**Nivolumab-Induced Interstitial Lung Disease in a Patient with Gastric Cancer**

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**1. Abstract**

We herein report a case of nivolumab-induced interstitial lung disease in a patient with gastric cancer. Nivolumab is a fully human IgG4 monoclonal antibody inhibitor of programmed death-1 (PD-1). A 69-year-old woman with recurrent gastric cancer being treated with nivolumab as fifth-line therapy developed interstitial pneumonia associated with decreasing oxygen saturation 27 months after starting treatment with nivolumab. Chest computed tomography demonstrated a cryptogenic organizing pneumonia pattern in both lung lobes. A diagnosis of interstitial lung disease was made by the analysis of the bronchoalveolar lavage fluid. This was believed to be a drug-induced disease, but stopping the administration of nivolumab alone failed to resolve the presence of a lung shadow. Treatment with steroid pulse therapy twice and subsequently with prednisolone 1.0 mg/kg daily gradually improved the pulmonary function. The administration of high-dose corticosteroid is therefore recommended after the diagnosis of immune-related adverse events in nivolumab treatment. Since recovering from pulmonary dysfunction, the patient remains alive with no disease progression. To our knowledge, this is the first report of nivolumab-induced interstitial lung disease treated with high-dose corticosteroid in a patient with advanced gastric cancer. The immediate diagnosis and treatment of immune-related adverse events are crucial for achieving a good outcome.

**2. Key Words:** Interstitial lung disease (ILD); Nivolumab; PD-1; Recurrent gastric cancer; Immune-related adverse events (irAEs)

**3. Introduction**

Immune checkpoint inhibitors enhance antitumor T-cell activity through the inhibition of immune checkpoints, such as the programmed death-1 (PD-1) receptor. Nivolumab is a fully humanized monoclonal antibody that blocks the engagement of programmed cell death-1 (PD-1) by its ligand PD-L1 and has shown clinical efficacy in patients with various types of cancer [1]. It was recently shown to confer a survival benefit compared with best supportive care in patients with gastric cancer who had become unresponsive to or intolerant of at least two previous chemotherapy regimens [2]. Discontinuation of nivolumab treatment and appropriate symptomatic treatment are necessary when specific immune-related adverse events (irAEs) developed due to abnormal activation of the immune system.

We herein report a case of nivolumab-induced interstitial lung disease and its resolution by steroid therapy in a patient with gastric cancer.

**4. Case Report**

A 69-year-old Japanese woman with recurrent gastric cancer, liver and lymph node metastases started nivolumab monotherapy (3 mg/kg, every 2 weeks) as fifth line treatment. Four years before starting nivolumab treatment, she had undergone distal gastrectomy with D2 resection and received chemotherapy with S-1 plus cisplatin in the first line for gastric cancer with liver and lymph node metastases for nine months. The liver metastases almost disappeared, but the para-aortic lymph node metastases showed progressive disease (PD). She then received ramucirumab...
after administration of PSL, she required oxygen inhalation therapy, and the serum KL-6 level increased to 2163 U/ml. Chest CT after two weeks of therapy displayed fibrous lesions and changed to a non-specific interstitial pneumonia (NSIP) pattern.

She therefore received pulsed high-dose methylprednisolone (mPSL) at 1000 mg daily for three days following PSL dose was tapered to 0.5 mg/kg (20 mg/body) daily for seven days, according to the respiratory status. The lung shadow was not ameliorated, and she still needed oxygen inhalation therapy. She was therefore treated with mPSL at 1000 mg daily for three days again, and the PSL dose was tapered to 1.0 mg/kg (40 mg/body) daily for seven days. This treatment was effective, and the hypoxemia improved slowly, so her PSL dose was reduced to 5 mg every week. The serum KL-6 level had decreased to 255 U/ml at eight months after the onset, but there after the pulmonary disorder was resolved. However, a scan of the chest showed residual GGOs, so nivolumab was no longer administered to the patient. The dose of PSL has been slowly tapered to 7.5 mg/body daily, and she remains alive with no disease progression (Figure 3).

Figure 3: The clinical course of the case. When GGOs appeared in both lung lobes, during 57 cycles of nivolumab treatment, nivolumab was discontinued for four weeks. Because the serum KL-6 had continued to increase, treatment with prednisolone (PSL) was started after bronchoscopy. (a) The transition of the PSL dose. Treatment with PSL at 0.5 mg/kg (20 mg/body) was started, and there after steroid pulse therapy twice and subsequently with prednisolone 1.0 mg/kg (40 mg/body) daily led to an improvement in the pulmonary function. (b) The transition of the serum KL-6. (c) Chest CT. The lung shadow gradually improved over the following 12 months.

5. Discussion

Immune checkpoint inhibitors are associated with unique adverse events known as irAEs [3,4]. ILD is considered as an irAE, and previous reports have revealed that the incidence of nivolumab-related death due to ILD is higher in patients with non-small cell lung cancer (NSCLC) than in patients with other cancers, such as melanoma. However, the risk factors for ILD in patients undergoing nivolumab treatment are unclear [5]. Generally, the risk factors for drug-induced ILD are thought to be advanced age (≥60 years of age), a smoking history, existing pulmonary lesions (especially for ILD), a history of pulmonary surgery, decreased respiratory function, oxygen inhalation, a history of radiotherapy, and existing renal impairment [6]. Because of the limited sample

plus paclitaxel in the second line, irinotecan monotherapy in the third line and paclitaxel monotherapy in the fourth line for the para-aortic lymph node metastases.

She showed stable disease (SD) without irAEs during 57 cycles of nivolumab treatment, but on follow-up computed tomography (CT), she suddenly showed ground glass opacities (GGOs) and small coin lesions in both lung lobes at 27 months after treatment with nivolumab had started.

She was a never-smoker and had no history of pulmonary disease. Although she had no respiratory symptoms, chest CT demonstrated a cryptogenic organizing pneumonia (COP) pattern in both lung lobes (Figure 1). Laboratory data and sputum cultures provided no evidence of infection. The serum KL-6 (stialulated carbohydrate antigen KL-6) had increased to 404 U/ml. She underwent a lung biopsy by bronchoscopy, which showed no signs of infection or inflammatory cells, including lymphocytes, or neutrophil infiltration. The bronchoalveolar lavage fluid (BALF) showed dominant lymphocytes (Figure 2). She was diagnosed with nivolumab-induced interstitial lung disease (ILD).

Figure 1: Follow-up chest X-ray (a) and computed tomography (b). Images were acquired after 57 cycles of nivolumab treatment. In both lung lobes, ground glass opacities and small coin lesions appeared.

Figure 2: The results of bronchoscopy. A diagnosis of interstitial lung disease (ILD) was made by bronchoalveolar lavage fluid (BALF) and a transbronchial lung biopsy (TBLB). In the BALF, there were no malignant cells, no underlying infection, and an increase in the numbers of lymphocytes. The CD4/CD8 ratio is typically low. In TBLB, (a) from the bronchus and (b) from the alveolus, there was diffuse damage of alveolar and interstitial lesions. To diagnose ILD, it is important to rule out infections and neoplastic lesions.

Although nivolumab was discontinued for four weeks, the blood oxygenation level was slightly lower than usual, and she did not complain of a cough, sputum or fever. On chest CT, the lung shadow was worsened compared to baseline, and the serum KL-6 had increased to 1608 U/ml. She was admitted to the hospital and treated with prednisolone (PSL) at 0.5 mg/kg (20 mg/body) daily by mouth. However, the blood oxygenation level was decreased...
size, the risk factors contributing to nivolumab-induced ILD could not be identified, but this case had no risk factors at all. According to the ATTRACTION-2 [2], the first randomized phase 3 trial in patients with advanced gastric or gastro-oesophageal junction cancer, ILD was reported in three patients (1%) in the nivolumab group. The present patient took part in this trial, and she was one of the three. It was described that, when these patients discontinued nivolumab treatment, they finally recovered from ILD. However, whether they needed treatment with corticosteroids was not mentioned. Treatment-related adverse events leading to death were reported in five patients (2%) receiving nivolumab, and death due to pneumonia was reported only one case. Whether the dead patient had ILD was not mentioned. Immune-related pneumonitis commonly occurs several months after anti PD-1 therapy. Some initial reports have said that drug-related grade 3 or 4 toxic effects occurred in 14% of patients who received anti–PD-1 antibody [7]. To our knowledge, there have been no reports of the treatment course of nivolumab-induced ILD in a patient with advanced gastric cancer.

Drug-induced lung injury is typically defined the diagnostic criteria [6]. The precise role of bronchoscopy and BAL in the management of pneumonitis as an irAE is currently unclear, but BAL and transbronchial lung biopsy (TBLB) may help identify an underlying pulmonary infection. A COP pattern of pneumonitis is characterized by the radiographic appearance of the lung abnormalities of pneumonitis [8]. The imaging characteristics of nivolumab-induced ILD can be broadly divided into two types: GGO mimicking hypersensitivity pneumonia but distinct from pneumocystis pneumonia, and consolidation classifiable as organizing pneumonia but distinct from bacterial pneumonia [9].

In patients with lung cancer, nivolumab-induced ILD differs in many aspects from ILD induced by other EGFR-TKIs, including the time to onset, disease progression, and mortality rate in early stages; thus, nivolumab-induced ILD may be different from ILD induced by other drugs. Chest CT findings suggestive of pulmonary fibrosis and other structural changes, such as traction bronchiectasis, have been reported and may affect the outcome of ILD. [9] ILD induced by EGFR-TKIs is characterized by an early onset (within the first four weeks of treatment), but nivolumab-induced ILD is not characterized by a particular timing of onset. Indeed, in the present case with gastric cancer, 27 months had passed after starting administration until the clinical onset. Some reports about irAEs (such as endocrine disorders) have stated that some patients may obtain a long-term benefit from immune checkpoint blockade or even be cured, implying that they should be carefully monitored for late-onset irAEs up to several years after the initiation of treatment [10]. We must therefore pay close attention to patients receiving the long-term administration of nivolumab to detect nivolumab-induced ILD as soon as possible.

The mortality of nivolumab-induced ILD is low because of its good response to steroid therapy, [9,11] although the present patient is alive with no disease progression despite not having a good response to steroid therapy.

Both the ASCO clinical practice guideline and ESMO clinical practice guideline describe how to treat the pneumonitis as an irAE. It is recommended that grade 2 toxicities be treated with prednisone 1-2 mg/kg/day and tapered by 5-10 mg/week over 4-6 weeks. If there is no clinical improvement with prednisone, methyl prednisone IV should be administered at 1-2 mg/kg/day with the addition of infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide [12,13]. If the patient’s condition does not improve or there is no imaging improvement after starting the steroid therapy, immunosuppressive strategies should be immediately adopted. If pneumonitis relapses during steroid tapering, immunotherapy should not be rechallenged. Since steroid therapy was tapered very slowly and carefully in the present case, over six weeks or more, ILD did not recur during steroid tapering.

In patients with melanoma it was reported that there was an association between the clinical benefit (measured by the overall survival) and the induction of cutaneous irAEs, emphasizing a close relationship between self-tolerance and tolerance to melanoma antigens. Cutaneous irAEs may be associated with a durable clinical benefit with nivolumab [14]. Similar articles on patients with NSCLC have described trends between irAEs and outcomes. [15]. There may be some important clues concerning a previously under-recognized role of PD-1 in modulating humoral immunity that may be relevant, both for considering the mechanism of PD-1-mediated toxicity and the anti-tumor efficacy.

6. Conclusion

We encountered a case of nivolumab-induced ILD with advanced gastric cancer. The characteristics of its onset after the long-term administration of nivolumab, no risk factors of lung disease, and its treatment course of steroid therapy were different from previous reports of nivolumab-induced ILD with other cancers. There is said to be a correlation between the presence of irAEs and an increased survival benefit with immune checkpoint inhibitors. Given there are a number of uncertain points concerning irAEs with immune checkpoint inhibitors, a careful long-term follow-up is needed.
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