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CASE REPORT

Case series of pleomorphic carcinomas of the lung treated with nivolumab

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Abstract

Pleomorphic carcinoma (PC) of the lung is a rare type of non-small cell lung cancer, exhibiting aggressive behavior and resistance to chemotherapy and radiotherapy. A previous study reported that PCs expressed high levels of PD-L1, suggesting the potential efficacy of immune checkpoint inhibitors in these tumors. We retrospectively reviewed the clinical records of three patients with PC of the lung treated with nivolumab: a 59-year-old woman (Case 1), a 66-year-old man (Case 2), and an 83-year-old man (Case 3). PD-L1 was highly expressed in their tumor cells. Two cases showed a partial response with long progression-free survival. However, in Case 2, brain and bone metastases progressed during nivolumab treatment in spite of high PD-L1 expression. This case series indicates that nivolumab is effective to some extent for PC of the lung. However, the clinical course of patients treated with nivolumab should be carefully observed, even when PD-L1 is highly expressed.

Introduction

Pleomorphic carcinoma (PC) of the lung is a rare type of non-small cell lung cancer (NSCLC), exhibiting aggressive behavior and resistance to chemotherapy and radiotherapy.[1–3] Genetic alterations are rare in PC, and patients are ineligible for molecular targeted therapy.[4,5]

Programmed death-1 (PD-1) is a receptor expressed on the surface of activated T cells, and binds to its ligands, PD-L1 and PD-L2. Engagement of PD-1 by its ligands suppresses T cell functions by inducing T cell apoptosis, anergy, exhaustion, and the production of immune suppressive cytokines.[6,7] A blockade of the PD-1/PD-L1 pathway restores effector T cell function and enhances anti-tumor immune responses.[8] Nivolumab is a fully human immunoglobulin G4 (IgG4) anti-PD-1 blocking monoclonal antibody approved for the treatment of NSCLC. Randomized phase III studies, CheckMate-017 and CheckMate-057, showed superior efficacy and tolerability of nivolumab over docetaxel in patients with NSCLC with disease progression after treatment with platinum-containing chemotherapy.[9,10]

A previous study reported that PCs expressed high levels of PD-L1, suggesting the potential efficacy of immune checkpoint inhibitors in these tumors.[11] Therefore, we describe three cases with PCs of the lung treated with nivolumab, and focus on the efficacy of nivolumab and PD-L1 expression in the tumor cells.

Case reports

Case 1

A 59-year-old woman underwent right upper lobe sectioning of the lung for early clinical stage NSCLC in September 2015. She was diagnosed with PC of the lung, and was proven to be at pathological stage IIIA. She underwent adjuvant chemotherapy, consisting of cisplatin (80 mg/m^2, day 1) and vinorelbine (25 mg/m^2, days 1 and 8), but was

treated with only one cycle of cisplatin plus vinorelbine because of adverse effects. Multiple brain metastases and left adrenal gland metastasis were recognized as recurrence (Fig 1a) by positron emission tomography-computed tomography (PET-CT) and magnetic resonance imaging in March 2016. She underwent radiosurgery for brain metastases and was treated with carboplatin (AUC 5, day 1), paclitaxel (200 mg/m^2, day 1) and bevacizumab (15 mg/kg, day 1, CPB) as systemic chemotherapy. After two cycles of CPB every three weeks, the adrenal gland metastasis progressed (Fig 1b). Nivolumab was administered as third-line chemotherapy in June 2016.

The adrenal grand gradually reduced in size, and CT images revealed a partial response (PR) after six months (Fig 1c). Furthermore, the accumulation of fluorodeoxyglucose (FDG) on the left adrenal gland disappeared (Fig 1d). Nivolumab treatment continues after 19 cycles. The tumor propensity score (TPS) of PD-L1 in Case 1 was 80–90% (Fig 2a,d).

Case 2

A 66-year-old man was diagnosed with PC of the lung at clinical stage IV in October 2015. He underwent first-line chemotherapy, consisting of carboplatin (AUC 6, day 1), pemetrexed (500 mg/m^2, day 1) and bevacizumab (15 mg/kg, day 1) (CPemB). After five cycles of CPemB every three weeks, the primary lung tumors progressed (best objective response: stable disease [SD]). Nivolumab was administered as second-line chemotherapy in March 2016.

Chest CT images revealed SD, but brain and bone metastases progressed during nivolumab treatment. In

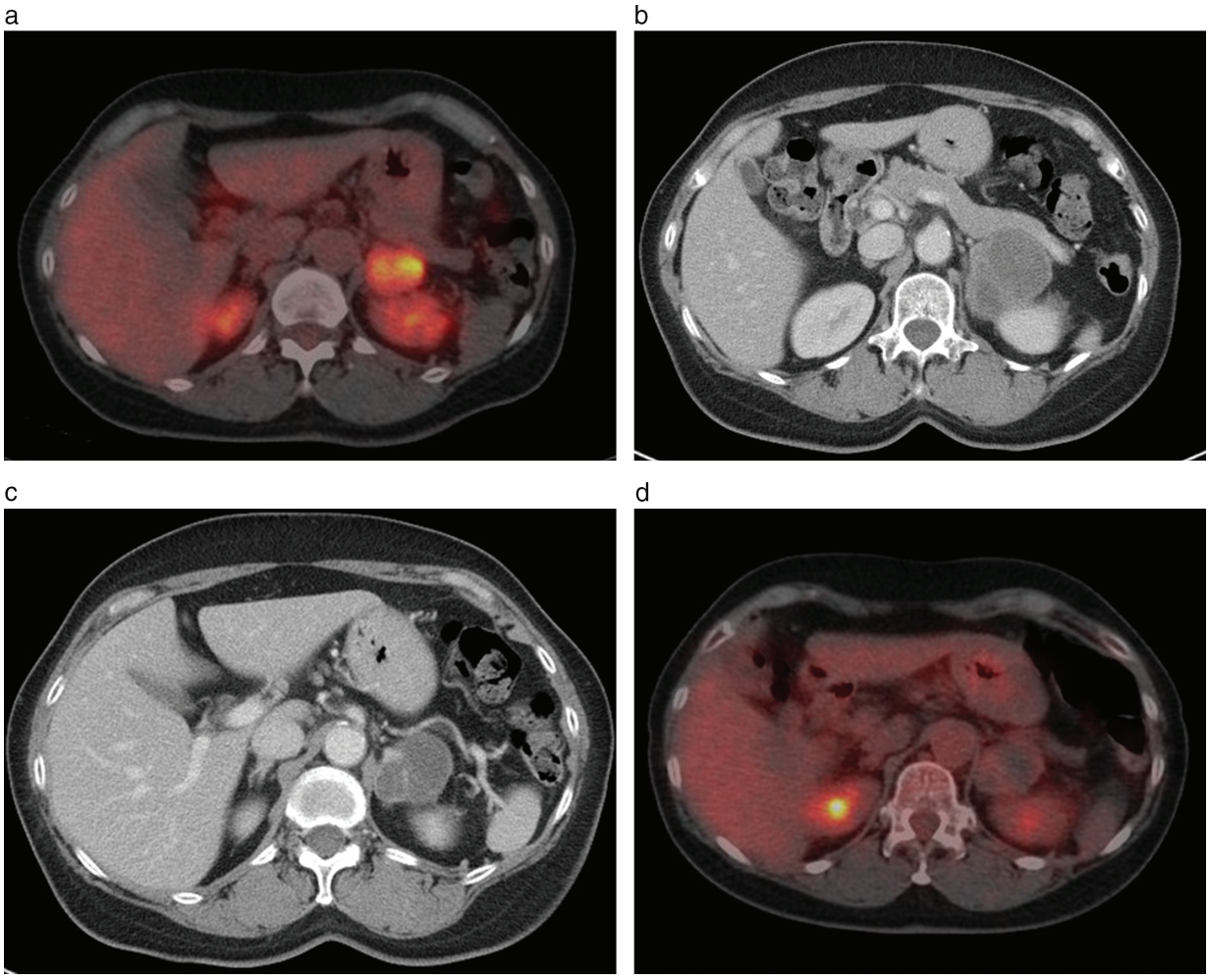

Figure 1 Case 1. (**a**) Positron emission tomography-computed tomography (PET-CT) showed accumulation of fluorodeoxyglucose (FDG) on the left adrenal gland. (**b**) After two cycles of chemotherapy, consisting of carboplatin (AUC 5, day 1), paclitaxel (500 mg/m^2, day 1) and bevacizumab (15 mg/kg, day 1), left adrenal gland metastasis progressed. (**c**) CT images revealed a partial response after 11 cycles of nivolumab treatment: the adrenal grand had reduced in size. (**d**) Accumulation of FDG on the left adrenal gland disappeared after 15 cycles of nivolumab treatment.

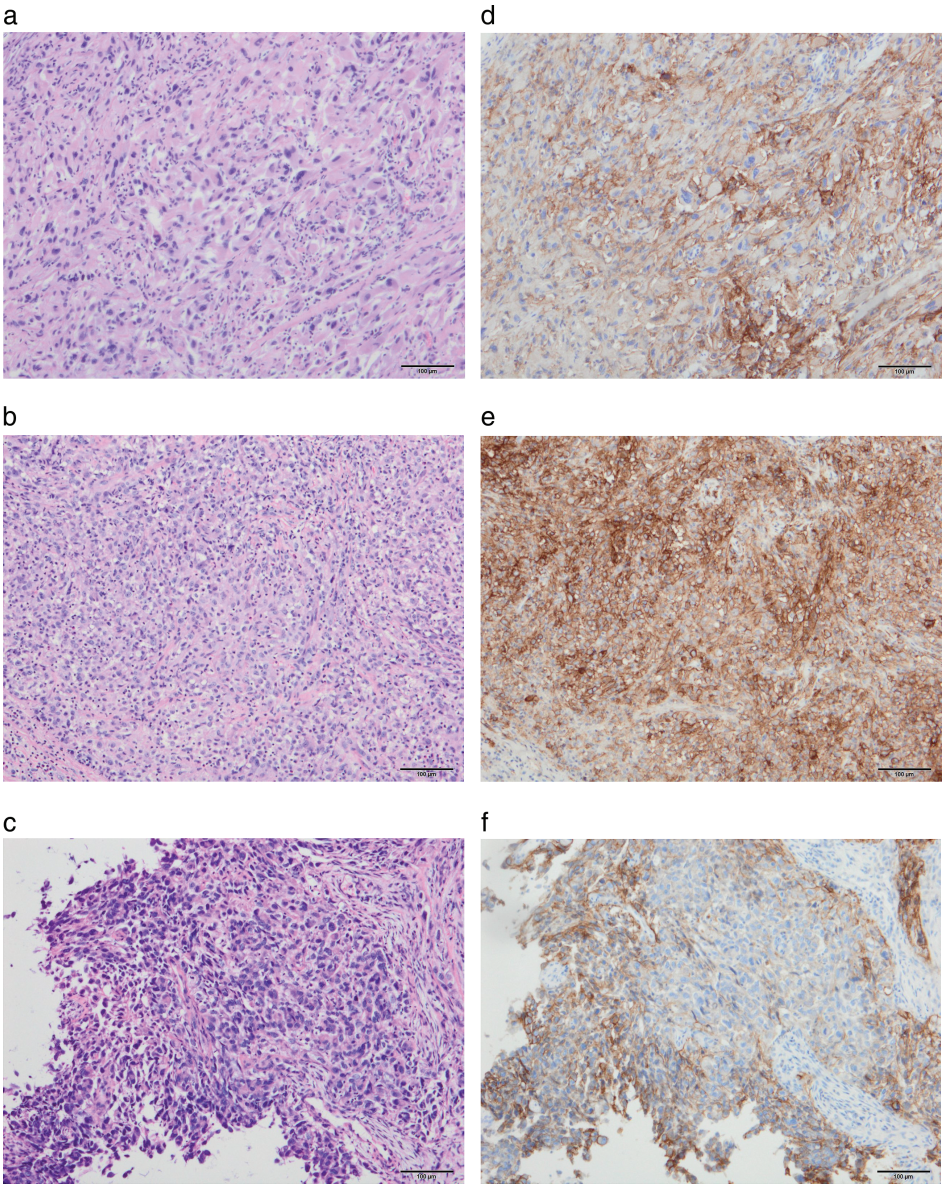

Figure 2 (**a–c**) Hematoxylin and eosin staining in Cases 1–3 (×100 magnification) demonstrated pleomorphic carcinomas with giant cells. (**d–f**) Immunohistochemistry analyses in Case 1–3 (×100 magnification) showed positive immune reactivity for PD-L1 using a rabbit anti-human PD-L1 antibody.

addition, lung tumors progressed after six cycles of nivolumab. The TPS of PD-L1 in Case 2 was over 95% (Fig 2b,e).

Case 3

An 83-year-old man was diagnosed with PC of the lung at clinical stage IIIA in August 2015. Curative radiotherapy was inadequate because of a wide irradiation range. He underwent docetaxel (60 mg/m^2, day 1, every three weeks, 10 cycles) as first-line chemotherapy (best objective response: SD). After two lines of cytotoxic chemotherapy of pemetrexed (500 mg/m^2, day 1, every three weeks, seven cycles; best objective response: SD) and vinorelbine (25 mg/m^2, days 1 and 8, every three weeks, two cycles; best objective response: progressive disease), left-sided pleural effusion emerged (Fig 3a). Nivolumab was administered as fourth-line chemotherapy in October 2016.

Three days after commencing nivolumab treatment, the left-sided pleural and pericardial effusion increased (Fig 3b) and chest drainage and pericardial drainage were required. However, the pleural and pericardial effusion did not increase after drainage. CT images revealed PR with tumor shrinkage (Fig 3c). Nivolumab treatment continues after 10 cycles. The TPS of PD-L1 in Case 3 was 60–70% (Fig 2c,f).

Discussion

This case series indicates that nivolumab is effective to some extent for PC of the lung, known to be generally

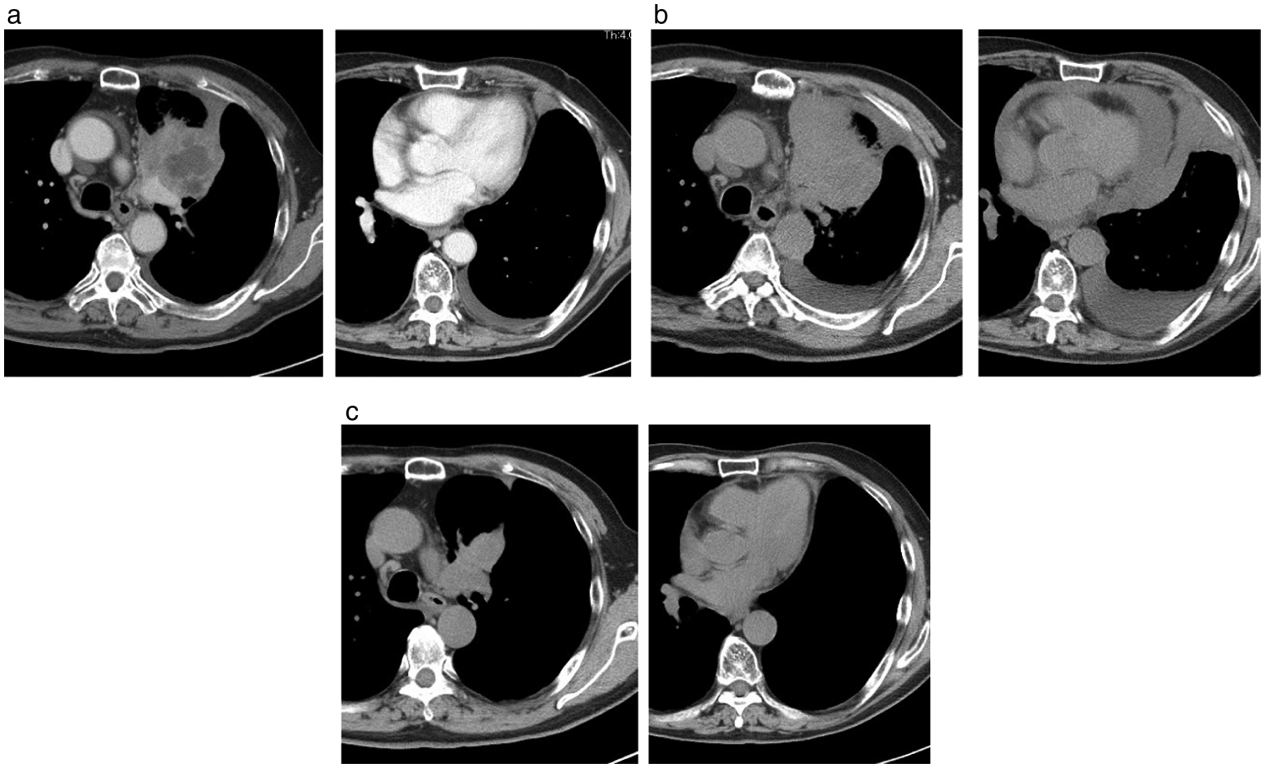

Figure 3 Case 3. (**a**) Chest computed tomography (CT) showed a tumor in the left upper lobe and pleural effusion emerged before nivolumab treatment was initiated. (**b**) Three days after the first administration of nivolumab, left-sided pleural effusion and pericardial effusion progressed. (**c**) After chest and pericardial drainage, a chest CT showed that the lung tumor had reduced, and the left-sided pleural and pericardial effusion did not increase after eight cycles of nivolumab treatment.

resistant to chemotherapy and radiotherapy. A previous study reported that TPS of PD-L1 and PD-L2 were approximately 90% in PCs of the lung.[11] PD-L1 positive PCs were infiltrated by high numbers of CD8 positive tumor-infiltrating lymphocytes. Of note, PD-L1 expression in PCs, but not PD-L2, was significantly higher in sarcomatous compared to carcinomatous areas. Considering several features of PCs, such as PD-L1 expression, marked epithelial-mesenchymal transition, and exuberant immune cell infiltration in tumors, PD-1/PD-L1 pathway-targeted immunotherapy may be a therapeutic avenue for PC of the lung.

A recent case report showed a clinical response in a patient with PC expressing PD-L1.[12] In our case series, PD-L1 was highly expressed in patients with PCs of the lung (Fig 2a–f). Two cases (cases 1 and 3) showed PR with a long period of SD. However, in Case 2, nivolumab achieved only a short progression-free duration, despite high PD-L1 expression. We could not locate any other factors from patient characteristics that would predict clinical outcomes (Table 1). Proposed reasons for the progression are as follows. First, PD-L1 could not reflect the efficacy of nivolumab to all target regions, because of tumor heterogeneity. Second, it could be indicated that there were distinct biomarkers except for PD-L1, predicting therapeutic outcomes of nivolumab. A recent report indicated that clinical failure in patients treated with immune checkpoint inhibitors resulted from an imbalance between T-cell reinvigoration and tumor burden.[13] An intermediate or high tumor mutation burden was identified in PC,[14] which might be a potent biomarker to predict therapeutic outcomes of immune checkpoint inhibitors.

Table 1 Treatment programs

Case	Age	Gender	Brinkman index	Lines of therapy	Nivolumab courses	Nivolumab response	TPS
Case 1	59	F	76	3	19 (ongoing)	PR	80–90%
Case 2	66	M	600	2	7	SD	95% ≥
Case 3	83	M	1200	4	11 (ongoing)	PR	60–70%

PR, partial response; SD, stable disease; TPS, tumor propensity score.

The clinical course of patients treated with nivolumab should be carefully observed, even when PD-L1 is highly expressed. Our case series warrants further investigation into the elucidation of PC of the lung, which could lead to the development of a new therapeutic strategy for this intractable disease.

Disclosure

No authors report any conflict of interest.

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