Clinical Case Report

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Immunotherapy for pulmonary squamous cell carcinoma and colon carcinoma with pembrolizumab

A case report

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Abstract

Rationale: Novel treatment strategies such as immunotherapy are being evaluated to further improve the outcomes of colorectal cancer patients. To our knowledge, this is the first report to show both the successful treatment of pulmonary squamous cell carcinoma (SCC) with pembrolizumab alongside histological and immunohistochemical findings of resected colon cancer under immunotherapy for lung cancer.

Patient concerns: This patient was a 70-year-old man who presented with a right lung tumor and simultaneous adenocarcinoma of the sigmoid colon.

Diagnoses: Biopsy examination revealed squamous cell carcinoma in the right lung and adenocarcinoma of the sigmoid colon.

Interventions: The patient underwent successful pembrolizumab treatment as first-line immunotherapy for lung cancer, as demonstrated by computed tomography, and the sigmoid colon tumor was excised during an immunotherapy-free window.

Outcomes: No unusual tumor growth in the right lung or abnormal abdominal signs was observed during the 9-month follow-up.

Lessons: Microscopically, the resected colon cancer specimen was characterized by numerous lymphoid cells in the partial stroma, with a large number of infiltrating lymphocytes consisting of CD3+, CD8+ T cells. In summary, this case demonstrates how immunotherapy affects PD-L1-negative colon cancer and indicates future treatment prospects.

Abbreviations: CEA = carcinoembryonic antigen, CT = computed tomography, CTL = cytotoxic T lymphocyte, FDG-PET = fluorodeoxyglucose-positron emission tomography, HE = hematoxylin and eosin staining, NSCLC = non-small cell lung cancer, PD-1 = programmed death 1, PD-L1 = programmed death-ligand 1, SCC = squamous cell carcinoma, SUVmax = maximum standardized uptake value.

Keywords: colorectal cancer, immune checkpoint, immunotherapy, PD-1, PD-L1

1. Introduction

Recently, programmed death 1 (PD-1)-blocking antibodies have been approved for the treatment of non-small cell lung cancer (NSCLC), melanoma, and renal cancer.[1,2] Pembrolizumab, a humanized monoclonal antibody against PD-1, was approved as a first-line treatment for NSCLC in cases in which programmed death-ligand 1 (PD-L1) is strongly expressed.[2] We here present a case of squamous cell carcinoma (SCC) in the right lung with simultaneous adenocarcinoma of the sigmoid colon. The patient underwent successful pembrolizumab treatment as a first-line immunotherapy for lung cancer, as demonstrated by computed tomography (CT). The sigmoid colon tumor was excised during an immunotherapy-free window. To our knowledge, little is known at the cellular level regarding the effects of PD-1 inhibition and this is the first report of the immunotherapeutic effects of T cell activation in resected sigmoid colon adenocarcinoma.

2. Case report

A 70-year-old Japanese man, who was a former light smoker (20 cigarettes a day, quit 5 years ago), was admitted to our hospital presenting with colon cancer and right chest pain. Colonoscopy revealed a Bormann type III tumor in the sigmoid colon, and histopathological evaluation of the biopsy specimen revealed a well-differentiated adenocarcinoma, showing unclear findings of necrotic tumor cells and infiltration of a small number of lymphocytes in the tumor (Fig. 1). Fluorodeoxyglucose-positron emission tomography (FDG-PET)-CT was performed, and FDG accumulation was observed in a solid tumor (maximum diameter, 47 mm) with a maximum standardized uptake value (SUVmax) of 11.4 in the periphery of the lower lobe of the right lung (Fig. 2). In addition, swelling of several mediastinal lymph nodes was observed with a SUVmax of 9.8, along with numerous nodule-like structures in the right pleura, indicating pleural seeding and right pleural effusion. FDG accumulation was also

Editor: N/A.

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:19(e0718)

Received: 17 January 2018 / Accepted: 18 April 2018

http://dx.doi.org/10.1097/MD.0000000000010718

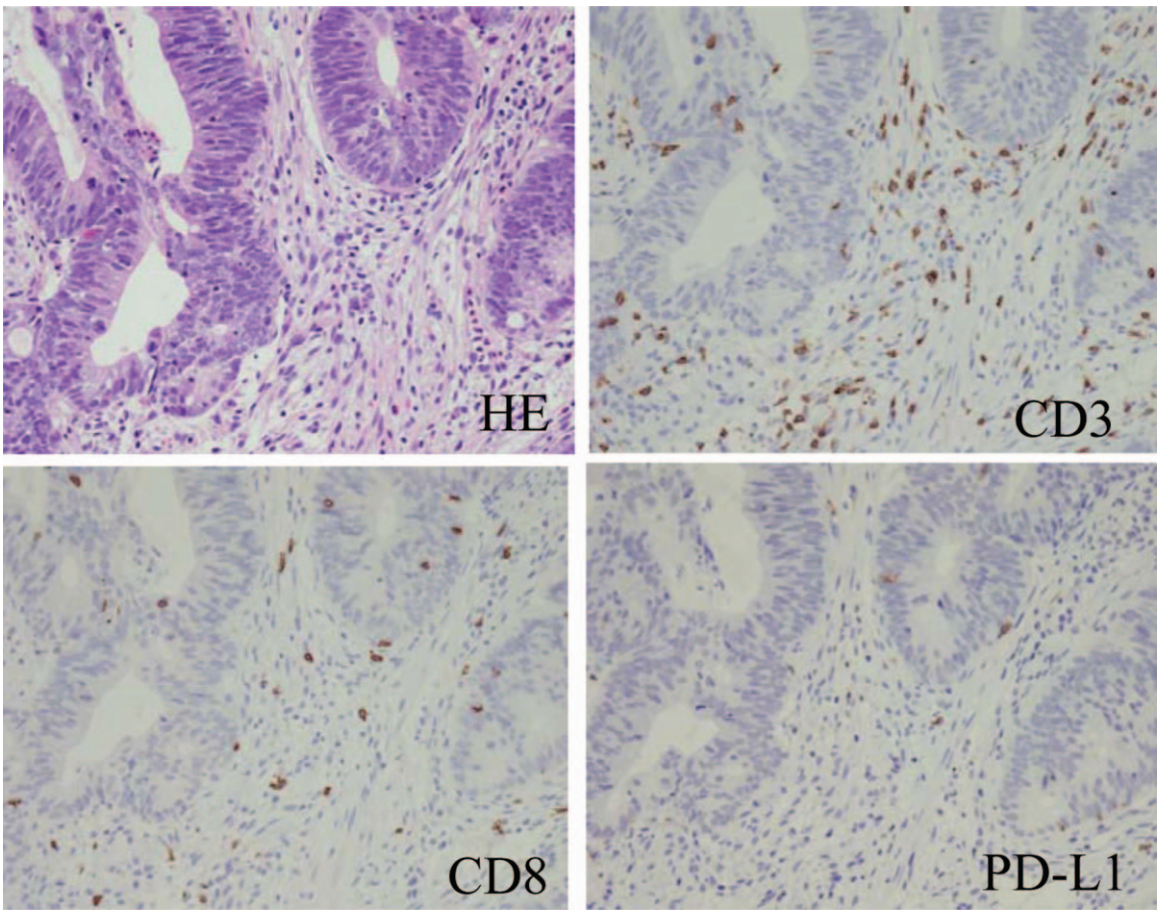

Figure 1. Histopathological examination of the colon biopsy specimen (HE: adenocarcinoma) and immunohistochemical staining of CD3, CD8, and PD-L1.

noted in the sigmoid colon with a SUVmax of 12.4. A CT-guided biopsy examination revealed lung cancer showing SCC, and immunohistochemistry indicated the tumor was 90–100% positive for PD-L1 (Fig. 3). The clinical stage was diagnosed as cT2bN3M1a, and TNM classification placed it as stage IVA. High levels of the tumor marker serum SCC antigen were recorded (6 ng/mL; normal range, <1.4 ng/mL), but carcinoembryonic antigen (CEA) levels were normal (normal range, <5.0 ng/mL).

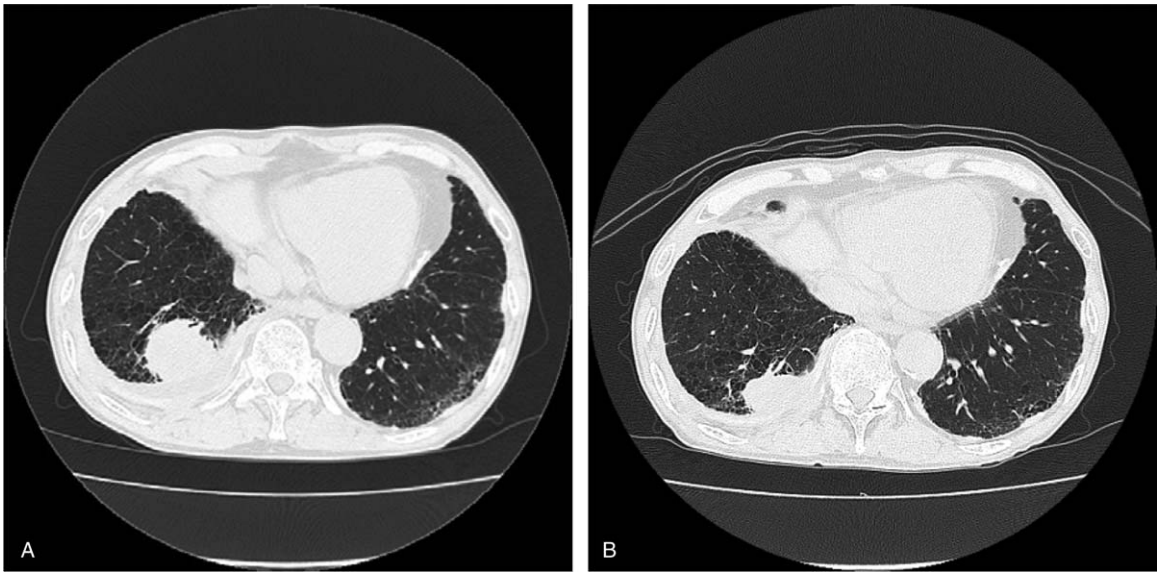

Figure 2. CT of lung before (A) and after (B) immunotherapy. CT = computed tomography, HE = hematoxylin and eosin staining.

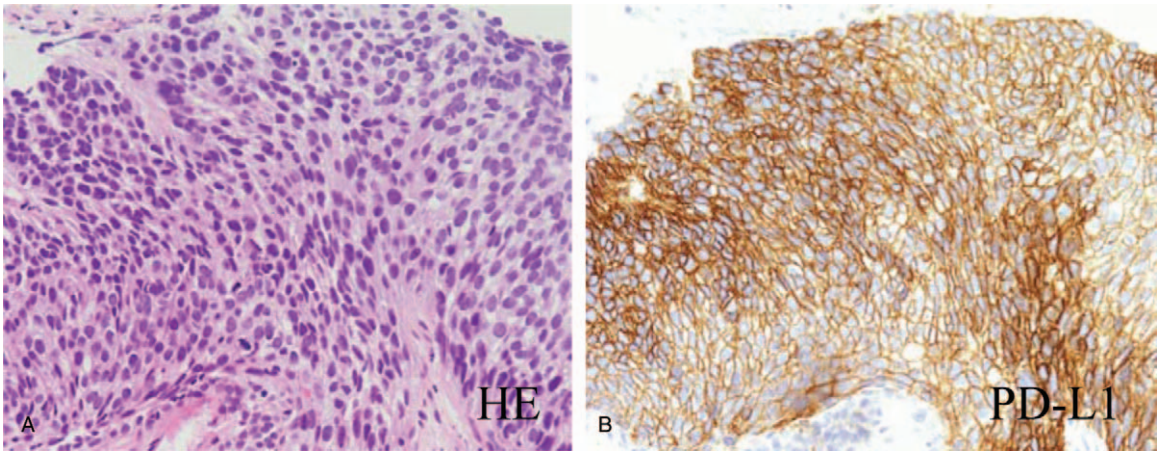

Figure 3. Histopathological examination of the pulmonary CT-guided biopsy specimen (HE: SCC) and immunohistochemical staining of PD-L1. CT = computed tomography, HE = hematoxylin and eosin staining.

First-line immunotherapy with pembrolizumab (200 mg) was initiated and one course of immunotherapy was carried out. After treatment with pembrolizumab for 2 weeks, the patient experienced a skin rash, mainly in the lower limbs (Grade 3) and liver dysfunction (Grade 1), and thus glucocorticoid treatment was administered in the form of prednisone (1.0 mg/kg/d) to treat these side effects. After 13 days of glucocorticoid treatment, the side effects recovered to Grade 1. CT examination after 34 days of treatment revealed decreased pleural effusion, reduced tumor size from 47.0 to 22.4 mm (Fig. 2), and serum SCC antigen levels within the normal range (0.9 ng/mL). Pembrolizumab led to a dramatic response in this patient, but administration was delayed for treatment of its side effects. After a drug holiday, the decision was taken to treat the sigmoid colon cancer and a laparoscopic sigmoidectomy was performed after 62 days.

Gross examination of the resected sigmoid colonic surgical specimen revealed a polyp of approximately 1.5 cm in size and an ulcerative, annular, neoplastic mass measuring about 6.5 cm at its largest diameter (Fig. 4).

Microscopically, the polyp revealed carcinoma in adenoma, and showed many lymphocytes infiltrating the stroma in the partial carcinomatous lesion, with a small number of lymphocytes infiltrating the adenoma. However, the neoplastic mass corresponded to a colonic carcinoma growing in an irregular tubular structure. It was characterized by a large number of lymphoid cells in the invasive carcinomatous margin, while denatured carcinoma and necrotic cells were conspicuous in carcinomatous glands. None of the dissected lymph nodes revealed tumor metastasis. The final pathological staging was pStageIIB (T4a, N0, and M0) according to TNM classification.

With respect to the immunohistochemistry, the biopsy specimen showed a small number of CD3+, CD4+ and CD3+, CD8+ T cells and it was almost negative for cytotoxic molecule expression (granzyme-B and TIA-1). PD-1 was expressed on a few lymphocytes, while the tumors were PD-L1-negative (Fig. 1). However, in >70% of the invasive carcinomatous margin of the resected specimen, the infiltrating lymphocytes consisted of CD3+ and CD8+ T cells with a large number of cytotoxic molecules (Fig. 4). PD-1 expression was observed on a few lymphocytes and stromal cells, and a small number of CD20+ B cells were among the infiltrating lymphocytes. PD-L1 expression was weakly observed on a few non-neoplastic stromal cells. The carcinomatous lesions in the adenoma also showed the same lymphocyte infiltration as those in the invasive carcinomatous margin.

The patient continues to be followed-up as an outpatient at 9 months postoperatively, and no colon cancer recurrence has been observed. Furthermore, their lung cancer has remained stable, and therapy with pembrolizumab was continued until February 2018.

The patient provided written informed consent prior to the preparation of this case report and this study also was approved by the ethics committee of our hospital (No.17-020).

3. Discussion

Immune checkpoint inhibitors have shown promising results in clinical trials and are considered to be the standard treatment for advanced NSCLC. However, novel treatment strategies such as immunotherapy are being evaluated to further improve the outcome of colorectal cancer patients. Here, we present a case report that may clarify the relationship between T cells and neoplastic cells in resected sigmoid colon cancer and concurrent PD-1 monoclonal antibody-treated lung cancer.

T cells, especially cytotoxic T lymphocytes (CTLs) and IFN-γ-secreting Th1 and polyfunctional T cells, play a critical role in controlling tumor growth.[3] Upon presentation of the specific antigen by antigen-presenting cells, CD8+ T cells can kill tumor cells by multiple mechanisms, mainly involving the release of perforin and granzymes. The presence of CD3+, CD8+ T cells in tumors correlates with a better prognosis for patients, as shown in cancer types including melanoma, colon cancer, breast cancer, renal cell carcinoma, and ovarian cancer.[4–11] The current case was characterized by a large number of lymphoid cells in the partial stroma. Furthermore, the first biopsy specimen showed a small number of CD4+ and CD8+ T cells, but in the partially invasive carcinomatous margin of the resected specimen a large amount of infiltrating lymphocytes consisted of a large number of CD8+ T cells with many cytotoxic molecules. Following immunotherapy, denatured and necrotic cells were observed. It is thought that the presence of many infiltrating CD8+ T cells with cytotoxic molecules within the tumor is a result of the immunotherapy and may be indicative of a better response to treatment.

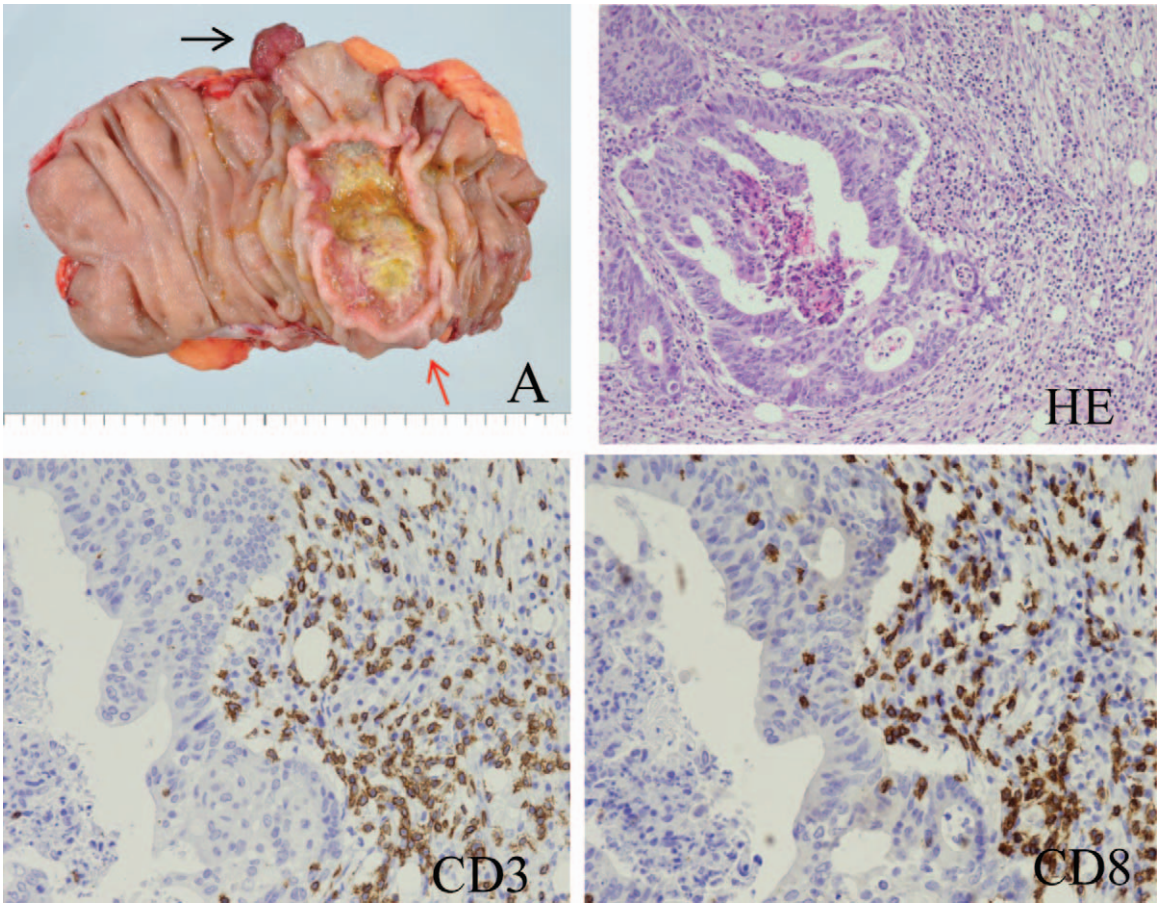

Figure 4. The resected sigmoid colon (A) contains two separate tumors; one is a polyp of carcinoma in adenoma (black arrow), and the other is an ulcerative, annular, neoplastic mass (red arrow). Microscopic findings of the resected specimen (HE) and immunohistochemical staining of CD3 and CD8. HE = hematoxylin and eosin staining.

The expression of PD-L1 correlated with worse prognosis in melanoma, RCC, and hepatocellular carcinoma patients.[12–14] In contrast, Dunne et al[15] found a correlation between PD-L1 expression and immune cell infiltration in colorectal cancer patients, and PD-L1 expression was correlated with better survival. PD-L1 expression was not significantly associated with CD3+, CD8+ or CD45RO+ cell density, pathological lymphocytic reactions or patient survival prognosis in colorectal cancer.[16] In this immunohistochemical study, PD-L1 was strongly expressed in pulmonary SCC, and the patient experienced excellent local control with immunotherapy as a first-line treatment for lung cancer. However, PD-L1 expression was observed neither in neoplastic cells nor in the stromal cells of the colon tumor. Pembrolizumab blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2, and the effect of blocking an interaction such as PD-L2 may be useful for CD8 + T cell activation and infiltration to the tumor in this case. However, no correlation between PD-L1 expression and the prognosis of this colon cancer case had been identified at the time of publication. This case, which was negative for PD-L1 expression, is an important example of how immunotherapy can affect colon cancer and suggests its potential as a future treatment option. Patients exhibiting PD-L1 expression on tumor cells and with preexisting CD8+ T cell infiltration may be more responsive to colon cancer immunotherapy.

In conclusions, to our knowledge, this is the first report to show both the successful treatment of pulmonary SCC with pembrolizumab and the histological and immunohistochemical findings of resected colon cancer under immunotherapy for lung cancer. These findings may indicate the promise of this treatment as a therapeutic candidate for several cancers.

Acknowledgments

The authors thank Hiroko Matuki, Terumi Futaki, Hirokatsu Moriai, and Hideki Kobayashi for their excellent work of IHC, and Dr H. Nikki March of Edanz Ltd. for carefully proofreading the manuscript.

Author contributions

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