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CASE REPORT

Successful treatment with nivolumab for lung cancer with low expression of PD-L1 and prominent tumor-infiltrating B cells and immunoglobulin G

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Abstract

Little is known about the anti-tumor activity of humoral immunity in lung cancer patients treated with nivolumab, an immune checkpoint inhibitor. Herein, we report a case of lung cancer with 5% expression of PD-L1, in which a partial response to nivolumab was sustained for > 7 months. Immunohistochemical analysis of the metastatic lymph node biopsy specimen showed prominent accumulation of plasma cells and immunoglobulin G. These findings suggest that pre-existing humoral immunity may be worth considering as a candidate therapeutic biomarker of nivolumab in some lung cancer patients.

Introduction

Programmed death-ligand 1 (PD-L1) expression is a biomarker predictive of clinical benefit of programmed death-1 (PD-1) blockade for lung cancer. In view of the response rate, the PD-1 blocker nivolumab is effective, even in the 11% of patients with pulmonary non-squamous cell carcinoma showing < 10% PD-L1 expression.[1] However, there may be unknown underlying mechanisms other than PD-L1 expression. A recent study showed that tumor mutation burden is a predictive factor for treatment with PD-1/PD-L1 inhibitors, irrespective of PD-L1 expression.[2] We have reported that both humoral and cell-mediated immunity against the cancer-testis antigen NY-ESO-1 was activated in a case of lung cancer expressing the antigen, in which the tumor spontaneously regressed.[3] The activation of humoral immunity may contribute to antitumor immunity. To the best of our knowledge, however, there have been no studies of humoral immunity in lung cancer patients treated with nivolumab. Thus, we report a lung cancer case with low PD-L1 expression showing a partial response to nivolumab, associated with prominent accumulation of B cells and immunoglobulin G (IgG).

Case report

A 56-year-old male current smoker was referred to our hospital for evaluation of a lung mass developing from a bulla wall on chest radiography. Chest computed tomography showed a 70 mm solid mass in the right upper lobe (Fig 1a, b). Although a diagnosis of pulmonary large-cell carcinoma was eventually made by transbronchial re-biopsy, there were inadequate cancer cells to examine therapeutic biomarkers, such as *EGFR* mutations, *ALK* rearrangements, and PD-L1 expression. A systemic survey including positron emission tomography showed stage IV (cT3N2M1b) disease with bone metastasis.

At the patient's request, two courses of the combination chemotherapy of cisplatin, pemetrexed, and bevacizumab

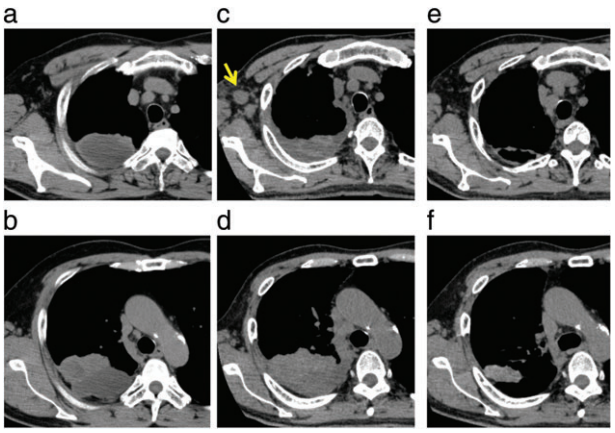

Figure 1 Chest computed tomography scans in a patient with pulmonary large cell carcinoma. Before treatment with cisplatin/pemetrexed/bevacizumab, (**a**) no tumor is observed in the right axillary lymph nodes, and (**b**) a 70 mm mass is detected in the right upper lung lobe. Before treatment with nivolumab, after two courses of cisplatin/docetaxel therapy, (**c**) new metastases are seen in the right axillary lymph nodes (arrow), and (**d**) the lung mass has increased to 75 mm in diameter. After the 10th administration of nivolumab, (**e**) axillary lymph node enlargement is no longer observed, and (**f**) the lung tumor has decreased to 30 mm in diameter.

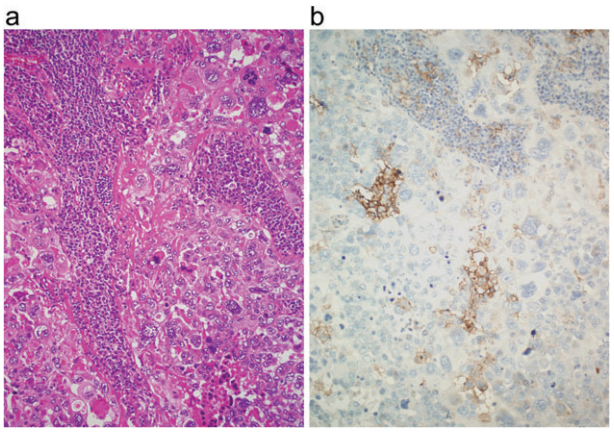

Figure 2 Photomicrographs of the lymph node biopsy specimen taken from a patient with pulmonary large-cell carcinoma. (**a**) Cancer cells with large-sized nuclei and clusters of plasma cells and lymphocytes are observed (hematoxylin & eosin stain, original magnification 200×). (**b**) Immunohistochemical examination shows that 5% of the tumor cells express PD-L1 at a weak intensity (22C3 clone stain, original magnification 200×).

were administered. New metastatic lesions in the right axillary lymph nodes appeared, and the patient did not respond to the two subsequent courses of cisplatin and docetaxel (Fig 1c,d). He underwent surgical biopsy of the right axillary lymph node to examine the therapeutic biomarkers. The whole lymph node had been overrun with cancer cells, along with prominent infiltration of plasma cells and lymphocytes (Fig 2a). On immunohistochemical examination, 5% of the cancer cells expressed PD-L1 (Fig 2b; 22C3, Dako, Santa Clara, CA, USA), but no *EGFR* mutations or *ALK* arrangements were detected. Five months after the initiation of chemotherapy, the treatment regimen was revised to nivolumab as third-line. The lung tumor and the metastases to the axillary lymph nodes regressed rapidly, and a partial response was achieved on the third administration. The patient's lung cancer has remained in partial remission for seven months (Fig 1e,f). Written informed consent for the publication of this case report was obtained from the patient.

Immunohistochemical examination of the lymph node biopsy specimen indicated prominent stromal infiltration of $CD138^+$ plasma cells and $CD20^+$ B cells, and IgG was also detected (Fig 3a–c), although IgG4 and IgA were hardly detected (Fig 3d,e). Infiltration of $CD3^+$ T, $CD8^+$, and $CD4^+$ cells was less predominant than that of the B cell lineage (Fig 4a–c). Small numbers of PD-1^+ small-sized mononuclear cells and $FOXP3^+$ regulatory T cells were scattered (Fig 4d,e). The antibody clones used were as follows: CD3 (F7.2.38, Dako); CD8 (4B11), CD20 (L-26), IgG

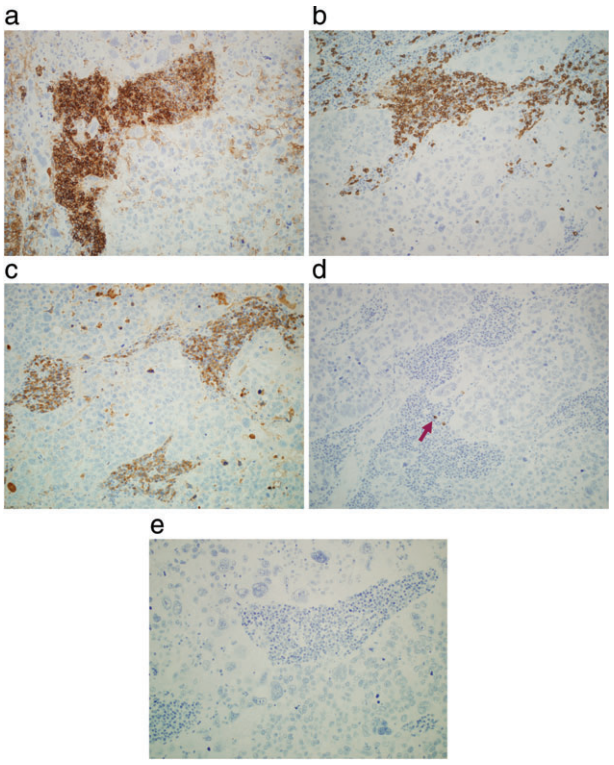

Figure 3 Immunohistochemical examination of tumor-infiltrating immune cells in a patient with pulmonary large-cell carcinoma. (**a**) $CD138^+$ plasma cells, (**b**) $CD20^+$ B cells, (**c**) immunoglobulin (Ig)G, and (**d**) IgG4 (arrow) are observed within the metastatic lymph node, while (**e**) IgA is not detected (original magnification 200×).

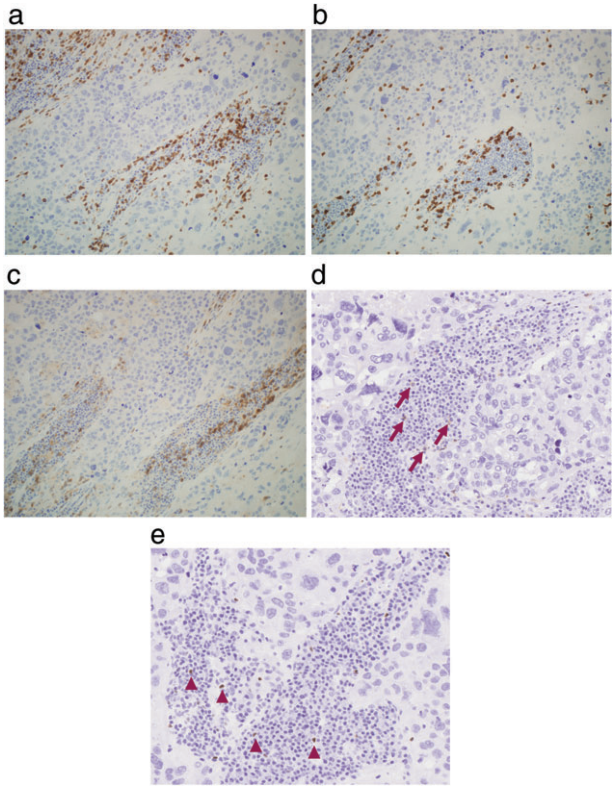

Figure 4 Immunohistochemical examination of tumor-infiltrating immune cells in a patient with pulmonary large-cell carcinoma. (**a**) $CD3^+$ T cells, (**b**) $CD8^+$ cells, (**c**) $CD4^+$ cells, (**d**) PD-1^+ cells (arrows), and (**e**) $FOXP3^+$ regulatory T cells (arrowheads) are observed within the metastatic lymph node (original magnification 200×).

(IS512), IgA (A0262), CD4 (4B12, Leica Biosytems, Nussloch, Germany); PD-1 (SP269, Spring Bioscience, Pleasanton, CA); FOXP3 (236A/E7, Abcam, Cambridge, UK); CD138 (B-A38, Nichirei Biosciences, Tokyo, Japan); and IgG4 (HP6025).

Discussion

In this case study, tumor-infiltrating plasma cells and IgG were prominent in the metastatic lymph nodes. In patients with resected lung cancer, tumor-infiltrating plasma cells and the Ig kappa chain are considered prognostic factors.[4] In contrast, the subgroup of plasma cells is known to suppress antitumor effects. These immunosuppressive plasma cells frequently express IL-10, IgG4, IgA, and PD-L1.[5–7] In the present case, plasma cells did not express these immunosuppressive phenotypes. Tumor-infiltrating plasma cells produced the various specific antibodies to cancer-testis antigens, such as LAGE-1, the MAGE family, and NY-ESO-1 in lung cancer.[8] In advanced lung cancer, the presence of circulating XAGE-1 antibody to its cancer-testis antigen indicated favorable survival in association with activating the antigen-specific T cells.[9] Tumor-infiltrating plasma cells may be, at least in part, involved in anti-tumor effects through the production of tumor-specific antibodies.

Another important finding in this case was that tumor-infiltrating B cells were prominent. B cells can inhibit tumor growth through antigen presentation to T cells, immunostimulatory cytokine secretion, and direct tumor cell killing.[10] In non-small cell lung cancer, tumor-infiltrating B cells were correlated with favorable survival.[8,11] In contrast, the subsets of B cells, known as regulatory B cells, can promote tumor growth, although a common marker of regulatory B cells has not been identified. Regulatory B cells frequently express IL-10, PD-L1, and PD-1, which inhibit T cell function through the expansion of regulatory T cells.[12] In the present case, B cells did not express PD-L1 or PD-1, and few regulatory T cells were observed. The present findings encourage further investigation to evaluate how much tumor-infiltrating B cells contribute to anti-tumor activity.

A limitation regarding the clinical course of our patient needs to be considered. The axillary lymph node specimen was obtained before treatment with nivolumab, thus little is known of the effects of nivolumab on B cells. The PD-1 blocker, pembrolizumab, is reported to increase the number of intratumoral B cells, as well as T cells.[13] In a mouse model, PD-1 blockade enhanced the response to the antigen-specific antibody by promoting the accumulation of helper T cells.[14] In a case of nivolumab-induced interstitial nephritis, IgG^+ plasma cells and T cells accumulated in the kidney.[15] Nivolumab can facilitate humoral immunity against cancers, as well as cell-mediated immunity. Investigations of humoral immunity using tissue biopsy specimens before and after nivolumab therapy may shed light on this issue.

In the present case, the antitumor activity of nivolumab may have been associated with pre-existing humoral immunity. Further studies using a large cohort are needed to elucidate whether intratumoral B cells and antibodies could serve as candidate therapeutic biomarkers of PD-1 blockade in some patients with lung cancer.

Disclosure

No authors report any conflict of interest.

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