Case Reports in Oncology

Case Rep Oncol 2018;11:688–692

DOI: 10.1159/000493187
Published online: October 31, 2018

Case Report

Successful Use of Pembrolizumab to Treat Refractory Thymic Carcinoma with High PD-L1 Expression

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Keywords
Thymic carcinoma · Pembrolizumab · PD-1 · PD-L1

Abstract
Thymic carcinoma is a relatively rare and aggressive thymic epithelial tumor. Herein, we report successful treatment of thymic carcinoma with pembrolizumab. A 68-year-old woman was admitted to our hospital for evaluation of chest pain. Chest computed tomography showed a mass in the anterior mediastinum and lymphadenopathy in the left cervical lymph node. Analysis of biopsy specimens detected squamous cell carcinoma in the left cervical lymph node, and immunohistochemical analysis showed 100% expression of programmed death-ligand 1 (PD-L1). Masaoka-Koga stage IVb thymic carcinoma was ultimately diagnosed. Since 3 cycles of first-line chemotherapy did not result in improvement, pembrolizumab was administered as second-line treatment every 3 weeks at a dosage of 200 mg. After 3 cycles of pembrolizumab treatment, the size of the anterior mediastinal tumor and metastatic lesions had notably decreased. Pembrolizumab may prove to be an effective therapy for thymic carcinoma with high PD-L1 expression.

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Introduction

Thymic carcinomas are rare and aggressive tumors [1, 2]. They arise from the thymic epithelium and constitute 10–40% of thymic epithelial tumors [3, 4]. Although the recommended treatment for localized disease is surgical resection, such tumors are often unresectable. For advanced-stage unresectable tumors, the standard treatment is systemic chemotherapy. Platinum-based regimens such as carboplatin plus paclitaxel [5] are generally used, but the response rate is disappointing: less than 50% [5, 6]. A novel treatment strategy is therefore urgently needed. However, the rarity of the disease precludes large clinical trials, and development of new drugs has been slow [1].

Immune checkpoint inhibitors have been effective for various cancer types. Anti-programmed cell death 1 (PD-1) is expressed on the surface of activated T cells, and it regulates T cell activity to prevent excess immune responses. Its ligand, programmed death ligand 1 (PD-L1), is reported to be expressed on T and B lymphocytes, antigen-presenting cells, and human cancer cells, including those of the skin (melanoma), ovary, colon, lung, and breast [7]. PD-L1 expression on tumor tissues, as detected by immunohistochemistry, was associated with response to anti-PD-1 treatment in non-small cell lung cancer [8, 9].

Herein, we describe treatment for a thymic carcinoma with high expression of PD-L1. Administration of the PD-1 antibody pembrolizumab resulted in marked tumor regression without severe adverse events.

Case Report

A 68-year-old woman was admitted to our hospital for evaluation of chest pain and swelling of the left cervical lymph node in October 2017. The Eastern Cooperative Oncology Group (ECOG) performance status was 1. She was a never-smoker and had no history of autoimmune disorders. Cardiomegaly was detected on chest radiography. Chest computed tomography revealed a large mass in the anterior mediastinum, lymphadenopathy in the left cervical lymph node, and dissemination to the right pleura (Fig. 1a, b), as well as high uptake of fluoro-2-deoxy-D-glucose in positron emission tomography (Fig. 2). Pathological analysis of the left cervical lymph node showed malignant cells with abnormal rounded nuclei composing an alveolar structure without immature lymphocytes in the background (Fig. 3a). Malignant cells were positive for p40 and CD117 (Fig. 3b). Thymic carcinoma was thus diagnosed, and the clinical stage corresponded to Masaoka-Koga stage IVb [2]. Immunohistochemistry (Dako 22C3 IHC platform) detected PD-L1 expression on 100% of tumor cells (Fig. 3c).

Carboplatin plus nab-paclitaxel was introduced as first-line therapy. However, after 3 cycles of therapy, the metastatic lesions in the right pleura had progressed (Fig. 1d). In addition, she developed sustained fever without evidence of neutropenia or infectious disease, as determined by clinical and laboratory investigations. Neoplastic fever was diagnosed, and first-line chemotherapy was judged ineffective. Pembrolizumab was then administered as second-line treatment every 3 weeks at a dosage of 200 mg from March 2018. After 3 cycles of pembrolizumab treatment, the size of the anterior mediastinal tumor and metastatic lesions of the right pleura notably decreased, indicating a partial response. Moreover, her body temperature normalized. Further reductions in tumor size were noted after 6 cycles of pembrolizumab (Fig. 1e, f). At this writing, pembrolizumab therapy has been ongoing for 8 cycles, and no serious adverse event or tumor progression has been observed.

Discussion

Several studies have investigated PD-L1 expression in thymic carcinomas. Although PD-L1 is primarily expressed on cortical and medullary thymic epithelial cells [10], Padda et al. [11] reported that staining intensity was significantly higher in thymic epithelial tumors than in normal thymus and that staining intensity inversely correlated with outcome. Katsuya et al. [12] reported that PD-L1 staining was positive in 22/102 (23%) thymic carcinomas, when 1% was used as the cutoff score. Weissferdt et al. [13] reported that PD-L1 staining was positive in 14/26 (54%) thymic carcinomas, when the cutoff value was defined as 5%. Although staining rates probably varied because of the different PD-L1 antibody clones used in immunohistochemical analysis and the different cutoff values utilized, the authors concluded that thymic carcinomas highly express PD-L1. Therefore, inhibition of the PD-1/PD-L1 axis by anti-PD-1 or anti-PD-L1 antibodies might be a promising treatment for thymic carcinoma.

Two recent phase 2 clinical trials studied PD-1 antibody treatment for thymic carcinomas [14, 15]. Giaccone et al. [14] recruited 37 patients with advanced thymic carcinoma treated by pembrolizumab. The overall response rate was 23%, and the disease control rate was 75%. Progression-free survival and overall survival were longer in patients with high PD-L1 expression (>50%) than in those with low or no PD-L1 expression. Cho et al. [15] studied 33 patients with thymic epithelial tumors for whom platinum-based systemic chemotherapies were unsuccessful. The overall response rate was 21%, and the disease control rate was 79% in their patients. All 5 patients with high (>50%) PD-L1 expression, as detected by immunohistochemistry, showed disease improvement after pembrolizumab treatment, whereas no response was observed in all 10 patients with low PD-L1 expression [15]. In the present patient, immunohistochemical analysis of tumor tissues showed 100% positivity for PD-L1 expression, and pembrolizumab treatment as second-line chemotherapy resulted in a significant response in primary and metastatic lesion of thymic carcinoma, as was the case in the clinical trials. These findings indicate that PD-L1 expression could be a useful biomarker for pembrolizumab treatment in thymic carcinomas, even in patients already treated with platinum-based chemotherapy.

In conclusion, this is the first report of successful pembrolizumab treatment of thymic carcinoma in a Japanese patient in a clinical setting. Our findings indicate that anti-PD-1 antibodies might be a novel treatment for thymic carcinoma, in particular for those with high PD-L1 expression.

Acknowledgement

We would like to thank David Kipler for English language editing.

Statement of Ethics

The authors have no ethical conflicts to disclose. Written consent was obtained from the patient for publication of this case report.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

Author Contributions

T.I. and K.I.: study design, manuscript preparation; N.T. and K.S.: analysis of pathology data and manuscript review; M.S., Y.N., S.S., T.I., and S.H.: clinical data analysis and manuscript review. All authors contributed to reviewing the manuscript and have approved the final version.

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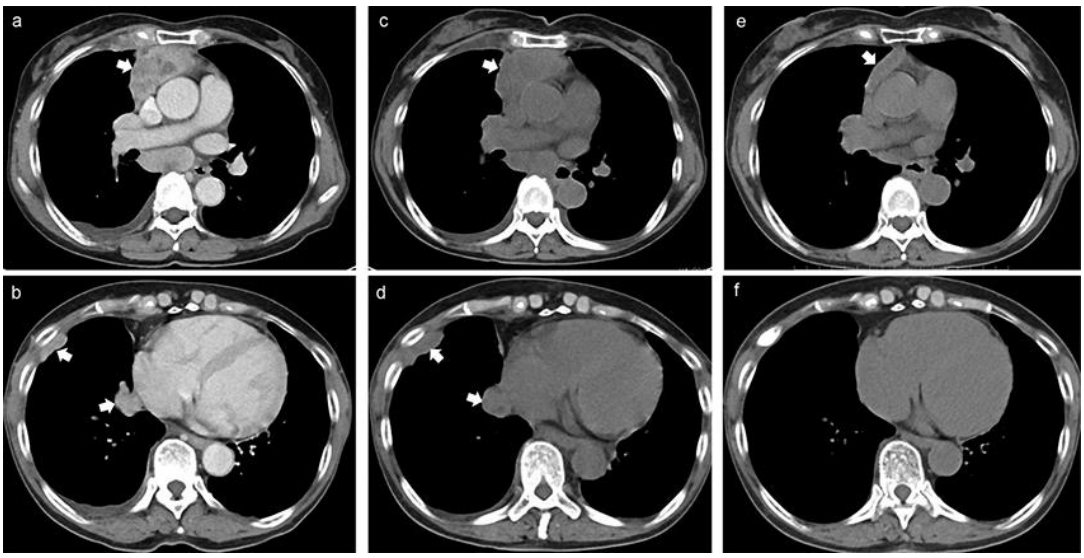

Fig. 1. Chest computed tomography (CT) images. **a**, **b** Chest contrast-enhanced CT images on admission. The white arrows indicate an anterior mediastinal tumor (**a**) and disseminations in the right pleura (**b**). **c**, **d** CT images after 3 cycles of first-line chemotherapy. The metastatic lesions of the right pleura had grown larger (**d**). **e**, **f** After 6 cycles of pembrolizumab treatment, the primary lesion and metastatic lesions were markedly smaller.

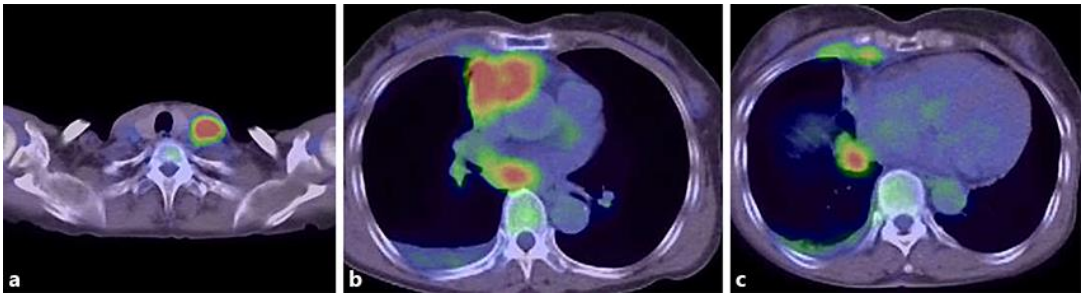

Fig. 2. Positron emission tomography revealed significant increases in fluoro-2-deoxy-D-glucose uptake in a left cervical lymph node (**a**), anterior mediastinal tumors (**b**), mediastinal lymph nodes (**b**), and a metastatic lesion in the right pleura (**c**).

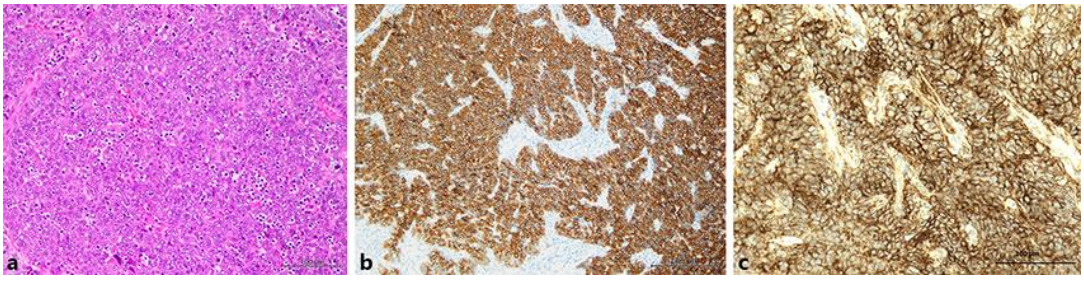

Fig. 3. Pathological analyses: hematoxylin and eosin staining (**a**), CD117 staining (**b**), and programmed death ligand 1 (PD-L1) staining (**c**). PD-L1 expression was 100% in tumor cells (**c**).