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Case Report

CASE REPORT

Nivolumab-induced interstitial lung disease in a patient with gastric cancer

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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. A 69-year-old woman with metastatic gastric cancer being treated with nivolumab as fifth-line therapy developed interstitial pneumonia 27 months after starting treatment with nivolumab. Chest computed tomography demonstrated a cryptogenic organizing pneumonia pattern in both lung lobes. This was thought as an immune-related adverse event (irAEs), but stopping the administration of nivolumab failed to resolve the presence of lung shadows. Treatment with steroid pulse therapy twice and subsequently with prednisolone gradually improved the pulmonary function. The administration of high-dose corticosteroid is recommended after the diagnosis of irAEs in nivolumab treatment. Since recovering from pulmonary dysfunction, the patient remains alive with no disease progression. The immediate diagnosis and treatment of irAEs are crucial for achieving a good outcome.

INTRODUCTION

Immune checkpoint inhibitors enhance anti-tumor 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 by its ligand PD-L1 and has shown clinical efficacy in patients with various types of cancer [1]. 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 (ILD) and its resolution by steroid therapy in a patient with gastric cancer.

CASE REPORT

A 69-year-old woman with metastatic gastric cancer, liver and lymph node metastases started nivolumab monotherapy as fifth line treatment. Four years before starting nivolumab treatment, she had undergone distal gastrectomy because of pyloric

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stenosis. After that, she received chemotherapy with S-1 plus cisplatin, ramucirumab plus paclitaxel, irinotecan monotherapy and paclitaxel monotherapy.

She received 3 mg/kg nivolumab intravenously every two weeks. 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 (Fig. 1).

She had no respiratory symptoms. She had no fever and the non-invasive oxygen saturation was 98–100% on room air which was equivalent to her baseline, before starting to treat with nivolumab. We thought that non-invasive arterial oxygen saturation measured by pulse oximeter was a substitute for gas transfer [2]. She had no risk factors, such as smoking, dust exposure, occupation, pets and birds. She had no medication besides nivolumab. Laboratory data and sputum cultures provided no evidence of infection. The value of beta D glucan and cytomegalovirus antibody were normal, but the serum KL-6 (sialylated carbohydrate antigen KL-6) had increased to 404 U/ml (normal range <500U/ml). We measured the SP-D level of 315.0 ng/ml (normal<110 ng/ml) and LDH level of 227 U/l (normal, 103–229 U/l). 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 (Fig. 2). She was diagnosed with nivolumab-induced ILD.

Nivolumab administration had stopped for 4 weeks after GGOs had appeared but the blood oxygenation level was slightly lower than usual (the oxygen saturation was 94–95% on room air). The lung shadow was worsened compared to baseline, and the serum KL-6 had increased to 1608 U/ml. She started to treat with prednisolone (PSL) at 0.5 mg/kg (20 mg/body) daily. However, the blood oxygenation level was decreased (the oxygen saturation was 96–97% on 3 l/min O_2) after administration of PSL and the serum KL-6 level increased to 2163 U/ml.

She received pulsed high-dose methylprednisolone (mPSL) at 1000 mg twice, and the PSL dose was tapered to 1.0 mg/kg (40 mg/body) daily according to the guideline. Hypoxemia improved slowly and the oxygen saturation was 98–100% on room air after discharge from hospital. 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, thereafter the pulmonary disorder was resolved. The dose of PSL has been slowly tapered to 7.5 mg/body daily, and she is alive with no progression of both ILD and cancer. She has not started to treat with chemotherapy yet (Fig. 3).

DISCUSSION

Immune checkpoint inhibitors are associated with unique adverse events including ILD known as irAEs [3]. The risk factors for general drug-induced ILD are thought to be advanced 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 [4], but the risk factors for nivolumab related ILD are still unclear [5].

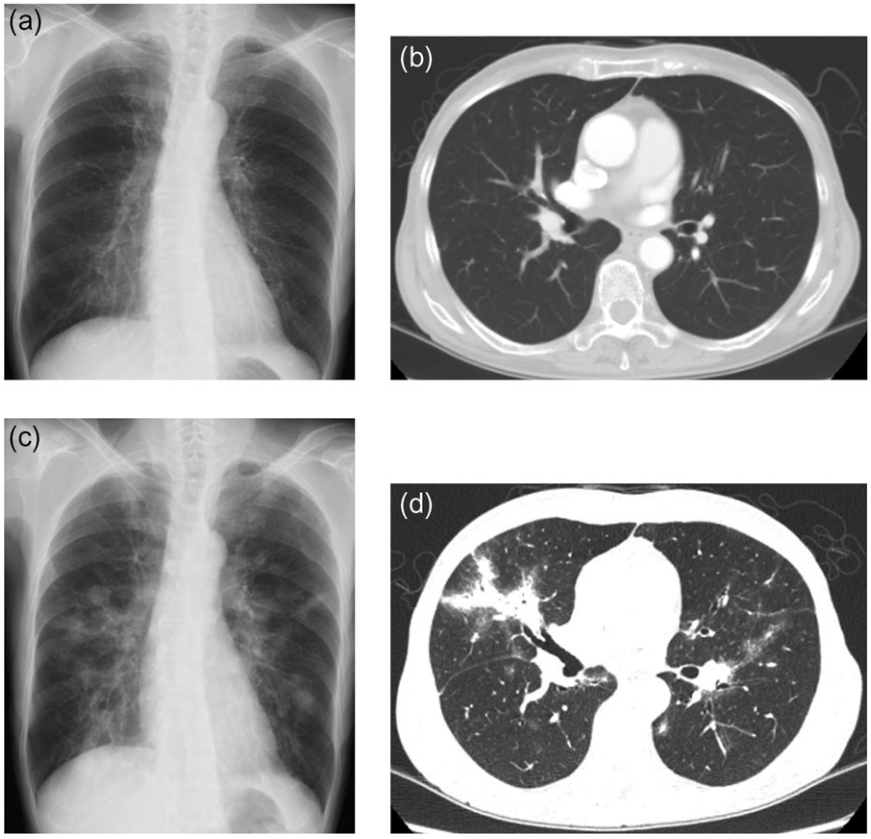

Figure 1: Follow-up chest X-ray and computed tomography (**a** and **b**) before treating with nivolumab, (**c** and **d**) after 57 cycles of nivolumab treatment. In both lung lobes, ground glass opacities and small coin lesions appeared.

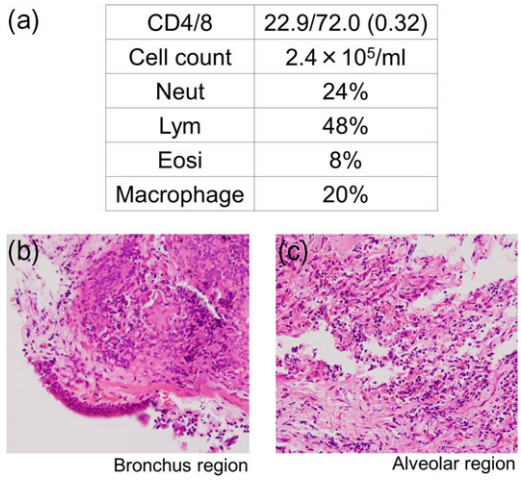

Figure 2: The results of bronchoscopy. A diagnosis of interstitial lung disease (ILD) was made by bronchoalveolar lavage fluid (BALF) and a transbronchial lung biopsy (TBLB). In the BALF, there were no malignant cells, no underlying infection, and an increase in the numbers of lymphocytes. The CD4/CD8 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.

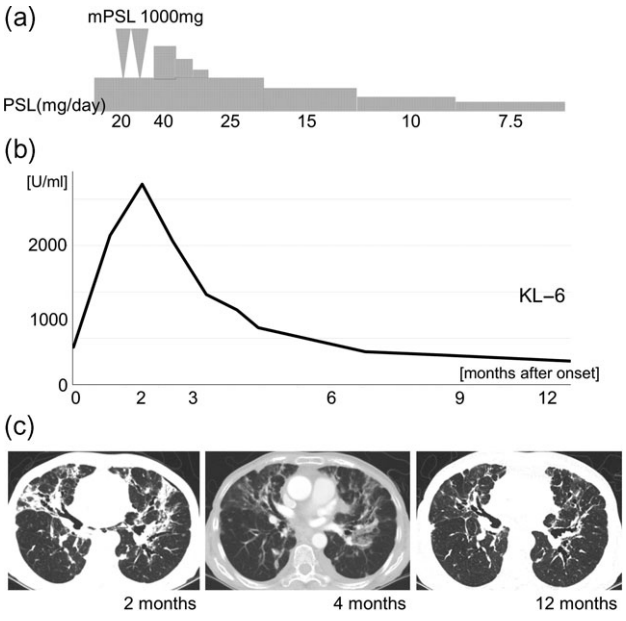

Figure 3: The clinical course of the case. When GGOs appeared in both lung lobes, during 57 cycles of nivolumab treatment, nivolumab was discontinued for four weeks. Because the serum KL-6 had continued to increase, treatment with prednisolone (PSL) was started after bronchoscopy. (**a**) The transition of the PSL dose. Treatment with PSL at 0.5 mg/kg (20 mg/body) was started, and thereafter 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. We measured KL-6 routinely [14]. (**c**) Chest CT. The lung shadow gradually improved over the following 12 months.

According to the ATTRACTION-2 [6], the first randomized phase 3 trial in patients with advanced gastric or gastro-esophageal 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. 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].

In patients with lung cancer, ILD induced by EGFR-TKIs is characterized by an early onset (within the first 4 weeks of treatment). In the present case, 27 months had passed after starting administration until the clinical onset. Some reports about irAEs (such as endocrine disorders) have stated that 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 [8]. The mortality of nivolumab-induced ILD is low because of its good response to steroid therapy [9]. This patient is alive with no disease progression despite not having a good response to steroid therapy [10].

Both the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) clinical practice guideline describe how to treat the pneumonitis as an irAE [11, 12]. 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 6 weeks or more, ILD did not recur during steroid tapering.

Cutaneous irAEs and NSCLC may be associated with a durable clinical benefit with nivolumab [13]. 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-1mediated toxicity and the anti-tumor efficacy.

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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The patient has given consent for her story to be published.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

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ETHICAL APPROVAL

IRB approval was given by IRB Review Committee of Osaka University.

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