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Peritumoural ground-glass opacity associated with tumour pseudoprogression in a patient with non-small cell lung cancer treated with nivolumab

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ABSTRACT

Nivolumab, a monoclonal antibody to programmed cell death protein-1 (PD-1), has revolutionised the management of patients with advanced non-small cell lung cancer (NSCLC). Treatment with nivolumab is associated with toxicities known as immune-related adverse events. Although pneumonitis is a potentially serious event, little is known of its clinical and radiographic features. We here report a case of NSCLC for which treatment with nivolumab resulted in the development of ground-glass opacity surrounding the primary lung tumour and an associated increase in tumour size. Administration of prednisone led to rapid resolution of both clinical symptoms and the abnormal shadow on the lung field as well as shrinkage of the tumour. However, retreatment with nivolumab induced clinical and radiographic manifestations similar to those triggered by the first challenge. Given the increasing use of PD-1 inhibitors in patients with NSCLC, further studies are warranted to provide a better understanding of this phenomenon.

CASE REPORT

A woman aged 39 years with a 40-pack-year history of smoking was diagnosed with T1aN2M0 lung adenocarcinoma of the right upper lobe that was negative for both epidermal growth factor receptor (*EGFR*) gene mutation and anaplastic lymphoma kinase (*ALK*) gene translocation. She experienced local recurrence after radical chemoradiotherapy with carboplatin and paclitaxel, and she was therefore then treated with sequential chemotherapy regimens including docetaxel, erlotinib, pemetrexed, carboplatin-pemetrexed-bevacizumab, S-1 and gemcitabine over 4 years before CT again revealed progression of the primary tumour (*figure 1A*). Nivolumab, a monoclonal antibody to the immune-checkpoint protein programmed cell death protein-1 (PD-1), was then administered. Four days after the first dose, the patient developed a high-grade fever without dyspnoea, cough or

Key questions

What is already known about this subject?

- Pneumonitis related to the use of nivolumab is recognised as a potentially serious immune-related adverse event. Additionally, clinical trials with nivolumab have reported initial tumour enlargement with delayed shrinkage, so-called pseudoprogression.

What does this study add?

- We report a case of nivolumab-related peritumoural ground-glass opacity (GGO) associated with apparent transient progression of the primary tumour in a patient with advanced non-small cell lung cancer. Administration of steroid resolved GGO with shrinkage of tumour. However, retreatment with nivolumab induced similar clinical and radiographic manifestations.

How might this impact on clinical practice?

- Tumour-infiltrating lymphocytes might contribute to pseudoprogression of the tumour to GGO surrounded the primary lung tumour. Histological assessment of both the lung tumour and the surrounding shadow would be necessary to confirm this possibility.

hypoxaemia. A chest CT scan revealed ground-glass opacity (GGO) surrounding the primary tumour associated with an increase in tumour size (*figure 1B*). The severity of pneumonitis defined according to the Common Terminology Criteria for Adverse Events was grade 2 (symptomatic; limiting instrumental activities of daily living). Nivolumab was discontinued, and prednisone was administered orally at 1 mg/kg, resulting in rapid amelioration of the fever. A follow-up CT scan 1 month after initiation of oral prednisone showed resolving GGO and definite shrinkage of the primary tumour (*figure 1C*). The carcinoembryonic antigen level as a serum tumour marker had also declined from 24.5 to 5.2 mg/dL. Three months later, when oral prednisone had

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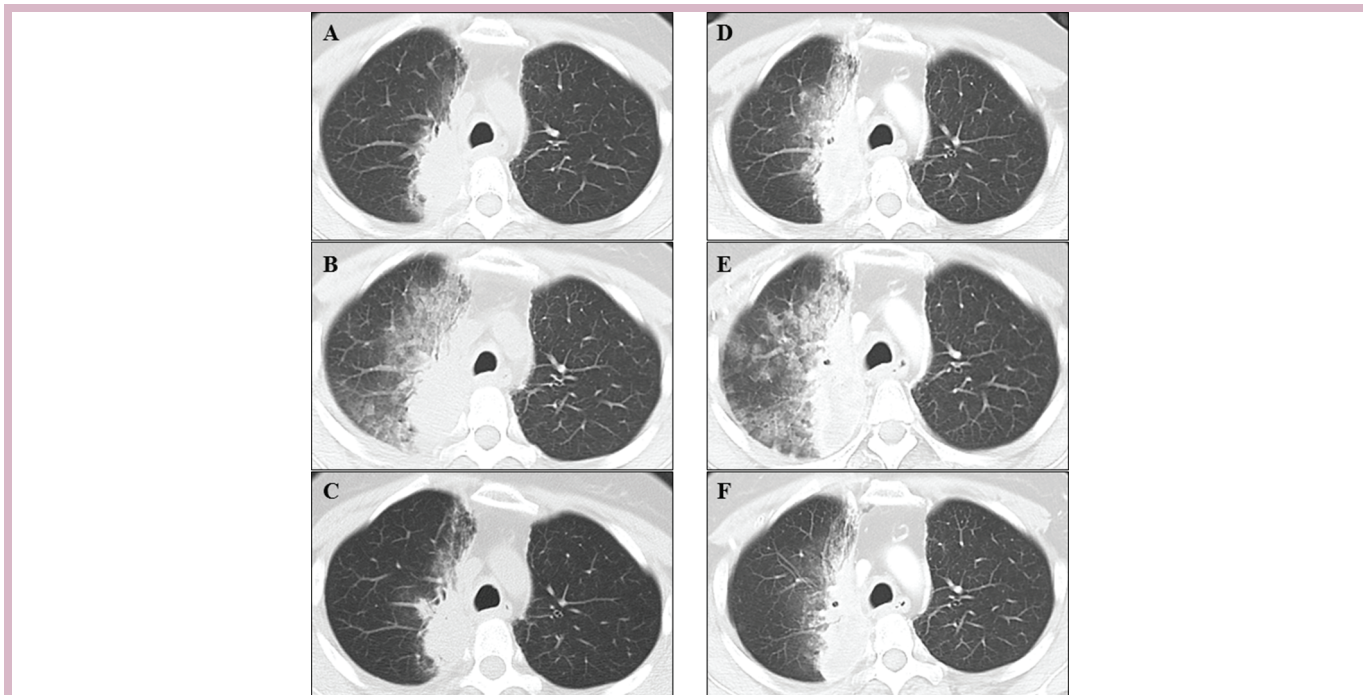


Figure 1 Chest CT scans showing the primary lung tumour in the right upper lobe before nivolumab therapy (A), development of ground-glass opacity (GGO) surrounding the primary tumour together with an increase in tumour size at 4 days after initiation of nivolumab therapy (B), resolution of GGO associated with shrinkage of the primary tumour after treatment with prednisone for 1 month (C), regrowth of the primary tumour (D), development of peritumoural GGO and a further increase in tumour size at 2 days after restarting nivolumab therapy (E) and resolution of GGO and tumour shrinkage at 3 months after restarting nivolumab and a subsequent increase in prednisone dose (F).

been tapered to 8 mg/day, CT assessment again revealed regrowth of the primary lesion (figure 1D). Given that the pneumonitis had improved from grade 2 to 1, the patient was rechallenged with nivolumab. Two days later, she again developed a fever, and a chest CT scan revealed peritumoural GGO and an increase in tumour size similar to the prior episode (figure 1E). An increase in prednisone dose to 1 mg/kg resulted in alleviation of the fever. A follow-up CT scan performed 3 months after reinitiation of nivolumab therapy again revealed attenuation of both the GGO and the increase in tumour size (figure 1F).

DISCUSSION

As far as we are aware, our report provides the first detailed description of the development of peritumoural GGO associated with apparent transient progression of the primary tumour in a patient with non-small cell lung cancer (NSCLC) treated with nivolumab. Of note, administration of steroid resulted in a rapid resolution of both clinical symptoms and the abnormal shadow on the lung field together with tumour shrinkage. However, rechallenge with nivolumab induced similar clinical and radiographic manifestations.

Antibodies to PD-1 such as nivolumab and pembrolizumab have shown marked clinical activity in patients with NSCLC.¹⁻⁵ Despite their clinical benefits, these inhibitors induce various types of immune-related adverse event (irAE).^{6,7} Among these irAEs, pneumonitis is an uncommon but potentially fatal toxicity.⁷ Recent

meta-analyses showed that incidence of anti-PD-1 inhibitor-related pneumonitis in patients with NSCLC was 3.8%–4.1% for all-grade and 1.8% for grade 3 or higher.^{8,9} Several studies have described distinct clinical and radiographic manifestations of pneumonitis related to anti-PD-1/programmed death ligand 1 (PD-L1) therapy in patients with advanced cancers, including lymphoma, melanoma and NSCLC.^{7,10-14} In these studies, median time from therapy initiation to pneumonitis was reported to be 2.2–2.8 months.^{7,11,12} The main clinical presentations of pneumonitis due to anti-PD-1 therapy were dyspnoea, cough, fatigue or respiratory failure.^{13,14} A recent study reported that the most common radiologic features of pneumonitis associated with anti-PD-1/ PD-L1 therapy was GGO type.¹² In addition, the most common distribution of CT findings for such pneumonitis appears to be multifocal with a relatively extensive lung involvement,¹¹ whereas a peritumoural distribution pattern has been observed in a few cases of nivolumab-induced organising pneumonia surrounding pulmonary metastases in patients with melanoma.^{15,16} The imaging features of the present case are similar to those of such previous cases, suggesting that a peritumoural shadow may be a unique characteristic of PD-1 inhibitor-related pneumonitis.

Our patient manifested pseudoprogression of her primary tumour. Recent studies of patients with advanced NSCLC treated with nivolumab have reported that a small proportion of such individuals manifested progressive disease according to the Response Evaluation Criteria in

Solid Tumors criteria at first assessment but then showed a clinical response at second assessment,²⁴ a phenomenon referred to as pseudoprogression.¹⁷ Histological analysis of a case of pseudoprogression in a patient with melanoma showed that the initial tumour enlargement was likely due to T-cell infiltration.¹⁷ Activation of the immune system is also usually responsible for irAEs.⁶ Given that the pulmonary GGO surrounded the primary lung tumour in the present case, tumour-infiltrating lymphocytes (TILs) might contribute to pseudoprogression of the tumour and to the abnormal shadow in the lung field. Any procedure to prove these assumptions was not performed in our case, and histological assessment, including detection of TILs, of both the lung tumour and the surrounding shadow would be necessary to confirm this possibility.

The present patient restarted nivolumab therapy and developed recurrent peritumoural GGO. In general, drug-related pneumonitis is a clinically serious and potentially life-threatening toxicity that necessitates the permanent cessation of treatment with the causative drug.¹⁸ However, previous studies on pneumonitis induced by EGFR-targeted or ALK-targeted tyrosine kinase inhibitors have demonstrated the safety and efficacy of treatment resumption.^{19,20} According to general guidelines for the management of irAEs, immunotherapy can be resumed in patients with adverse events of grade 2 when the events improve to grade 1.⁶ Indeed, a recent study reported resumption of nivolumab therapy in five patients after resolution of grade 2 pneumonitis.¹¹ Two of these five patients experienced recurrent pneumonitis but had a favourable response to prednisone therapy, similar to the present case. Given that little is known about the safety of nivolumab rechallenge, careful assessment of such retreatment is warranted in future studies.

In summary, we here report a case of nivolumab-related peritumoural GGO associated with pseudoprogression in a patient with advanced NSCLC. The patient was responsive to prednisone and restarted nivolumab therapy, but she experienced recurrent pneumonitis. Further studies of more patients are needed to provide a better understanding of the clinical and radiographic manifestations of PD-1 inhibitor-related pneumonitis as well as to characterise the biological mechanisms underlying peritumoural pneumonitis.

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Contributors RK and HH were responsible for clinical management of the patient, acquisition of data and drafting the manuscript. JT, KT, MT and KN were responsible for interpretation of data and critical revision of the manuscript. All authors read and approved the final version of the manuscript.

Competing interests HH has received lecture fees from AstraZeneca, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan K.K., Ono Pharmaceutical and Taiho Pharmaceutical as well as advisory fees from AstraZeneca, Boehringer-Ingelheim Japan and Eli Lilly Japan. KT has received lecture fees from AstraZeneca. KN has received lecture fees and advisory fees from Chugai Pharmaceutical, AstraZeneca and Boehringer-Ingelheim Japan. All other authors declare no potential conflicts of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from the patient of this study.

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