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Case Report

Sarcoid-Like Granulomatosis Induced by Nivolumab Treatment in a Lung Cancer Patient

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Keywords
Nivolumab · Sarcoid-like granulomatosis · Lung cancer · Pleomorphic carcinoma

Abstract
Nivolumab, an anti-PD-1 antibody, inhibits binding between PD-1 and PD-1 ligand and activates antigen-specific T cells that have become unresponsive to cancer cells. Although it is recommended as a second-line therapy in gene mutation-negative non-small-cell lung cancer, interstitial pneumonia is a well-known side effect of the drug; however, granulomatous lesions have rarely been reported. We describe the case of an 81-year-old male with cT1aN2M1b stage IV pleomorphic carcinoma of the left upper lobe of the lung. After primary treatment with carboplatin and paclitaxel, recurrence was observed in the left supraclavicular lymph node and left adrenal gland. We initiated the administration of nivolumab as a secondary treatment. Reduction was observed in the swelling of the left supraclavicular lymph node and left adrenal gland, but the tumor shadow in the right upper lobe appeared to increase. Bronchoscopy was performed, and the biopsy result showed granulomas; the findings resembled a sarcoid-like granulomatous reaction. The shadows eventually disappeared with nivolumab discontinuation; thus, we concluded that the sarcoid-like granulomatous reaction had resulted from nivolumab administration. Based on our observations, we suggest that when invasive shadows are observed after nivolumab administration, it is necessary to differentiate between disease progression and interstitial pneumonia. Moreover, the decision to reinitiate nivolumab treatment requires careful judgment in future instances of cancer recurrence.

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Introduction

Nivolumab is an anti-PD-1 monoclonal antibody. By inhibiting binding between PD-1 and PD-1 ligand, nivolumab activates antigen-specific T cells that have become unresponsive to cancer cells, thereby demonstrating an antitumor effect. It is recommended as second-line therapy in gene mutation-negative (e.g., EGFR, ALK, ROS-1) non-small-cell lung cancer. Although interstitial pneumonia is a known side effect of the drug, granulomatous lesions have rarely been reported.

Case Presentation and Results

An 81-year-old male was admitted to our hospital after a computed tomography (CT) scan had shown an increasing nodule (11 mm in diameter) in the upper left lobe of the lung. Video-assisted thoracic surgery biopsy was then performed for diagnostic purposes. Pathological analysis confirmed cT1aN2M1b stage IV pleomorphic carcinoma with bone metastasis. We initiated treatment with carboplatin and paclitaxel in January 2014 as first-line chemotherapy. Follow-up observation after 4 cycles of treatment indicated that partial response was achieved. However, in June 2016, a swelling of the left supraclavicular lymph node and left adrenal gland was observed (Fig. 1a). We suspected recurrence and initiated the administration of nivolumab as a second-line treatment. After 4 cycles, the swelling of the left supraclavicular lymph node and left adrenal gland were reduced, and partial response was obtained (Fig. 1b). However, a gradually increasing tumorous shadow comprising an uneven invasion shadow of solid marginal irregularity was observed in the upper right lobe. The patient's general condition did not change remarkably, thus nivolumab treatment was continued. However, after 10 cycles of treatment, shadow enlargement was observed (Fig. 2a, b). Bronchoscopy was performed to determine whether this shadow indicated recurrence or another condition, such as interstitial pneumonia. There was no increase in the serum carcinoembryonic antigen or KL-6 levels. Biopsy showed many epithelioid granulomas in the bronchial wall (Fig. 2d); histopathological staining with Periodic acid Schiff and Ziehl-Neelsen, as well as anti-BCG immunostaining were negative. Polymerase chain reaction of bronchial lavage fluid was negative for both Mycobacterium tuberculosis and *M. avium complex*. Further, no general bacteria, acid-fast bacteria, or fungi were detected in the culture. Taken together, these findings suggested a sarcoid-like granulomatous reaction. Nivolumab was discontinued, and after 6 months, the shadows disappeared (Fig. 2c). Thus, we determined that nivolumab treatment led to the development of granulomas. Following discontinuation of nivolumab, no recurrence of lung cancer has been observed for 1 year.

Discussion

Nivolumab is an anti-PD-1 monoclonal antibody that is currently approved for use as a secondary therapy for non-small cell lung cancer. Known adverse events include immune-related events and interstitial pneumonia of an organizing pneumonia pattern for lung field lesions. We used nivolumab as a second-line treatment for recurrent lung cancer and observed the development of granulomatous lesions. Sarcoidosis and sarcoid-like reactions have been reported when nivolumab is used alone or in combination with ipilimumab in the treatment of melanoma [1–4]. It has also been reported that sarcoidosis can develop following

pembrolizumab treatment in sarcoma [5]. For lung cancer, there have been reports of skin sarcoidosis during the treatment with nivolumab alone or in combination with ipilimumab [6, 7]. Moreover, granulomatous lesions have been observed in the mediastinal lymph node with the use of nivolumab alone [8]. However, the present case may be the first case to demonstrate granuloma development in the lung. Although the mechanism underlying the development of sarcoidosis and sarcoid-like reactions has not been clearly elucidated, the use of an immunity checkpoint inhibitor may inhibit PD-1 and enhance the proliferation of lymphocytes and the release of IFN-γ; this may be involved in the genesis of granulomas [1, 2]. Further, in sarcoidosis, PD-1 is upregulated, which has been suggested to be related to the occurrence of sarcoidosis; however, sarcoidosis occurs by blocking PD-1. Therefore, the upregulation of PD-1 may be a secondary change, and further study is necessary [7]. In this case, the granulomatous lesions were sporadic, and no other clinical features of sarcoidosis, such as mediastinal lymph node enlargement, were observed. There was no obvious exacerbation of the primary lesion, and the granuloma was reduced by the discontinuation of nivolumab. This was a strong indication that the granuloma was a side effect of nivolumab treatment. As improvement was observed by discontinuation of nivolumab alone, we did not administer steroid treatment [3]. Additionally, follow-up observation indicated that the primary lesion did not progress after the discontinuation of nivolumab. Based on the clinical course in this case study, we suggest that when invasive shadows are observed after the administration of nivolumab, it is necessary to differentiate between disease progression and interstitial pneumonia. Moreover, the decision to reinitiate nivolumab treatment requires careful judgment in future instances of cancer recurrence.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Hiroshi Yoshida and Satoshi Terashita performed bronchoscopy with Susumu Noguchi who is the guarantor of this article.

Takakazu Sugita was responsible for bronchoscopy and respiratory medicine, and issued the instruction for inspection.

The treatment policy of this case was confirmed by all authors, and all authors contributed to the preparation and review of this article.

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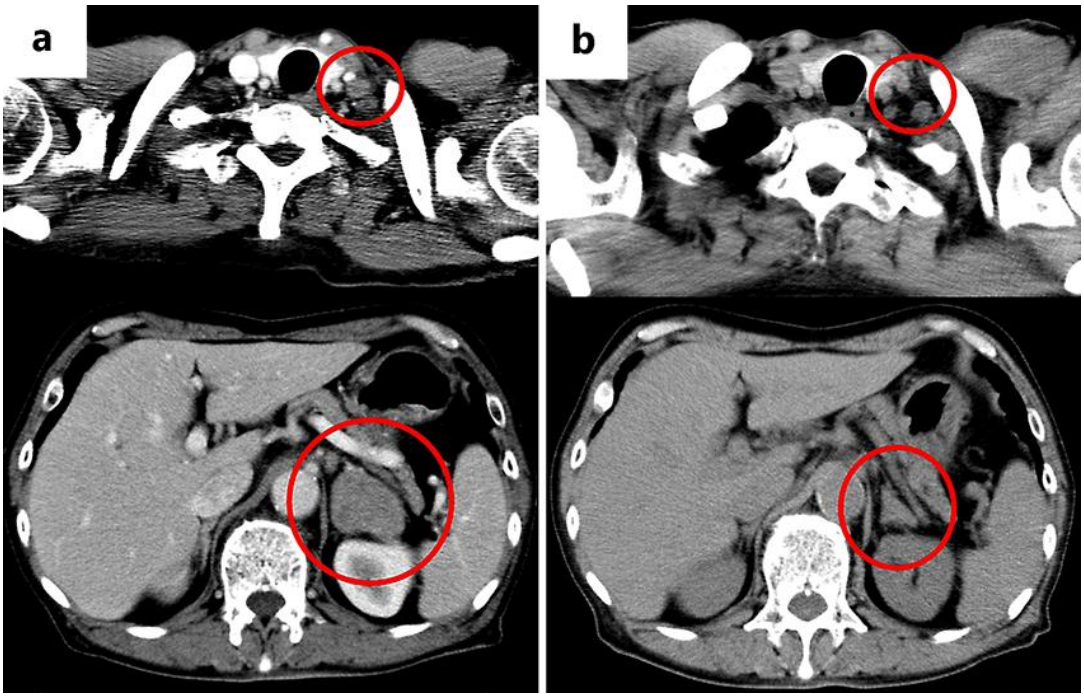

Fig. 1. The course of the target lesion. **a** Recurrent lesion before nivolumab administration. CT scan showing an enlarged left supraclavicular lymph node and left adrenal gland. **b** CT scan after 4 cycles of nivolumab treatment, revealing that the swelling of the left supraclavicular lymph node and left adrenal gland has reduced.

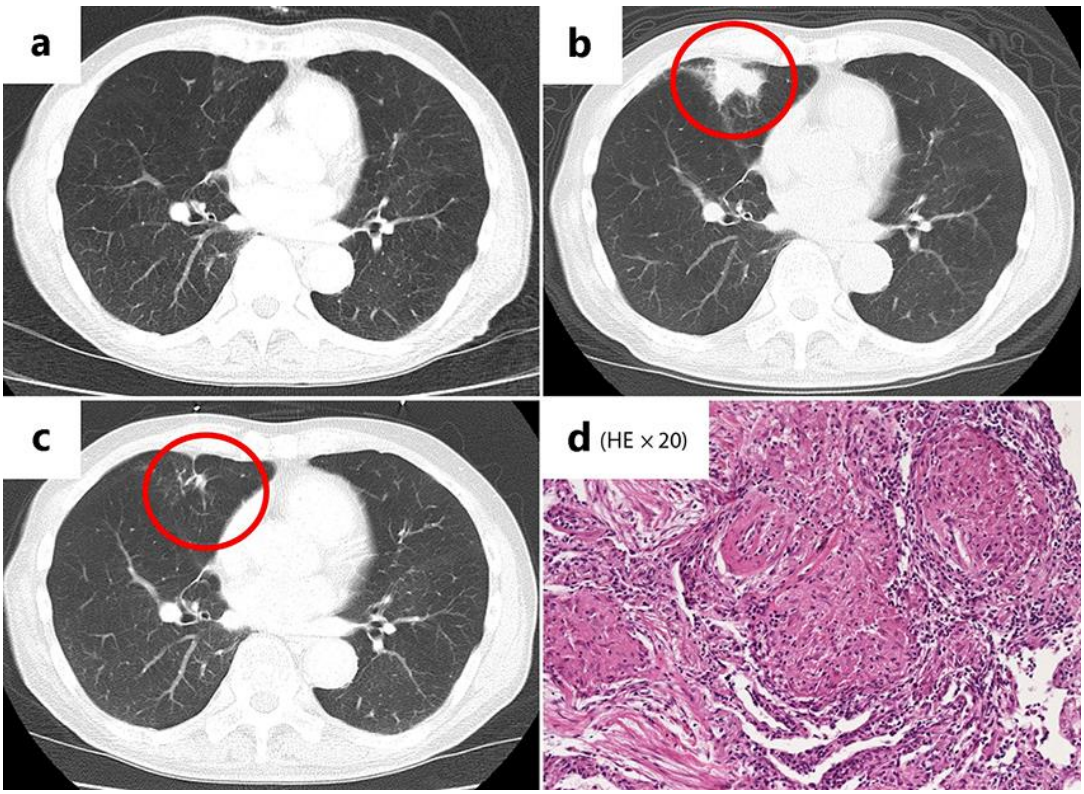

Fig. 2. The course and histological findings of granulomas. **a** CT scan of the recurrent lesion before nivolumab administration. **b** Six months after the start of treatment with nivolumab. CT scan showing shadows in the upper right lobe. **c** Six months after discontinuing nivolumab. The shadow in the upper right lobe has disappeared. **d** HE staining of the biopsy tissue from **b**. Many epithelioid granulomas were found in the bronchial wall.