CASE REPORT

Granuloma-forming interstitial pneumonia induced by nivolumab: a possible immune-related adverse event of the lung

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Abstract Nivolumab, a monoclonal antibody targeting the PD-1, has recently been used as a standard treatment for lung cancer, melanoma and renal cell carcinoma. We herein report the case of a patient undergoing treatment for non-small cell lung cancer (NSCLC) who developed interstitial pneumonia which featured nivolumab-induced granuloma formation. An 82-year-old male patient with NSCLC was initially treated with radiation therapy and chemotherapy. Five years later, however, he developed metastatic carcinoma in a hilar lymph node accompanied by ground glass opacity (GGO), suggesting tumor cell invasion. Treatment with nivolumab was initiated. At 21 days after the first dose of nivolumab, he complained of cough and dyspnea. Chest computed tomography scans demonstrated tumor progression and newly formed GGO in the area surrounding the primary tumor. Fibrosing active alveolitis with granuloma formation and organizing pneumonia findings were observed in the pathological examination of a transbronchial lung biopsy (TBLB) specimen. No malignant cells were found in TBLB. A bacteriological analysis of cultures, a PCR, and special staining did not reveal any infections. The patient's pneumonitis improved after treatment with systemic corticosteroids. Granuloma-forming interstitial pneumonia may be a feature of nivolumab-associated pneumonitis.

Keywords Nivolumab · Granuloma · Interstitial pneumonia · Immune checkpoint inhibitor · Drug-induced lung disease

Introduction

The immune checkpoint inhibitors have changed the therapeutic strategy for lung cancer. Nivolumab is a monoclonal antibody that targets the programmed death-1 (PD-1), cell death receptor on the surface of T lymphocytes, B lymphocytes, natural killer T cells, monocytes, and dendritic cells [1]. A phase III study in advanced non-squamous non-small cell lung carcinoma (NSCLC) patients showed that second-line nivolumab therapy extended the median overall survival (OS) from 9.4 to 12.2 months in comparison to patients who received docetaxel therapy [2]. Nivolumab also improved the survival in comparison to accepted chemotherapy for malignant melanoma and renal cell carcinoma [3, 4]. Consequently, nivolumab has recently been used as a standard treatment for NSCLC and melanoma.

The reported side effects of immune checkpoint inhibitors include conditions of excessive inflammation, such as dermatitis, colitis, hepatitis and pneumonitis. Pneumonitis, which represents a potentially life-threatening complication, was observed in 3–6% of the clinical trials involving NSCLC patients. The characteristics of pulmonary adverse events induced by immune checkpoint inhibitors are diverse and unclear [2, 5, 6]. We herein present the case of an NSCLC patient who developed granuloma-forming interstitial pneumonia, which was attributed to nivolumab therapy.

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Case report

The patient was an 82-year-old man who had been diagnosed with NSCLC five years previously. His NSCLC was initially treated with radiation therapy and chemotherapy with carboplatin and paclitaxel. He suffered from radiation pneumonitis at 2 months after primary therapy for the thoracic mass, which was successfully treated with steroids. Five years later, new progression was observed in a hilar lymph node on follow-up computed tomography (CT). Ground glass opacity (GGO) and consolidation mainly in the peripheral area of the lymph node, suggesting tumor cell invasion, were also found. Treatment with nivolumab was initiated at a dose of 3 mg/m² every two weeks (Fig. 1a, b).

Twenty-one days after the initiation of nivolumab therapy, he was admitted to our hospital with cough and dyspnea. The laboratory data obtained on admission showed the elevation of the patient's KL-6 (793.3 U/ml) and SP-D (244.1 ng/ml) levels. The serum KL-6 levels were higher than they had been before the initiation of nivolumab (595.7 U/ml). Chest CT scan showed the worsening of pre-existing GGO in the right lower lobe and a slight increase in the size of the primary tumor (Fig. 1d). Newly formed GGOs were also observed in both the right upper lobe and the left lung (Fig. 1c). These findings were mainly localized around the primary tumor. We, therefore, suspected that an immune-related adverse event had been induced by nivolumab. Accordingly, we conducted transbronchial

lung biopsy (TBLB) to rule out other etiologies, such as an exacerbation of carcinomatous lymphangiosis or infectious diseases. The lung tissue specimen showed thickness of the alveolar walls with fibrous and lymphocytic infiltration changes and some organizing pneumonia (OP) findings (Fig. 2). Moreover, granuloma formation was observed in the air spaces of the alveoli in a TBLB specimen from the new GGO lesion. No acid-fast bacilli, fungi or malignant cells were found in the TBLB specimens. Bronchoalveolar lavage (BAL) from the right upper lobe showed 413,000 cells/ml with 2% macrophage, 69% lymphocytes (CD4/8 ratio, 1.7), 18% neutrophils and 11% eosinophils. No microorganisms were cultured, and PCR assays to detect *Mycobacterium tuberculosis* DNA and *Mycobacterium avium-intracellulare* DNA in the patient's BAL fluid were negative. The patient was started on intravenous methylprednisolone (1000 mg) for 3 days and treated continuously with oral prednisolone (1 mg/kg). His respiratory status improved over 2 weeks. Three months later, chest CT showed the significant improvement of the GGOs and the regression of the primary tumor after the tapering of prednisolone to 10 mg/body (Fig. 1e, f).

Discussion

Interstitial pneumonia is a potentially fatal complication of anticancer agents. In a phase I study of nivolumab, pneumonitis occurred in 3% of the patients, with 1% developing

Fig. 1 Chest CT scans before and after treatment with nivolumab. **a, b** A chest CT image showing a metastatic hilar lymph node accompanied with ground glass opacity (GGO) and consolidation in the peripheral area, suggesting tumor cell invasion, before the initiation of nivolumab treatment. **c, d** A CT scan demonstrating a slight

increase in the size of the primary tumor and the worsening of pre-existing GGO around the primary mass, on the 21st day of nivolumab therapy. **e, f** A CT scan revealing the significant improvement of the GGOs and regression of the primary tumor after corticosteroids therapy

Fig. 2 Granuloma-forming interstitial pneumonia with OP findings. **a** Interstitial lymphocytic inflammation and the fibrous thickening of the alveolar walls accompanied by organizing pneumonia (OP) find-

ing (*). **b, c** Intra-alveolar granulomas were focally observed (arrows) in Elastica Masson–Goldner (EMG) staining (**b**) and an enlarged view from the boxed areas of **b** (**c**) (Scale bars 50 μ m)

grade 3–4 pneumonitis [7]. Previous case reports have attributed the development of acute respiratory distress syndrome (ARDS), non-specific interstitial pneumonia (NSIP), and OP to nivolumab [8–10]. Recently, OP, GGO, and hypersensitivity pneumonitis (centrilobular nodules) have been demonstrated as the main characteristics of pneumonitis induced by PD-1/PD ligand 1(PD-L1) inhibitors [11, 12].

The immune-related response is the most distinctive feature of the lung side effects induced by immune checkpoint inhibitors. Some patients who receive immune checkpoint inhibitors experience an increase in tumor size, known as pseudoprogression, and develop new lesions around the primary tumor. In these cases of pseudoprogression, delayed tumor regression is also observed [13]. Although few studies have investigated the lung immune-related response pathologically, edema and infiltrates of immune cells containing activated cytotoxic T lymphocytes have been implicated in the mechanisms underlying the responses in the skin, colon and other organs [14, 15].

Our case showed interstitial pneumonitis as GGOs shortly after the initiation of nivolumab treatment for lung cancer. Chest imaging showed the transient progression of the tumor and a delayed clinical response findings consistent with an immune-related adverse events and pseudoprogression. A pathological examination for GGOs revealed granuloma formation in addition to fibrosing active alveolitis. A bacteriological analysis with cultures and PCR as well as special staining did not reveal any bacterial infection. An examination of the patient's BAL fluid showed an increase in the number of lymphocytes with a high level of CD4/CD8 ratio, suggesting CD4-positive T cell-associated granuloma formation. Some reports have implicated immune checkpoint inhibitors in the induction of sarcoid-like granulomas in the lung, lymph nodes and skin [15, 16]. However, the granulomas that formed in the airspace

of the alveoli in our case did not resemble the granulomas associated with sarcoidosis. Granulomatous inflammation may occasionally occur as a manifestation of a pulmonary drug reaction. The agents that have been shown to induce granulomatous interstitial pneumonia include methotrexate, nitrofurantoin, BCG, fluoxetine, procarbazine, acetylsalicylic acid, sulfasalazine, statins, interferons, sirolimus, cromolyn sodium, cocaine, and everolimus [17, 18]. In drug-related pneumonitis, granulomas are seen within the airspaces and tend to be loosely formed and non-necrotizing [17].

We initially believed that the GGO and consolidation before nivolumab administration had been induced by tumor cell invasion, because they were accompanied by primary tumor growth. However, given that no cancer cells were detected by a TBLB, we could not confirm that the GGO had indeed been induced by carcinoma. This might be explained by the following two points: regression of cancer after nivolumab therapy, or a false-negative result for the TBLB, with the small tissue obtained from the peripheral region actually containing cancer cells. One possible differential diagnosis was radiation-induced pulmonary fibrosis. However, given that radiation fibrosis occurs typically between 6 and 12 months and up to 2 years after the completion of radiotherapy, this hypothesis is unlikely to hold. Drug-induced interstitial lung disease can cause GGO, as in the present case; however, the patient had not taken any new medications before nivolumab therapy. Cultures and a PCR analysis of a bronchoscope specimen did not reveal any infections. We, therefore, concluded that the GGO and consolidation on CT before nivolumab was highly likely tumor cell invasion, and the new GGO that developed after the initiation of nivolumab treatment was likely an immune-related response.

We reported a case of granuloma-forming interstitial pneumonia in a patient who was undergoing treatment with immune checkpoint inhibitors. GGOs, which were

consistent with interstitial pneumonia, were predominantly seen around the primary tumor, implicating the recruitment of inflammatory cells into the tumor vicinity. Nivolumab increases anticancer immunity and may be related to macrophages recruitment, alveolitis, and granuloma development in the neighborhood of the tumor.

The disruption of T cell homeostasis is suspected to be associated with the pathogenesis of granuloma formation [16]. On the other hand, in granulomatous diseases such as sarcoidosis or chronic beryllium disease, the upregulation of the PD-1 pathway in T cells has been reported [19, 20]. Recently, Naidoo et al. observed poorly formed granulomas in a lung biopsy specimen from 3 of 11 (27%) patients with pneumonitis induced by PD-1/PD-L1 inhibitors treatment [11]. Furthermore, at ASCO 2016, Gettinger et al. reported (not published) that 9 of 20 (45%) pneumonitis patients with PD-1 inhibitors treatment had granuloma [12]. Thus, an imbalance of cytokines and T cell homeostasis in association with the PD-1 pathway might be associated with the pulmonary reaction that occurred in patients receiving nivolumab therapy. The adverse lung events induced by immune checkpoint inhibitors are diverse and complicated. Further investigation will be required to elucidate their mechanisms.

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