

CASE REPORT

Well-controlled pleural effusion indicated pseudoprogression after immunotherapy in lung cancer: A case report

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Abstract

Squamous cancer (SqCC) of the lung has a poor prognosis. With the advent of immunotherapy, prognosis has tended to improve; however, pseudoprogression poses a challenge to the management of immunotherapy. Herein, we discuss the case of a 47-year-old heavy smoker with advanced SqCC. The patient had recurrent disease after initial successful control of the tumor by concurrent radiochemotherapy, together with ample pleural effusion. Pleural effusion was well controlled with systematic nivolumab and intra-thoracic recombinant endostatin; however with simultaneous deterioration of performance and tumor progression. Nivolumab was maintained with the addition of nab-paclitaxel. The combination soon led to a partial response and rapid improvement of the patient's performance. During treatment of this case, we advocated the early control of pleural effusion as an indicator for pseudoprogression. Our experience might be helpful to identify pseudoprogression for the clinical management of immunotherapy.

Introduction

Squamous cancer (SqCC), which accounts for a quarter of new cases of non-small cell lung cancer (NSCLC), has a notoriously poor prognosis with a five-year survival rate of $\leq 15\%$, even after surgery, radiotherapy, or chemotherapy.¹ Targeted therapy is far less applicable for SqCC than adenocarcinoma. With the advent of immunotherapy, prognosis has tended to improve. The United States Food and Drug Administration (FDA) approved nivolumab, a fully humanized IgG4 PD-1 antibody, for the second-line treatment of SqCC based on the superior survival rate over docetaxel in the CheckMate 017 trial.² Nivolumab blocks interaction between PD-1 and its ligands, PD-L1 and PD-L2, and disrupts the negative signal that regulates T-cell activation and proliferation.³ However, pseudoprogression in immunotherapy where initial tumor growth was followed by regression poses a challenge to the management

of immunotherapy.^{4,5} Herein, we report a case of a patient with advanced SqCC successfully treated with nivolumab.

Case presentation

A 47-year-old man with a 30 pack-year history of smoking presented with hemoptysis in September 2012. An enhanced computed tomography (CT) scan showed a 3.7 cm mass located in the lower right hilum, wrapped by the right intermediate bronchus, and accompanied by mediastinum and hilar lymph node enlargement. A bronchoscopy was performed, and a pathological diagnosis of clinical stage cT4N3M0 (stage III) SqCC was confirmed. No *EGFR* mutations were identified. He was prescribed with concurrent chemoradiotherapy consisting of four cycles of paclitaxel plus cisplatin chemotherapy and 66Gy/33f radiotherapy and achieved a partial response (PR).

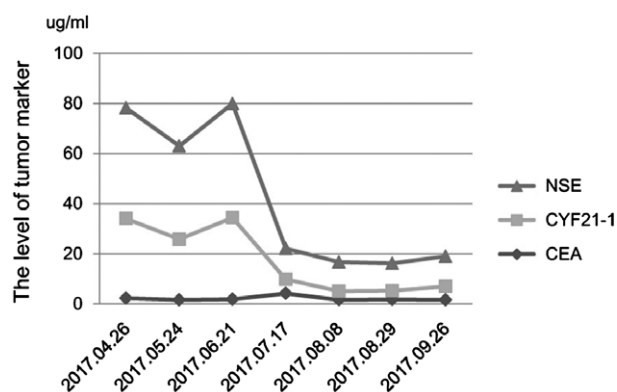
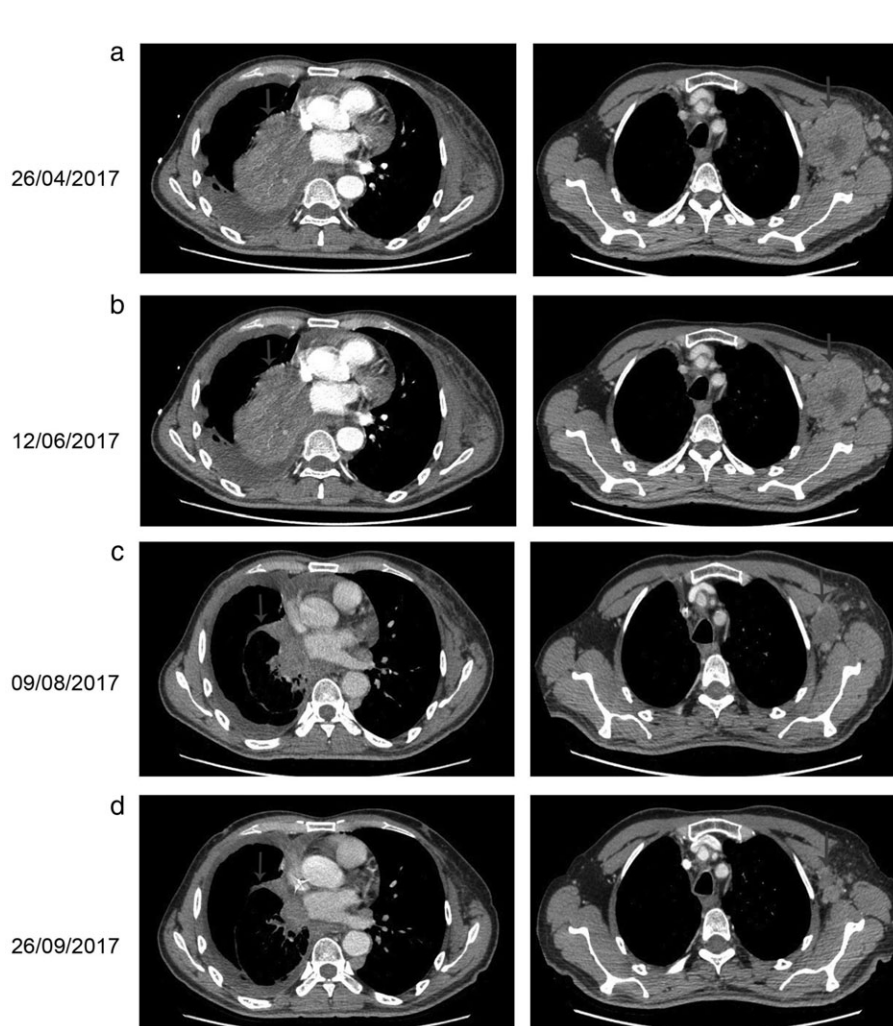


Figure 1 The serum tumor marker levels were stable after three cycles of nivolumab. After chemotherapy is administered, the serum tumor marker level continues to reduce.

The patient experienced recurrent hemoptysis in March 2017. He was in poor condition, with an Eastern Cooperative Oncology Group (ECOG) performance status

(PS) score of 2. A chest CT showed a 7.3 cm mass in the lower right hilum, an enlarged 6.8 cm lymph node in the left axillary, and pleural effusion on the right side. Serum tumor marker levels, including carcinoembryonic antigen, cytokeratin 19 fragments, and neuron-specific enolase, were high. We recommended immunotherapy with nivolumab at a dose of 3 mg/kg, once every two weeks from 3 May 2017 and thoracic perfusion treatment with recombinant endostatin. Pleural effusion was well controlled after four cycles of nivolumab and endostar, but the tumor continued to progress. The patient's condition deteriorated further, to an ECOG PS score of 3. At this time, DNA profiling was introduced, but no mutations in known driver genes (*EGFR*, *ALK*, *ERBB2*, *BRAF*, *MET*, *RET*, *ROS1*, and *KRAS*) were identified. This profiling also showed that the patient had a high tumor mutation burden. Nivolumab plus nab-paclitaxel were administered. Two cycles of therapy led to a PR in his tumor, sharply decreased tumor markers (Fig 1), and an improved ECOG PS score of 1. Another two cycles were implemented and the lesion

Figure 2 Computed tomography (CT) findings. (a) The CT scan taken on 26 April 2017 shows a lesion in the right lung and left axillary (arrows). (b) The following CT scan shows no effect after three cycles of nivolumab (arrows). (c,d) A restaging CT scan shows the lesion in the right lung and left axillary has reduced after two and four courses of nivolumab plus chemotherapy, respectively (arrows).



shrank further (Fig 2). Nivolumab therapy was maintained and the patient was regularly followed-up. The response was stable up to January 2018.

Discussion

Pleural effusion can be caused by a variety of malignancies and is accompanied by poor survival of approximately three months. The common treatment strategy is chemotherapy to reduce the tumor and adsorb effusion, which is rarely successful in NSCLC.^{6,7} Anti-angiogenesis was proposed in this case because of the angiogenic nature of the pleural effusion.⁸ Endostar inhibits angiogenesis mainly by counteracting the effects of vascular endothelial growth factor. It was approved by the Chinese Food and Drug Administration for the treatment of NSCLC and was expected to play a role in effusion control; however, its effectiveness for pleural control has not been confirmed by subsequent clinical analyses.^{9–11} As a consequence, endostar is rarely used as monotherapy. The long-term control of pleural effusion in this patient was reasonably attributed to nivolumab.

Previously, docetaxel, pemetrexed, or erlotinib monotherapy was established as the standard of care in second-line therapy, with an objective response rate (ORR) ranging from 8.2% to 9.1%.^{12–14} Nab-paclitaxel, another chemotherapy agent, achieved a better but still unsatisfactory ORR of 14.5%.¹⁵ However a disappointing ORR of 0% was reported for patients with recurrent or platinum-refractory SqCC.¹⁶ A good response was observed in our patient after combination treatment of nab-paclitaxel and nivolumab. In this regard, the effect was achieved by nivolumab, or a possible synergy between chemotherapy and nivolumab. This conclusion is supported by the results of the phase III Check-Mate057 study and others.^{17,18}

Immunotherapy response patterns differ from those of cytotoxic agents. Pseudoprogression in immunotherapy, where initial tumor growth is followed by regression, has been reported in 6.7–12% of melanoma patients.¹⁹ Another study reported that 13% of NSCLC patients experienced pseudoprogression during immunotherapy.²⁰ The underlying mechanism was either continued tumor growth until a sufficient immune response occurred, or a transient immune-cell infiltrate. Regardless, pseudoprogression in immunotherapy poses a great challenge to response evaluation using the current Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization criteria, thus novel criteria such as immune-related response criteria (irRC) or immune-related RECIST (iRECIST) have been proposed.⁴ Pseudoprogression is established in a post hoc fashion, that is, recognition of pseudoprogression is extremely difficult at the first sign of tumor progression.

It was interesting to explore scenarios to explain the dissociation of primary tumor progression from effusion control in our case. Firstly, pleural effusion was attributed to pleural tumor dissemination, which is typically manifested as small loci (2–3 cm)²¹ compared to the large mass of the primary tumor, providing suitable options for immunotherapy. Secondly, pseudoprogression cannot be ruled out after primary tumor progression.^{4,22} In a recent report, the larger tumor mass detected after the administration of nivolumab only contained immune cells and no tumor cells.²³ Thirdly, the later reduction of the primary tumor was possibly a result of the addition of chemotherapy, which modulated the inflammation milieu.^{24,25}

In conclusion, we report a case of the successful treatment of advanced SqCC with nivolumab and chemotherapy. The early control of pleural effusion preceded that of the primary tumor, and is proposed as an indicator for pseudoprogression. Our experience might be helpful to identify pseudoprogression for the clinical management of immunotherapy.

Disclosure

No authors report any conflict of interest.

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