weeks passed between the modification and the emergence of changes on CT. Infection and interstitial lung disease were considered unlikely because there were no symptoms such as fever, cough, or sputum, and blood tests did not show an increased inflammatory response. The primary tumor was stable for 4 years until it showed a rapid change in a few weeks, which we considered atypical for cancer progression.

The SARS-CoV-2 vaccine has been found to elicit a robust immunological response, inducing $CD4^+$ and $CD8^+$ T-cell responses [5]. There has been one report of cytokine release syndrome in a patient with colorectal cancer after BNT162b2 vaccination during ICI treatment [6], which was thought to have been triggered possibly by the vaccine against a patient background of immune activation secondary to PD-1 blockade that resulted in T-cell proliferation and increased effector function. However, subsequent studies have revealed no significant increase in the incidence of immune-related adverse events among patients who

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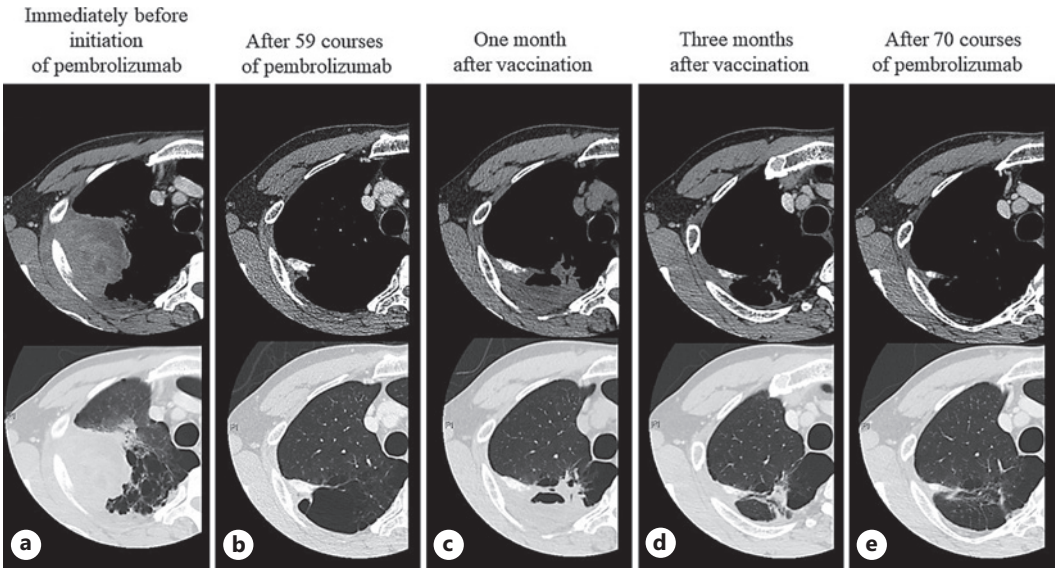

Fig. 1. An overview of the primary lesion in the upper lobe of the right lung at different time points before and after SARS-CoV-2 vaccination (vaccine BNT162b2). **a** Computed tomography (CT) images prior to the initiation of pembrolizumab treatment showing a 7.7-cm large mass with chest wall infiltration in the upper lobe of the right lung. **b** CT images after 59 courses of pembrolizumab treatment showing, that the primary lesion is approximately 3 cm long with calcification. **c** CT images weeks after vaccination showing no significant changes in the primary lesion, whereas fluid retention and consolidation can be seen adjacent to it. **d** CT images 3 months after vaccination, showing that the fluid retention and consolidation seen in **c** have improved, and the primary lesion is smaller than before vaccination. **e** CT images at the time of course 70 showing further reduction of the primary lesion.

received mRNA vaccines during ICI treatment [2]. The incidence of adverse events related to the vaccine was also reportedly not significantly different in patients with or without ICI administration except for rash [2]. Thus, it is believed that mRNA vaccines can be used safely and not significantly affect the course of cancer treatment in patients receiving ICIs.

However, one case report described spontaneous regression of a lung tumor that had metastasized from a salivary gland myoepithelial carcinoma after mRNA-1273 vaccination [7]. Histological and immunophenotypic analysis of the post-vaccination lung biopsy specimens showed immune cell infiltration, including $CD4^+$ T cells, $CD8^+$ T cells, natural killer cells, B cells, and dendritic cells, which contrasted with the low levels of these cells in the pre-vaccination primary tumor and lung metastasis samples. CT images obtained 9 months after the vaccination revealed persistent tumor shrinkage. To our knowledge, this is the only case report that described the effect of a SARS-CoV-2 vaccine on cancer immunity; the effect of other vaccines for infectious diseases, such as the influenza vaccine, has not been reported. Similar to this case, our case showed a decrease in the primary lesion size after SARS-CoV-2 vaccination. We speculate that this decrease was related to the PD-L1 tumor proportion score of 100% and high tumor mutational burden. A higher tumor mutational burden generally indicates a higher neoantigen load, thus increasing the probability that antigens that can stimulate an immune response will be expressed on the tumor cell surface and be recognized by T cells [8]. Therefore, the tumor in this case may have been susceptible to the immune response induced by the mRNA vaccine. This case provides indirect evidence that cancer immunity is continuously active even after long-term ICI treatment and may be further activated.

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The KEYNOTE-024 trial was an open-label randomized controlled trial that compared pembrolizumab for up to 35 courses with platinum-based chemotherapy in patients with previously untreated non-small cell lung cancer, a PD-L1 tumor proportion score of ≥50%, and no sensitizing epidermal growth factor receptor or anaplastic lymphoma kinase alterations. Progression-free survival in the pembrolizumab treatment arm continued to decline in the 5-year updated analysis, raising questions about the validity of discontinuing pembrolizumab after 35 courses [9]. Additionally, many patients who received a second course of pembrolizumab treatment after progressive disease following completion of the first 35 courses of pembrolizumab did not respond to pembrolizumab (partial response, 4/12 cases; stable disease, 6/12 cases) [9]. On the other hand, a retrospective, population-based cohort study showed no difference in overall survival between those who terminated pembrolizumab at 2 years and those who continued treatment beyond 2 years [10]. Researchers' current efforts are to reduce unit doses, achieve less-frequent schedules, and/or shorten treatment durations [11, 12].

We report a case of lung adenocarcinoma that decreased in size after SARS-CoV-2 vaccination during long-term ICI treatment. This report suggests that cancer immunity remains functional and can be further activated after long-term treatment with ICI.

Acknowledgment

We thank the members of our department for their valuable discussions.

Statement of Ethics

This study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine of the University of Tokyo (approval number: 2739). Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Koki Fujii: conceptualization, investigation, and writing – original draft preparation. Kensuke Fukuda: validation, investigation, and writing – review and editing. Masanori Kawakami, Akihisa Mitani, and Goh Tanaka: validation and writing – review and editing. Hidenori Kage: conceptualization, writing – review and editing, and supervision.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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