

Organizing Pneumonia after Nivolumab Treatment in a Patient with Pathologically Proven Idiopathic Pulmonary Fibrosis

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Acute exacerbation of pre-existing interstitial lung disease (ILD) associated with systemic anticancer therapy is recognized as a life-threatening adverse event of lung cancer treatment. Programmed cell death 1 (PD-1) checkpoint inhibitors, such as nivolumab, often induce pneumonitis in patients with cancer; however, the tolerance and safety of nivolumab for advanced lung cancer with ILD are unclear. We report a 72-year-old patient with lung cancer with pathologically proven idiopathic pulmonary fibrosis who was treated with nivolumab. She demonstrated pneumonitis with an organized pneumonia (OP) pattern, but no acute exacerbation of ILD featuring a diffuse alveolar damage (DAD) pattern. She was successfully treated with corticosteroid therapy, and maintained good disease control after the discontinuation of nivolumab. She also showed pseudoprogression of the primary tumor, implying infiltration of T-cells into the lung. These findings suggest that T-cell activation by nivolumab treatment might not be directly associated with acute ILD exacerbation, and that treatable OP might be a major pulmonary complication of nivolumab in patients with pre-existing ILD, similar to patients without underlying ILD. (J Nippon Med Sch 2019; 86: 43–47)

Key words: interstitial lung disease, nivolumab, drug-induced pneumonitis

Introduction

Interstitial lung disease (ILD) is considered a risk factor for lung carcinogenesis. In particular, the incidence of lung cancer in patients with idiopathic pulmonary fibrosis (IPF), the most common type of ILD, is significantly higher than that in the general population¹. In patients with pre-existing ILD, cancer therapy including surgery, radiotherapy, and chemotherapy can cause acute exacerbation of ILD (AE-ILD), characterized by sudden, progressive, and severe respiratory failure with new lung opacities and pathological lesions of diffuse alveolar damage (DAD). AE-ILD is a fatal complication in many patients, contributing to the challenge of treating patients with lung cancer and ILD.

Nivolumab is a programmed death receptor 1 (PD-1)-specific monoclonal antibody used as a standard treatment for lung cancer^{2,3}. A recent meta-analysis showed

that 4.2% of patients developed pneumonitis after nivolumab treatment for non-small-cell lung cancer (NSCLC)⁴. Organizing pneumonia (OP), ground glass opacity (GGO), and hypersensitivity pneumonitis are the main characteristics of pneumonitis induced by PD-1/PD ligand 1 (PD-L1) inhibitors^{5,6}. Nivolumab-induced ILD has shown a better response to corticosteroid therapy than pneumonitis induced by cytotoxic agents or epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)⁷. The incidence and pattern of pneumonitis induced by nivolumab in patients with ILD are not elusive, particularly in those with definitive IPF.

We herein report a patient with NSCLC with histologically proven IPF who was treated with nivolumab. She demonstrated pneumonitis with an OP pattern, but no DAD pattern, and was successfully treated with corticosteroid therapy. She maintained good disease control

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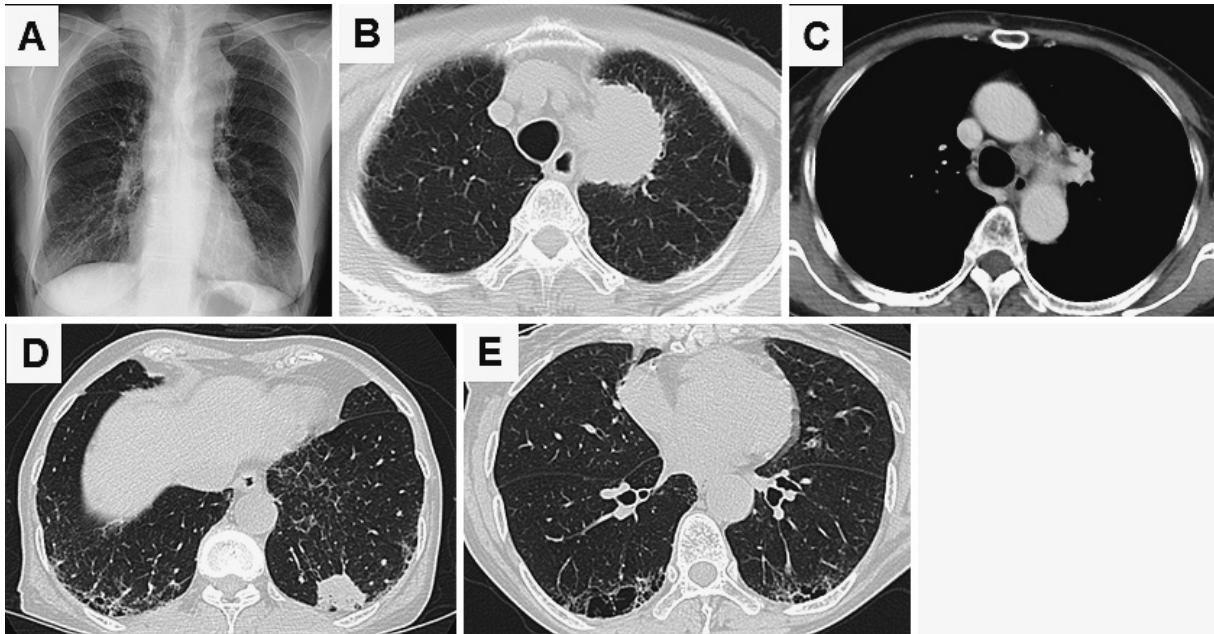


Fig. 1 (A) Chest X-ray image showing a lung mass in the left upper lung field and reticular shadows in the bottom field of the contralateral lung. (B, C, D) Chest computed tomography (CT) image showing a tumor in the left upper lobe attaching to the mediastinum (B), lymph node swelling (C), and left lower lobe nodule (D). (E) High-resolution computed tomography (HRCT) images demonstrating subpleural reticular opacities and clustered cystic airspace with traction bronchiectasis in the lung parenchyma.

after the discontinuation of nivolumab, and her PFS with nivolumab was six months.

Case

A 72-year-old woman, who was a former smoker, was found to have a left upper lobe lung tumor, left lower lobe nodule, and hilar-mediastinum lymph node swelling by chest X-ray and computed tomography (CT) (Fig. 1A-D). The histological diagnosis based on trans-bronchial lung biopsy of the left upper lobe mass was squamous cell carcinoma. High-resolution CT (HRCT) further revealed reticular shadows and traction bronchial ectasia mainly in the subpleural basal area of the bilateral lower lobe that suggested interstitial pneumonia, classified according to the IPF guidelines as the possible usual interstitial pneumonia (UIP) pattern on CT (Fig. 1E). Although we assumed the lymph node swelling was associated with the upper lobe lung cancer, we could not be certain whether the nodule in the left lower lobe was metastatic cancer or another primary lung cancer. If these two tumors in the upper and lower lobes were coincidental, double-primary lung cancers, curative treatment with radiation therapy could be a treatment option, based on the risk of AE-ILD. She then underwent video-assisted thoracic surgery (VATS) on the small nodule and reticular shadow in the left lower lobe to make a patho-

logical diagnosis of the nodule and confirm the ILD pattern. Pathological examination of the VATS specimen revealed a pulmonary fibrotic lesion with a UIP pattern, including microscopic honeycomb changes with fibroblastic foci (Fig. 2A-D). Squamous cell carcinoma was also confirmed in the left lower lobe nodule, and diagnosed as cancer metastasis from the left upper lobe tumor (cT4 N1 M0, stage 3a). Considering the risk of AE-ILD, radiation therapy was not recommended, and the patient was initially treated by chemotherapy with carboplatin and nab-paclitaxel. The initial tumor reduced in size with the chemotherapy treatment, but follow-up radiological examination at seven months after the end of treatment showed re-growth of the primary tumor (Fig. 3A). There is no established second-line chemotherapy for lung cancer with ILD, thus we initiated treatment with nivolumab at 3 mg/m² every 2 weeks in accordance with the patient's informed consent regarding ILD risk. Pulmonary function testing before treatment revealed a predicted forced vital capacity (%FVC) of 101.8% and a predicted diffusion capacity for carbon monoxide (%DLCO) of 83.3%.

On day 57 of nivolumab treatment, chest CT revealed a reticular opacity and a slight increase in size of the primary tumor, consistent with an immune-related adverse event (irAE) associated with nivolumab (Fig. 3B). The

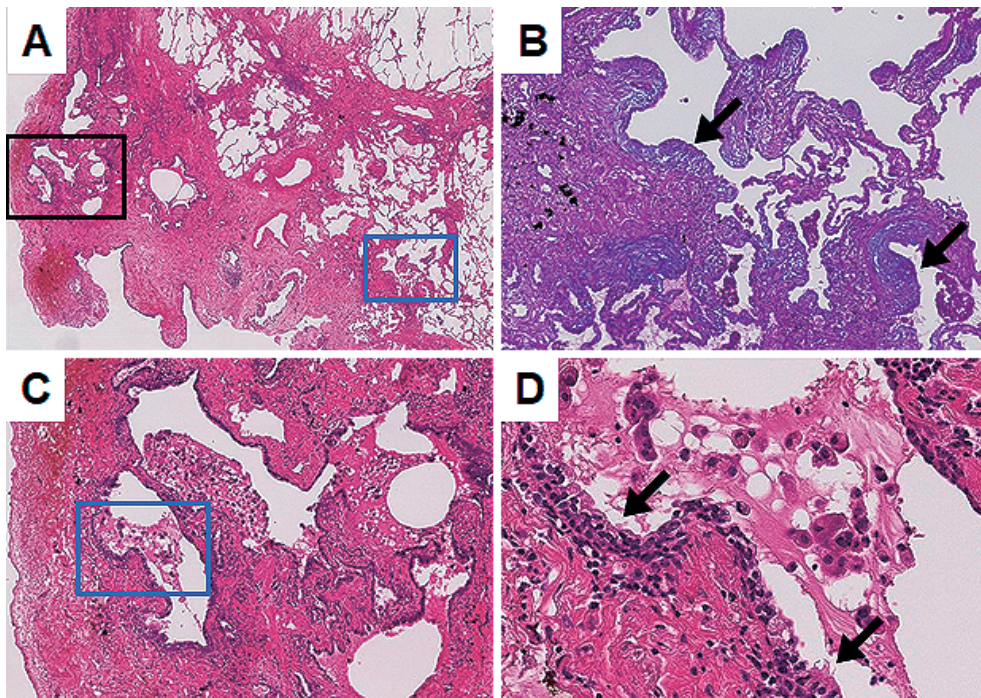


Fig. 2 (A) Low-power views of the video-assisted thoracic surgery (VATS) specimen showing a pulmonary fibrotic lesion of a usual interstitial pneumonia pattern with microscopic honeycomb changes (**blue rectangle**) (hematoxylin-eosin staining [HE]). (B) High-magnification views of the area in the black rectangle in (A) showing fibroblastic foci (**black arrows**) (AL-PAS). (C) High-magnification views of the area in the blue rectangle in (A) showing honeycomb changes with bronchiolization (HE). (D) Enlarged images of the blue-boxed region in (C) showing bronchiolization (**black arrows**).

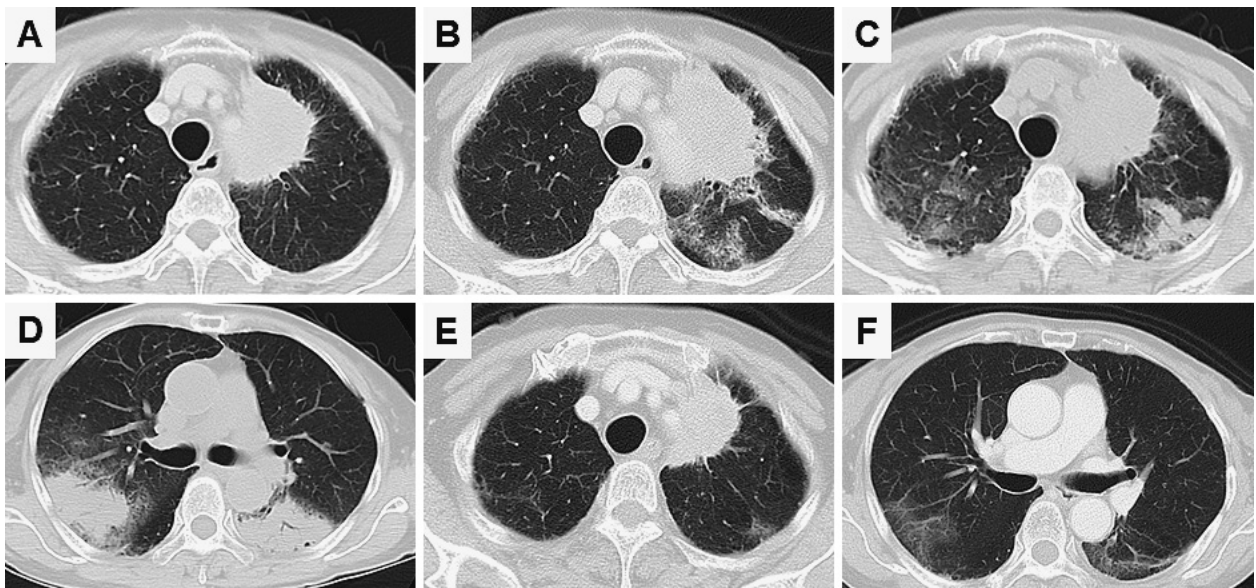


Fig. 3 (A) Chest computed tomography (CT) image showing the primary tumor before nivolumab treatment. (B) CT scan demonstrating ground glass opacity (GGOs) around the primary mass and a slight increase in the size of the primary tumor on day 57 of nivolumab therapy. (C. D) CT performed on day 99 of nivolumab therapy showing new GGOs and consolidations in both lung fields. (E. F) CT image showing significant improvement in the GGOs and regression of the primary tumor after corticosteroid therapy.

nivolumab was withdrawn and prednisolone at 15 mg/day was administered, resulting in immediate improvement in the GGOs and a decrease in size of the primary tumor. Nivolumab treatment was then re-started on day 85.

The patient noticed gradual dyspnea and a productive cough on day 99 of nivolumab treatment. Chest CT revealed new GGOs and consolidations in both lung fields (Fig. 3C, D), and blood tests revealed serum levels of KL-6 (552.5 U/mL) that were higher than those measured before the initiation of nivolumab (436.4 U/mL). We did not perform a bronchoscopy since the patient's consent was not obtained. No microorganisms were cultured, and polymerase chain reaction results were negative for *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare* DNA in the patient's sputum. The patient was started on intravenous methylprednisolone (500 mg) for 1 day and continuous oral prednisolone (1 mg/kg). Six weeks later, chest CT showed significant improvement in the GGOs and regression of the primary tumor after tapering the prednisolone to 10 mg per day (Fig. 3E, F). HRCT featuring GGOs and patchy air-space consolidations with a predominantly peripheral distribution was consistent with OP pattern pneumonitis. The patient showed no widespread GGOs with traction bronchiectasis, suggesting AE-ILD featuring a DAD pattern pneumonitis. The patient's response to corticosteroid therapy also supported these findings, reflecting an OP pattern pneumonitis. Although we discontinued nivolumab therapy because of recurrent pneumonitis, the tumor regression persisted for six months.

Discussion

Herein we report a case of nivolumab-induced pneumonitis, which was confirmed by its recurrence after re-starting nivolumab. HRCT showed consolidation with GGOs and a rapid response to corticosteroids that was consistent with an OP pattern. Importantly, an AE of underlying ILD was not involved in the present case. In general, since AE occurs more frequently in IPF than with other types of idiopathic interstitial pneumonitis (IIPs)⁸, definitively diagnosed IPF patients should be considered as the highest risk group in lung cancer treatment. To our knowledge, this is the first case describing nivolumab-induced pneumonitis in a patient with lung cancer with pathologically proven IPF. Khunger et al.⁹ reported a case of NSCLC with concomitant IPF treated with nivolumab; however, that patient did not show significant complications and experienced eight months of

disease control. In addition, Fujimoto et al.¹³ recently reported six patients on nivolumab treatment for NSCLC with mild IIPs, wherein pneumonitis was not observed, leading to the authors' proposal that nivolumab might be a well-tolerated treatment in patients with ILD.

The etiology of AE-IPF is not clear. Several reports have implicated fibroblasts and type 2 epithelial cells as associated with AE-IPF^{11,12}, and these cells are upregulated in patients with stable IPF. Such infiltration of epithelial cells and fibrocytes in stable IPF might promote AEs in drug treatment. T lymphocytes have been implicated in the mechanisms of irAEs of PD-1 inhibitors¹³, whereby infiltrates of immune cells containing activated cytotoxic T-cells have been observed around the primary tumor, known as pseudoprogression. Lymphocytes are also commonly associated with OP or NSIP, but not with DAD. We observed pseudoprogression surrounding the primary tumor in the present case, suggesting infiltration of T-cells into the lung. Nivolumab increased the anticancer immunity, which might have been related to the T-cell activation, thereby inducing OP pattern pneumonitis, regardless of the underlying IPF. This is supported by previous findings of a positive correlation between OP pattern pneumonitis and an improved prognosis in patients with drug-induced ILD, but not in those with the DAD pattern¹⁴. No other cases of pneumonitis induced by nivolumab with pathologically confirmed IPF have been reported, and because patients with NSCLC and ILD have limited treatment options, our case findings suggest the importance of considering treatment with PD-1 inhibitors when appropriate.

Conclusion

We described a patient with NSCLC with pathologically confirmed IPF who developed nivolumab-induced OP. She was successfully treated after the discontinuation of nivolumab and the initiation of corticosteroids, and achieved a PFS of six months due to nivolumab. Pre-existing ILD can lead to DAD pattern exacerbation in cancer treatment with EGFR-TKIs or cytotoxic chemotherapy; however, OP is a possible major pulmonary complication of nivolumab in patients with ILD, as for patients without underlying ILD. Further investigations will be needed to determine the clinical benefits and safety of treatment with immune checkpoint inhibitors in patients with ILD.

Conflict of Interest: The Department of Pulmonary Medicine and Oncology, Nippon Medical School received research sup-

port from ONO PHARMACEUTICAL CO. Masahiro Seike, Yoshinobu Saito, Kaoru Kubota, and Akihiko Gemma received honorariums from ONO PHARMACEUTICAL CO. or Bristol-Myers Squibb CO. The remaining author declares no conflict of interest. This manuscript itself has not received any funding. No funding was received for production of this manuscript.

References

- Hubbard R, Venn A, Lewis S, Britton J: Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. *Am J Respir Crit Care Med* 2000; 161: 5–8.
- Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Aren Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudalet C, Harbison CT, Lestini B, Spigel DR: Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* 2015; 373: 123–135.
- Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhaufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crino L, Blumenschein GR Jr, Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR: Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med* 2015; 373: 1627–1639.
- Wu J, Hong D, Zhang X, Lu X, Miao J: PD-1 inhibitors increase the incidence and risk of pneumonitis in cancer patients in a dose-independent manner: a meta-analysis. *Sci Rep* 2017; 7: 44173.
- Nishino M, Ramaiya NH, Awad MM, Sholl LM, Maattala JA, Taibi M, Hatabu H, Ott PA, Armand PF, Hodi FS: PD-1 Inhibitor-Related Pneumonitis in Advanced Cancer Patients: Radiographic Patterns and Clinical Course. *Clin Cancer Res* 2016; 22: 6051–6060.
- Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, Chaft JE, Segal NH, Callahan MK, Lesokhin AM, Rosenberg J, Voss MH, Rudin CM, Rizvi H, Hou X, Rodriguez K, Albano M, Gordon RA, Leduc C, Rekhman N, Harris B, Menzies AM, Guminski AD, Carlino MS, Kong BY, Wolchok JD, Postow MA, Long GV, Hellmann MD: Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol* 2017; 35: 709–717.
- Kato T, Masuda N, Nakanishi Y, Takahashi M, Hida T, Sakai H, Atagi S, Fujita S, Tanaka H, Takeda K, Satouchi M, Namba Y, Tamura T: Nivolumab-induced interstitial lung disease analysis of two phase II studies patients with recurrent or advanced non-small-cell lung cancer. *Lung Cancer* 2017; 104: 111–118.
- Arai T, Kagawa T, Sasaki Y, Sugawara R, Sugimoto C, Tachibana K, Kitaichi M, Akira M, Hayashi S, Inoue Y: Heterogeneity of incidence and outcome of acute exacerbation in idiopathic interstitial pneumonia. *Respirology* 2016; 21: 1431–1437.
- Khunger M, Velcheti V: A Case of a Patient with Idiopathic Pulmonary Fibrosis with Lung Squamous Cell Carcinoma Treated with Nivolumab. *J Thorac Oncol* 2017; 12: e96–e97.
- Fujimoto D, Morimoto T, Ito J, Sato Y, Ito M, Teraoka S, Otsuka K, Nagata K, Nakagawa A, Tomii K: A pilot trial of nivolumab treatment for advanced non-small cell lung cancer patients with mild idiopathic interstitial pneumonia. *Lung Cancer* 2017; 111: 1–5.
- Moeller A, Gilpin SE, Ask K, Cox G, Cook D, Gaultie J, Margetts PJ, Farkas L, Dobranowski J, Boylan C, O’Byrne PM, Strieter RM, Kolb M: Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009; 179: 588–594.
- Collard HR, Calfee CS, Wolters PJ, Song JW, Hong SB, Brady S, Ishizaka A, Jones KD, King TE Jr, Matthay MA, Kim DS: Plasma biomarker profiles in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2010; 299: L3–7.
- Chiou VL, Burotto M: Pseudoprogression and Immune-Related Response in Solid Tumors. *J Clin Oncol* 2015; 33: 3541–3543.
- Endo M, Johkoh T, Kimura K, Yamamoto N: Imaging of gefitinib-related interstitial lung disease: multi-institutional analysis by the West Japan Thoracic Oncology Group. *Lung Cancer* 2006; 52: 135–140.

(Received, April 17, 2018)

(Accepted, September 21, 2018)