



Letter to the Editor

Severe pneumonitis after nivolumab treatment in a patient with melanoma



Dear Editor,

Nivolumab is an immune checkpoint inhibitor that binds to the Programmed death 1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2, thereby reversing tumor-induced suppression of tumor-specific T cells.^{1,2} Nivolumab is currently approved for the treatment of metastatic melanoma, squamous cell lung cancer, and renal cell cancer. Although generally well tolerated, nivolumab can induce immune-related pneumonitis. We herein describe a case of severe pneumonitis after nivolumab treatment for melanoma.

A 73-year-old woman with metastatic melanoma (brain, lung) presented to our institution with fever, fatigue, and non-productive cough. Five months prior to presentation, she had begun treatment with nivolumab (2 mg/kg, every three weeks). After six cycles of treatment, one week prior to presentation, she developed fever, fatigue, and non-productive cough. Her past medical history was significant for thoracic aortic aneurysm status post stent graft. She was a non-smoker and had no history of chronic lung disease. On examination, body temperature was 37.0 °C, blood pressure was 121/75 mm Hg, heart rate was 82/min, and oxygen saturation on room air was 95%. Her physical examination was unremarkable. Laboratory tests demonstrated white blood cell count of 10,970/ μ L with 85.6% neutrophils and 6.1% lymphocytes, C-reactive protein level of 14.3 mg/dL (normal <0.3 mg/dL), serum lactate dehydrogenase (LDH) level of 138 IU/L (normal, 119–229 IU/L), and Krebs von den Lungen-6 (KL-6) level of 250 U/mL (normal <500 U/mL). Arterial blood gas analysis on room air showed pH of 7.479, PaCO₂ of 37.6 mmHg and PaO₂ of 61.0 mmHg. Chest radiography showed a right lung infiltrate and blunting of the right costophrenic angle. Chest computed tomography (CT) scan revealed a consolidation with air bronchograms, ground-glass attenuations, and patchy shadows, predominantly in the right lung. These abnormalities mainly involved the dependent lung regions. A right pleural effusion was also present. A metastatic lung tumor was found in the left lower lobe, but no abnormalities were observed around the tumor (Fig. 1). Although sputum culture did not reveal any microorganisms, including mycobacteria and fungi, she was initially diagnosed with bacterial pneumonia due to her symptoms and CT findings. Nivolumab was discontinued, and tazobactam/piperacillin (TAZ/PIPC) and levofloxacin (LVFX) antibiotics were initiated, but her symptoms did not improve. On hospital day 11, TAZ/PIPC was switched to meropenem (MEPM). However, she developed progressive dyspnea with severe hypoxemia, and the diffuse consolidation, ground-glass attenuations, and pleural effusions worsened on CT imaging, in a pattern suggestive of diffuse

alveolar damage. On hospital day 16, she was transferred to the intensive care unit and started on mechanical ventilation. The serum level of surfactant protein-D was increased to 213.7 ng/mL (normal <110 ng/mL), but LDH (243 IU/L) and KL-6 (327 U/mL) were within normal limits. Bronchoalveolar lavage (BAL) showed a total cell count of 3.1×10^5 cells/mL with 77.7% macrophages, 8.7% lymphocytes, and 14.3% neutrophils, with no evidence of bacteria, fungi or malignancy. The pleural fluid was also sterile. An echocardiogram did not demonstrate any underlying cardiac dysfunction. Her PaO₂/FIO₂ ratio was 131, and she was ultimately diagnosed with acute respiratory distress syndrome secondary to nivolumab treatment (Grade 4). Intravenous methylprednisolone (mPSL) pulse therapy (1 g per day for three days) and continuous infusion of sivelestat sodium hydrate were initiated. Her respiratory failure continued to worsen, prompting the administration of 500 mg of intravenous cyclophosphamide (IVCY) and repeat mPSL pulse therapy. Shortly thereafter, her respiratory status and radiographic findings began to improve. Following the mPSL pulses, oral prednisolone (PSL) at a dose of 2 mg/kg/day was administered and gradually tapered (Fig. 2). The patient was discharged from the intensive care unit 35 days after presentation, liberated from mechanical ventilation after 65 days, and was discharged from our hospital after 120 days. One year following the last administration of nivolumab, pneumonitis had not returned and the metastatic lung tumor was stable on chest CT imaging.

In a phase I study of nivolumab, 3% of patients (9 of 269) experienced drug-related pneumonitis, and 1% (3 of 269) developed grade 3–4 pneumonitis.³ Long-term safety outcomes from another phase I study revealed similar results.⁴ Three treatment-related deaths occurred as a result of pneumonitis; 2 of these patients were being treated for non-small cell lung cancer and 1 was being treated for colorectal cancer.^{3,4} Currently, management guidelines for immune-mediated adverse reactions include discontinuation of nivolumab, with the addition of corticosteroids and immunosuppressants (infliximab, cyclophosphamide, intravenous immune globulin, or mycophenolate mofetil) in grade 3 or 4 pneumonitis.⁵ We used cyclophosphamide for our patient because we had very little experience with other immunosuppressants.

Very few cases of nivolumab-induced pneumonitis have been reported in detail. Nishino *et al.* recently reported the development of pneumonitis in 3 patients with melanoma who had received either nivolumab alone or nivolumab and ipilimumab sequentially.⁶ In each case (one case of grade 2 and two cases of grade 3 pneumonitis), findings were associated with anti-PD-1 antibodies. All cases had evidence of ground glass, reticulations and consolidations on chest CT imaging, and one case developed a pleural effusion. Discontinuation of nivolumab and initiation of oral

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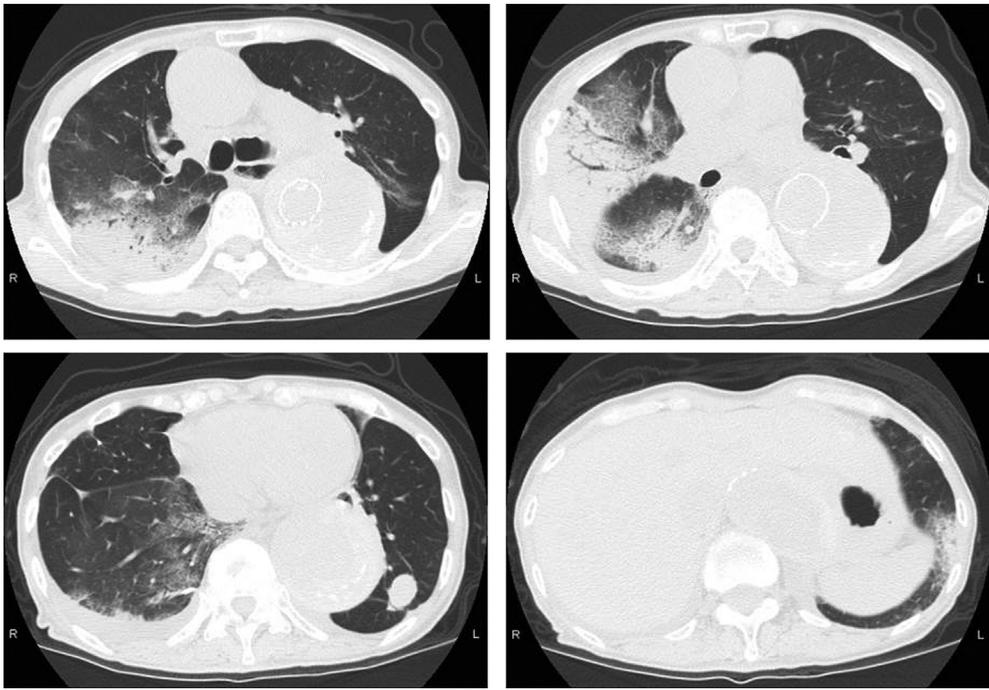


Fig. 1. Chest computed tomography showing consolidation with air bronchograms, ground-glass attenuations, and patchy shadows, predominantly in the right lung. A right pleural effusion is also present. No abnormalities were observed around the metastatic tumor in the lung.

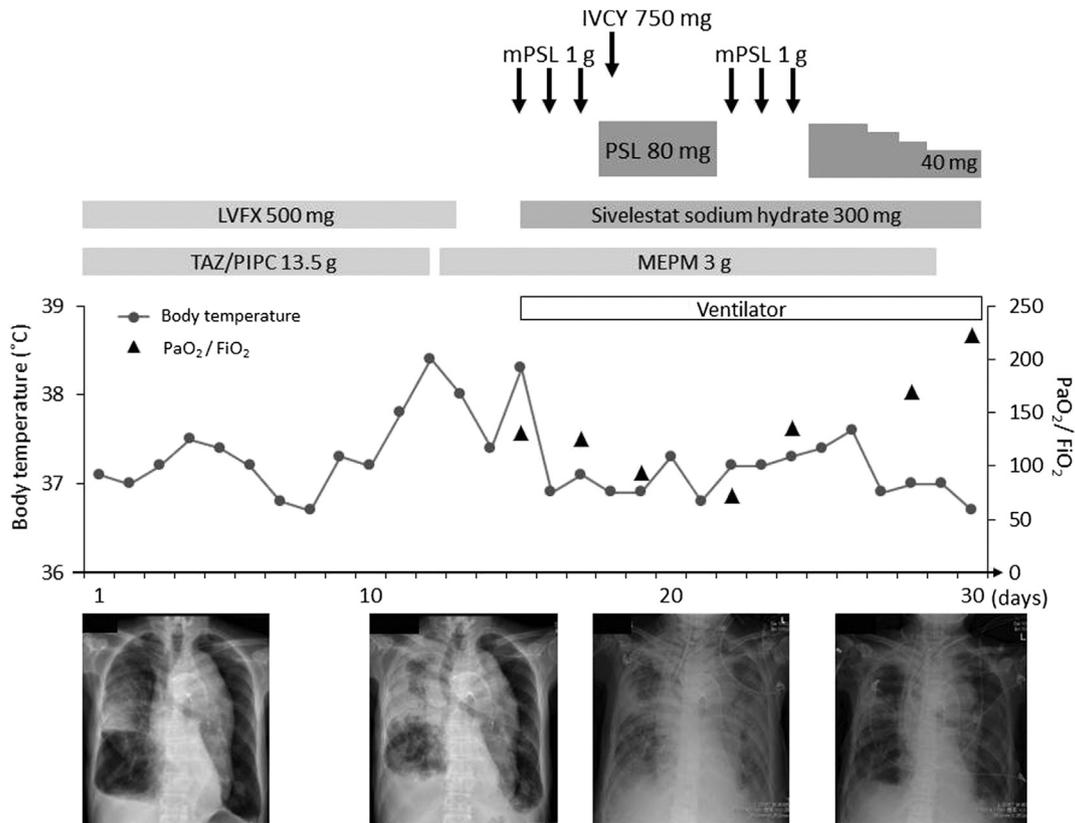


Fig. 2. Clinical course. Abbreviations: mPSL, methylprednisolone pulse therapy; IVCY, intermittent pulse intravenous cyclophosphamide therapy; PSL, prednisolone; LVFX, levofloxacin; TAZ/PIPC, tazobactam/piperacillin; MEPM, meropenem.

corticosteroids led to resolution of the grade 2 pneumonitis, however the grade 3 cases required additional treatment with infliximab. With this additional treatment, one case resolved after 10 weeks and one case ended in the patient's death 4 weeks after diagnosis. Nivolumab has also been associated with the development of organizing pneumonia in a patient with metastatic melanoma; the patient improved with corticosteroid therapy.^{7,8} Thus, nivolumab may cause several types of adverse lung reactions, each with different severity and treatment response.

Identifying drug-induced pneumonitis can be difficult. For example, our patient was initially treated for bacterial infection based on CT findings of asymmetrical consolidation with air bronchograms and pleural effusion. However, given the lack of improvement with antibiotics, as well as negative sputum, BAL and pleural fluid cultures, she was ultimately diagnosed with nivolumab-associated pneumonitis. Though she improved with discontinuation of nivolumab and initiation of corticosteroids and cyclophosphamide, the delay in diagnosis may have contributed to her prolonged clinical course. Another challenging point is differentiating between immune-related adverse events and immune-reactions against tumor cells. In clinical trials of PD-1 or PD-L1 antibodies, some patients experienced a transient increase in the size of tumor lesions. The increase was associated with edema and immune cell infiltrates.⁹ In our case as well as previously reported cases,^{7,8} extensive ground-glass opacities and consolidations were observed in areas without tumor lesions, but similar findings were not observed around the metastatic tumors. This observation might be useful in differentiating these two immune reactions.

As nivolumab is approved for additional therapeutic indications, the number of patients treated with this drug is expected to increase. Hence, the incidence of nivolumab-induced pneumonitis may also increase. This adverse event should be suspected in patients receiving nivolumab who present with acute onset respiratory failure or worsening of chronic respiratory symptoms. Given the high mortality risk of nivolumab-induced pneumonitis, any suspicion of this etiology of respiratory failure should prompt clinical investigations including cross-sectional imaging and bronchoscopy, if appropriate, and treatment should include immediate cessation of nivolumab and addition of corticosteroids and immunosuppressants. Further studies on the prevalence, risk factors, clinical features, chest CT findings and treatment outcomes for nivolumab-induced pneumonitis are warranted.

Conflict of interest

The authors have no conflict of interest to declare.

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References

1. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol* 2008;**26**:677–704.
2. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol* 2010;**28**:3167–75.
3. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;**366**:2443–54.
4. Topalian SL, Sznol M, Brahmer JR, McDermott DF, Smith DC, Gettinger SN, et al. Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients with advanced solid tumors: survival and long-term safety in a phase I trial [abstract]. *J Clin Oncol* 2013;**31**:173S.
5. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;**372**:320–30.
6. Nishino M, Sholl LM, Hodi FS, Hatabu H, Ramaiya NH. Anti-PD-1-related pneumonitis during cancer immunotherapy. *N Engl J Med* 2015;**373**:288–90.
7. Nakashima K, Naito T, Omori S, Yoshikawa S, Endo M, Kiyohara Y, et al. Organizing pneumonia induced by nivolumab in a patient with metastatic melanoma. *J Thorac Oncol* 2016;**11**:432–3.
8. Sano T, Uhara H, Mikoshiba Y, Kobayashi A, Uchiyama R, Tateishi K, et al. Nivolumab-induced organizing pneumonia in a melanoma patient. *Jpn J Clin Oncol* 2016;**46**:270–2.
9. Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. *J Clin Oncol* 2015;**33**:3541–3.

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