# Severe Pneumonitis after Nivolumab Treatment Accompanied by Acute Pulmonary Embolism in a Patient with Lung Adenocarcinoma

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**Key words:** Nivolumab; Pneumonitis; Pulmonary Embolism

A 75-year-old Han Chinese man presented with a 1-day history of acute shortness of breath. His medical history included lung adenocarcinoma, hepatitis B virus (carrier), hypertension, previous deep vein thrombosis (DVT), smoking for 45 years, and drinking for 35 years. He underwent dissection of his right upper and middle lobes and mediastinal lymph nodes 5 years previously and developed pleural and multiple pulmonary metastasis 3 months postoperatively. Molecular tests for epidermal growth factor receptor, KRAS, and anaplastic lymphoma kinase rearrangement were negative. He received 33 cycles of chemotherapy and 2 sessions of radiotherapy for lung metastases. However, he still developed bilateral lung metastases and multiple thoracic and lumbar vertebral metastases. Six weeks before the current presentation, he received nivolumab (3 mg/kg every 2 weeks, three cycles).

Physical examination revealed 92% oxygen saturation on room air, clubbed fingers, rales in the right lower lung, a higher second sound in the pulmonary than aortic area, and symmetrical edema of the lower limbs. Laboratory tests demonstrated a D-dimer level of 18.9 mg/L (normal, <0.24 mg/L), brain natriuretic protein level of 343 pg/ml (normal, <100 pg/ml), and cardiac troponin I level of 0.113 ng/ml (normal, <0.03 ng/ml). Platelet aggregation tests showed an increased adenosine diphosphate level of 75.36% (normal, 42–68%), Col level of 77.1% (normal, 56–75%), and Ris level of 85.9% (normal, 58–76%). Arterial blood gas analysis showed a pH of 7.405, $PaCO_2$ of 37.3 mmHg (1 mmHg = 0.133 kPa), and $PaO_2$ of 75.8 mmHg while breathing 5 L/min of oxygen by nasal cannula. Computed tomography pulmonary angiography (CTPA) showed pulmonary artery emboli at multiple left segments and right anterior basal segments [Figure 1]. Doppler ultrasound showed right popliteal vein thrombosis and left lower-limb calf vein thrombosis. Echocardiography showed an enlarged right atrium and right ventricle, and the systolic pulmonary artery pressure was 63 mmHg. Intravenous infusion of 50 mg of recombinant tissue plasminogen activator (rt-PA) followed by low-molecular-weight heparin was administered. The patient's dyspnea was significantly improved 8 h after treatment.

From days 5–7, the patient developed increasingly worsening respiratory distress. Repeat CTPA [Figure 1] on day 7 showed extensive bilateral infiltration and ground-glass attenuations, the pulmonary artery thrombosis had been significantly absorbed. Laboratory tests demonstrated a white blood cell count of 12,500/ml with 89.1% neutrophils and 3.2% lymphocytes, a C-reactive protein level of 303.8 mg/L (normal, <3 mg/L), and lactate dehydrogenase level of 306 U/L (normal, 100–240 U/L). Piperacillin/sulbactam was initiated on day 8. Sputum smears and culture revealed no microorganisms. Cytomegalovirus DNA and Epstein–Barr virus DNA in the blood were negative, and the procalcitonin level was <0.25 ng/ml. The patient was diagnosed with acute respiratory distress syndrome (ARDS) secondary to nivolumab treatment (Grade 4). Intravenous

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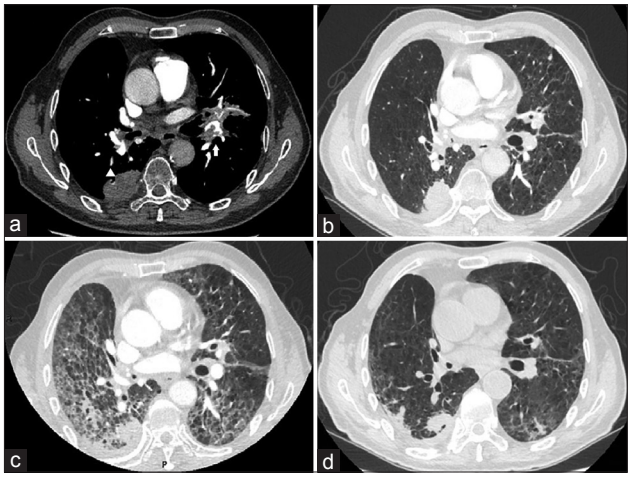


**Figure 1:** Chest computed tomography. (a and b) Pulmonary embolism (arrow) and metastasis (triangle) on the day of admission. (c) New bilateral infiltration and ground-glass attenuations on day 8 after admission. (d) The infiltration resolved 2 weeks after methylprednisolone treatment.

high-dose methylprednisolone (mPSL) therapy (160 mg/d for 1 day, 200 mg/d for 2 days) and gamma globulin therapy (20 g/d for 3 days) were initiated. Three days later, his respiratory status began to improve. The mPSL was continued for 4 days (120 mg/d for 1 day, 80 mg/d for 3 days), and oral prednisolone was begun at a dose of 1 $mg \cdot kg^{-1} \cdot d^{-1}$ and gradually tapered. Chest CT showed that the infiltration had absorbed 2 weeks after treatment [Figure 1]. He was discharged 2 months after admission.

Drug-related pneumonitis is a rare but clinically serious and potentially life-threatening adverse reaction to programmed cell death 1 (PD-1) inhibitors. In one study, the incidence of all-grade pneumonitis was 2.7% (95% confidence interval [*CI*], 1.9–3.6%) and that of Grade 3–4 pneumonitis was 0.8% (95% *CI*, 0.4–1.2%). The incidence of all-grade pneumonitis (4.1% vs. 1.6%) and Grade ≥3 pneumonitis (1.8% vs. 0.2%) was higher in patients with nonsmall cell lung carcinoma than those of melanoma.[1] The median time from therapy initiation to pneumonitis was 2.6 months. The most common radiographic pattern was cryptogenic-organizing pneumonia, acute interstitial pneumonia(AIP)/ARDS represents the pattern of Grade 3-4 pneumonitis.[2]

Our patient developed Grade 4 pneumonitis 6 weeks after nivolumab treatment, and the radiographic pattern was AIP/ARDS. Management guidelines for immune-mediated adverse reactions include discontinuation of nivolumab, with the addition of corticosteroids and immunosuppressants (infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil) in patients with Grade 3 or 4 pneumonitis. Our patient's respiratory status improved within 3 days of receiving high-dose corticosteroid and immunoglobulin therapy; therefore, we did not administer other immunosuppressants. Nishino *et al*. reported two patients with Grade 3 pneumonitis with melanoma who had received nivolumab. Both patients received glucocorticoids, infliximab, and antibiotic agents. One patient required intubation and improved over the course of 10 weeks, and the other died 4 weeks after diagnosis.[3] Watanabe *et al*. recently reported nivolumab-induced Grade 4 pneumonitis in a patient with melanoma. The patient continued to worsen for 3 days after mPSL pulse therapy, and cyclophosphamide with repeat mPSL pulse therapy resolved her condition.[4] Our patient had multiple risk factors for venous thromboembolism (VTE), including end-stage lung cancer, metastasis, hypertension, old age, increased platelet aggregation, and previous DVT. A recent large cohort study in Europe showed that people with lung cancer had a 3.92% overall incidence of VTE, and independent factors associated with VTE were metastatic disease, the adenocarcinoma subtype, chemotherapy, and diagnosis via emergency hospital admission.[5] Therefore, the acute pulmonary embolism probably resulted from the primary disease (lung cancer with widespread metastasis); whether it can be an adverse effect of nivolumab requires further observation.

In summary, we have described a patient who developed late-onset Grade 4 pneumonitis after nivolumab treatment accompanied by acute pulmonary embolism; rt-PA, high-dose corticosteroid therapy, and intravenous immunoglobulin therapy were lifesaving. The association between VTE and PD-1 inhibitors requires further investigation.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

## References

1. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: A Systematic review and meta-analysis. JAMA Oncol 2016;2:1607-16. doi: 10.1001/jamaoncol.2016.2453.
2. Nishino M, Ramaiya NH, Awad MM, Sholl LM, Maattala JA, Taibi M, *et al.* PD-1 inhibitor-related pneumonitis in advanced cancer patients: Radiographic patterns and clinical course. Clin Cancer Res 2016;22:6051-60. doi: 10.1158/1078-0432.CCR-16-1320.
3. 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. doi: 10.1056/NEJMc1505197.
4. Watanabe S, Kimura H, Takato H, Waseda Y, Hara J, Sone T, *et al.* Severe pneumonitis after nivolumab treatment in a patient with melanoma. Allergol Int 2016;65:487-9. doi: 10.1016/j.alit. 2016.04.009.
5. Walker AJ, Baldwin DR, Card TR, Powell HA, Hubbard RB, Grainge MJ, *et al.* Risk of venous thromboembolism in people with lung cancer: A cohort study using linked UK healthcare data. Br J Cancer 2016;115:115-21. doi: 10.1038/bjc.2016.143.