Clinical Oncology: Case Reports

Case Report

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A Case of Lung Adenocarcinoma Associated with Eosinophilic Sinusitis Induced by Pembrolizumab Administration

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Abstract

The frequency of immune checkpoint inhibitor (ICI) use in lung cancer chemotherapy has increased and has been associated with an increasing frequency of Immune-Related Adverse Events (IRAEs). Although IRAEs mainly include interstitial pneumonia, colitis, thyroid dysfunction and type 1 diabetes, other adverse events have been reported.

Case: A 46-year old man was admitted to our hospital with chest pain. Computed Tomography (CT) of the chest showed a mediastinal nodule and osteolysis at the Th8 level. Lung adenocarcinoma was diagnosed from transbronchial biopsy during bronchoscopy, and expression of programmed death-ligand 1 was 95%, so chemotherapy with pembrolizumab monotherapy was started. After pembrolizumab administration, serum eosinophil count increased, and systemic fatigue appeared during the 14th cycle of pembrolizumab. We diagnosed eosinophilic rhinosinusitis based on the Japanese epidemiological survey of refractory eosinophilic chronic rhinosinusitis score and sinus CT and stopped chemotherapy.

Conclusion: We encountered a case of eosinophilic sinusitis resulting from eosinophilia caused by pembrolizumab administration. This report suggests that ICIs including pembrolizumab may induce allergic diseases.

Keywords

Adenocarcinoma; Sinusitis; Pembrolizumab

Background

Immune Checkpoint Inhibitors (ICIs) are frequently used to treat various types of cancer, including lung cancer. Pembrolizumab monotherapy appears useful against lung cancer when the expression of programmed death-ligand 1 (PD-L1) in tumor tissue is ≥ 1% [1]. The frequency of pembrolizumab use is increasing, because this agent can be combined with cytotoxic agents even when the expression of PD-L1 in the tumor is negative [2,3]. ICIs have been reported to show various adverse events, including liver dysfunction, neuropathy, endocrinal dysfunction and interstitial pneumonia [4], but eosinophilic rhinosinusitis does not appear to have been reported previously as an Immune-Related Adverse Event (IRAE). We report herein a case of lung adenocarcinoma associated with eosinophilic sinusitis induced by pembrolizumab administration.

Case

A 46-year-old man presented with a 6-month history of chest pain. He was admitted to our hospital and underwent contrast-enhanced Computed Tomography (CT) of the chest that revealed a nodule in the right upper lobe near the superior vena cava and lymphadenopathy. Left supraclavicular lymph node metastasis was also suspected (Figure 1a and 1b). In addition, 18-F-fluoro-2-deoxyglucose positron emission tomography showed hot lesions corresponding to the lung nodule and the Th8 vertebra (Figure 2a and 2b). The nodule was diagnosed as adenocarcinoma with high PD-L1 expression (95%) based on endobronchial ultrasound-guided transbronchial needle aspiration. The clinical stage was categorized as cTxN2M1b. We initiated chemotherapy with pembrolizumab (200 mg) monotherapy

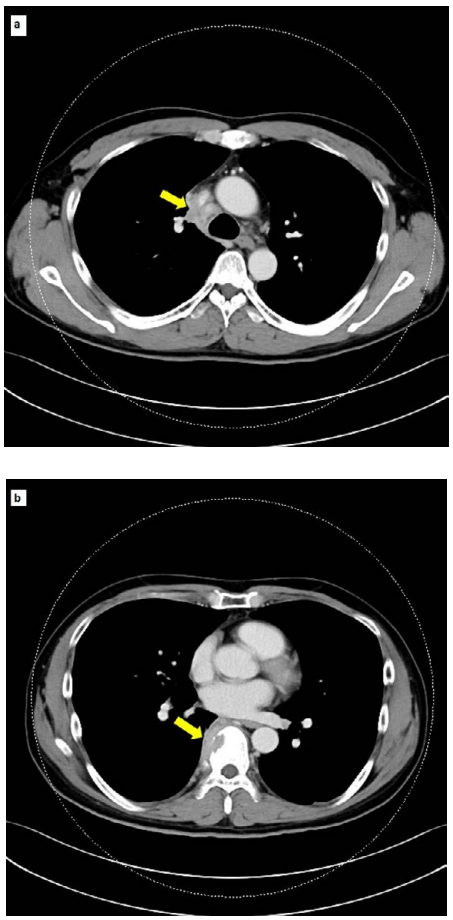

Figure 1: Chest CT images on the first visit: (a): Contrast-enhanced chest CT of the chest before pembrolizumab administration shows a nodule in the middle mediastinum; (b): Osteolytic change of Th8.

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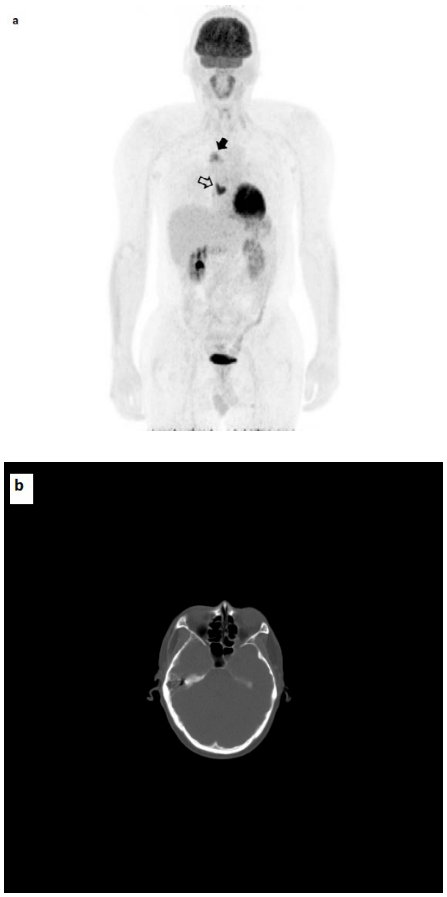

Figure 2: FDG-PET/CT image: (a): FDG-PET/CT before pembrolizumab administration shows FDG accumulation in a nodule (➡) and bone (⇨); (b): CT of the head shows no soft-tissue density in the sinus.

every 3 weeks from day 1. Clinical symptoms including chest pain improved after pembrolizumab administration. Furthermore, nodule size and osteolytic change in Th8 appeared dramatically decreased after 4 cycles of pembrolizumab. However, serum levels of eosinophils began to rise after pembrolizumab administration around day 42, and the number of serum eosinophils exceeded 1000/μL in the 5th cycle (Figure 3). Given the good efficacy of pembrolizumab against cancer and the lack of clinical symptoms, pembrolizumab administration was continued up to a total of 14 cycles. We discontinued pembrolizumab administration when the patient showed systemic fatigue, nose closure, nasal drip and olfactory disturbance during the 14th cycle of the chemotherapy. Sinuses CT showed soft-tissue density in bilateral maxillary sinuses and ethmoid sinus (Figure 4) and serum concentration of C-reactive protein were slightly elevated. From these findings, we diagnosed acute sinusitis and administered levofloxacin at 500 mg/day. However systemic fatigue was not improved and olfactory disturbance remained. We then decided to stop pembrolizumab administration. As antibiotics proved ineffective, examination was performed and showed no nasal polyps, but otolaryngologists in our hospital diagnosed eosinophilic rhinosinusitis using the diagnostic algorithm of the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) score, comprising findings from bilateral sinusitis (3 points), ethmoid sinus-dominant soft-tissue density (2 points), and serum eosinophilia increased to ≥ 10% (10 points). This score of 15 significantly exceeded the cut-off of 11 required to diagnose eosinophilic rhinosinusitis. Treatment for eosinophilic rhinosinusitis was started on day 315 with clarithromycin at 200 mg/day and steroid nasal drops, but as of the time of writing on day 387, serum eosinophil count has not improved and chemotherapy has not yet been resumed.

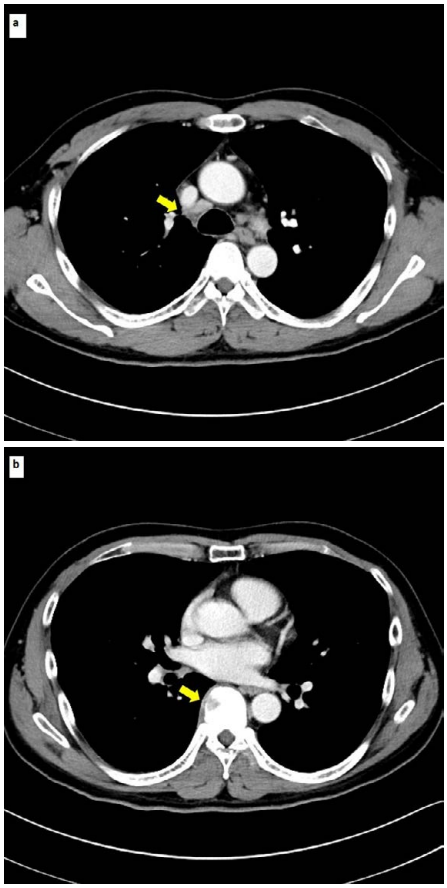

Figure 3: Chest CT images after treatment: (a): Contrast-enhanced CT after 4 cycles of pembrolizumab shows that the nodule in the middle mediastinum has almost disappeared; (b): Osteolytic change of Th8 has also improved.

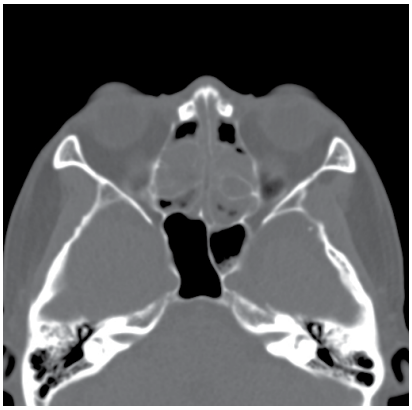

Figure 4: Sinus CT image on 14 cycles: CT of the ethmoid sinus after 14 cycles of pembrolizumab shows soft-tissue density in the ethmoid bone.

Discussion

This appears to be the first report of eosinophilic rhinosinusitis due to pembrolizumab administration associated with eosinophilia. Adverse events of pembrolizumab mainly include interstitial pneumonia, colitis, and thyroid dysfunction. Although eosinophilia due to ICI administration has been reported [5], eosinophilic rhinosinusitis associated with eosinophilia due to pembrolizumab administration has not been described. Tessier et al. investigated immune-related eosinophilia associated with PD-1 and PD-L1 antibodies [6]. They reported that serum eosinophil count started to increase after 3 months of ICI administration, peaking after a median of 6.4 months [6]. Although serum eosinophil count increased, chemotherapy was continued in that report. Furthermore, they reported that eosinophilia did not induce systemic symptoms, including allergic symptoms. In the present case, serum eosinophil count started to increase from the 3rd cycle of pembrolizumab (Day 63), and peaked during the 6th cycle (Day 126), broadly consistent with the report by Tessier et al. [6]. Systemic symptoms did not appear despite increased serum eosinophils, so we continued chemotherapy. However, in the present case, serum eosinophils exceeded 1500/μL, a level that has been associated with causing organ dysfunction [7], in the 14th cycle of pembrolizumab and sinusitis appeared (Figure 5). Hypereosinophilia is defined as an eosinophil count ≥ 1500 lasting more than 1 month [7]. After excluding other diseases causing eosinophilia, cases showing organ damage are defined as Hypereosinophilic Syndrome (HES). Major organ damage in HES is considered to be fibrosis, thrombosis and neuropathy. Sinusitis is not included as a cause of eosinophilia, and whether this symptom can be considered organ damage is unclear [8].

CD8-positive T cells are reportedly related to the elevation of eosinophils caused by ICIs [9]. Chemokines recruited from CD8-positive T cells such as chemokine ligand 5 (CCL5), CXCL9 and CXCL10 are supplied to the tumor by infiltration of eosinophils into the tumor and are suggested to lead to tumor rejection and prolonged survival [9]. In addition, PD-1, PD-L1 and PD-L2 are reportedly not only associated with anti-cancer immune functions but also play important roles in maintaining homeostasis of type 2 cytokines and allergic disease [10]. Khoja et al. reported fasciitis caused by nivolumab, in which muscle biopsy showed infiltration of CD8-positive cells coexisting with eosinophils, suggesting the involvement of CD8-positive cells and eosinophils with ICIs [11]. That case report was consistent with our findings for increased numbers of eosinophils and organ damage caused by eosinophil infiltration.

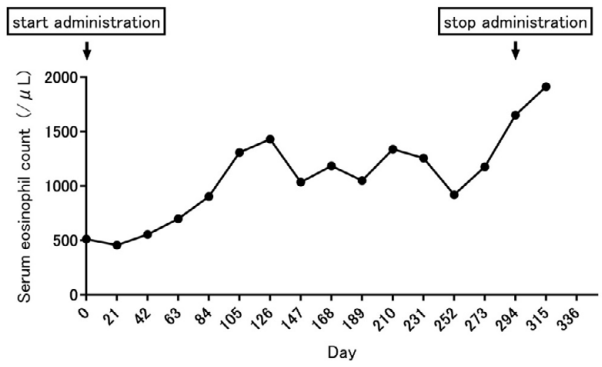

Figure 5: Course of serum eosinophil count during treatment: Changes in serum eosinophil count during the course of treatment. Pembrolizumab was administered every 21 days until cycle 13. Administration of pembrolizumab was stopped at 14 cycles due to common cold symptoms.

Clinical characteristics of eosinophilic rhinosinusitis include eosinophilic mucin, nose closure due to multiple nasal polyps, olfactory disturbance from an early stage, eosinophilia and ethmoid sinus-dominant sinusitis. These symptoms occur when eosinophils that have migrated into the blood infiltrate the sinus mucosa and cause eosinophilic inflammation. Fujieda et al. proposed new diagnostic criteria for eosinophilic rhinosinusitis resulting from the JESREC study [12], and these criteria have been widely adopted throughout Japan. In our case, no nasal polyps were observed, but eosinophilic rhinosinusitis was diagnosed using the JESREC criteria.

Hypereosinophilia is defined as a blood eosinophil count exceeding 500/μL, and this diagnostic criterion was established by Chusid et al. [8]. In the respiratory tract, eosinophils produce leukotriene C4 and prostaglandins to enhance bronchial vascular smooth muscle constriction and vascular permeability. Furthermore, eosinophils are involved in the enhancement and control of inflammation by secreting cytokines. The inflammation induced by eosinophils is also considered to cause tissue damage by secondary infiltration [8,13,14]. In our case, the serum eosinophil count was considered to have been increased by pembrolizumab administration, which may facilitate the induction of eosinophilic rhinosinusitis. The eosinophilic rhinosinusitis may also have been caused by secondary infiltration of eosinophils due to pembrolizumab-induced immune inflammation.

Steroid therapy is commonly used for IRAEs and in the treatment of eosinophilic rhinosinusitis. However, when steroid treatment is performed for IRAEs, the anti-tumor effects of ICIs may be counteracted by the immunosuppressive effects of the steroid [15-17]. On the other hand, one report found that ICIs did not affect overall survival or time to treatment failure even in combination with drugs aimed at immunosuppression, such as steroids and tumor necrosis factor α inhibitors [18]. Steroid treatment of IRAEs thus remains controversial, particularly for the purpose of maintaining quality of life. Further study of steroid treatment for IRAEs is clearly warranted.

Conclusion

We encountered a case of lung adenocarcinoma associated with eosinophilic sinusitis induced by pembrolizumab administration. ICIs, including pembrolizumab, are commonly used around the world for various cancers. Since eosinophilia due to pembrolizumab is not a rare side effect, attention must be paid to the development of allergic systemic disorders, including eosinophilic sinusitis.

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