


Asthma caused by durvalumab after chemoradiotherapy in two patients with non-small cell lung cancer

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Abstract

Durvalumab, an anti-programmed cell death-ligand 1 (PD-L1) antibody, is currently used in the maintenance therapy for patients with stage III non-small cell lung cancer after platinum-based chemoradiotherapy. A 69-year-old male with lung adenocarcinoma, clinical stage IIIA, was treated with chemoradiotherapy. As the treatments progressed, his dry cough gradually subsided. After chemoradiotherapy had been completed, we started durvalumab administration. One month later, his dry cough relapsed and persisted. Based on the changes of his blood eosinophil counts, we clinically diagnosed him with asthma. A 71-year-old male with lung adenocarcinoma, clinical stage IIIB, was treated with chemoradiotherapy. After completing chemoradiotherapy, we initiated durvalumab administration. After 6 months, his dry cough was noticed to involve wheezing. Based on his spirometric values and the fraction of exhaled nitric oxide, a clinical diagnosis of asthma was established. Asthma should be considered as one of the possible side effects when immune checkpoint inhibitors are used in cancer treatment.

KEYWORDS

adverse event, asthma, durvalumab, immune checkpoint inhibitors, non-small cell lung cancer

INTRODUCTION

Durvalumab is an anti-programmed cell death-ligand 1 (PD-L1) antibody that binds to PD-L1, but not to PD-L2, thereby helping T-cells recognize and neutralize tumour cells. In the phase III PACIFIC study, durvalumab as maintenance therapy was associated with longer progression-free survival and overall survival than placebo in patients with stage III non-small cell lung cancer (NSCLC) who did not experience disease progression after platinum-based chemoradiotherapy.¹ The side effects of durvalumab after chemoradiotherapy are usually manageable; however, some uncommon side effects occur. This study reported two cases in which asthma was caused by durvalumab after chemoradiotherapy in patients with NSCLC.

CASE REPORT

Case 1

A 69-year-old male presented to our hospital with a bulky mediastinal tumour accompanied by dry cough that persisted for 2 months. Although he had not been diagnosed with bronchial asthma, both of his parents had histories of asthma. He had a 25 pack-year history of smoking. His spirometric values before treatment were as follows: forced vital capacity (FVC), 3400 ml (96.6% of predicted); forced expiratory volume in 1 s (FEV₁), 2730 ml (93.2% of predicted); and FEV₁/FVC, 97.7%. Computed tomography (CT) did not effectively reveal the primary site of cancer. Because only bulky lymph nodes were observed around the tracheal bifurcation, we obtained tissue via open chest surgery. Finally, we

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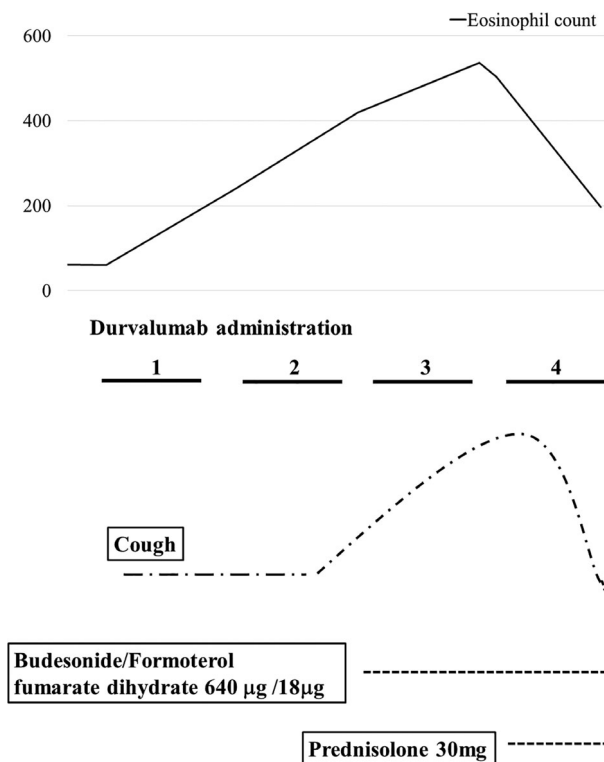


FIGURE 1 The treatment course, eosinophil count and cough severity in case 1

diagnosed the patient with stage IIIA lung adenocarcinoma (*TTF-1*- and *ALK*-positive; and tumour proportion score using 22C3 antibody, 15%). Surgery or radiotherapy was challenging because of the multiple mediastinal lymph node enlargement and the large irradiation field; thus, we initially began the treatment with chemotherapy consisting of cisplatin and vinorelbine in consultation with thoracic surgeons and radiation oncologists. After two cycles of this regimen, we delivered radiotherapy to the mediastinal field including the bulky adenopathy in tracheal bifurcation with two additional cycles of chemotherapy. As these treatments progressed, his dry cough gradually subsided. When chemotherapy was completed, his dry cough had almost disappeared. After chemoradiotherapy, we started durvalumab (10 mg/kg every 2 weeks) as maintenance therapy. One month later, his dry cough relapsed and persisted. His cough was more severe at bedtime, and it involved wheezing. Initially, we suspected cancer recurrence or pneumonitis caused by radiotherapy or durvalumab; however, the bulky lymph nodes around the tracheal bifurcation had shrank, and CT revealed only a slight degree of pneumonitis in the irradiation field. After 2 weeks, his cough worsened, and we suspected asthma. We administered budesonide/formoterol fumarate dihydrate (BUD/FOR) as two inhalations twice daily, but his cough persisted and worsened. After durvalumab administration, the patient's blood eosinophil counts had gradually increased (Figure 1). Breathing became difficult; therefore, he could not undergo spirometry, and the fraction of exhaled nitric oxide could not be assessed. Based on these findings,

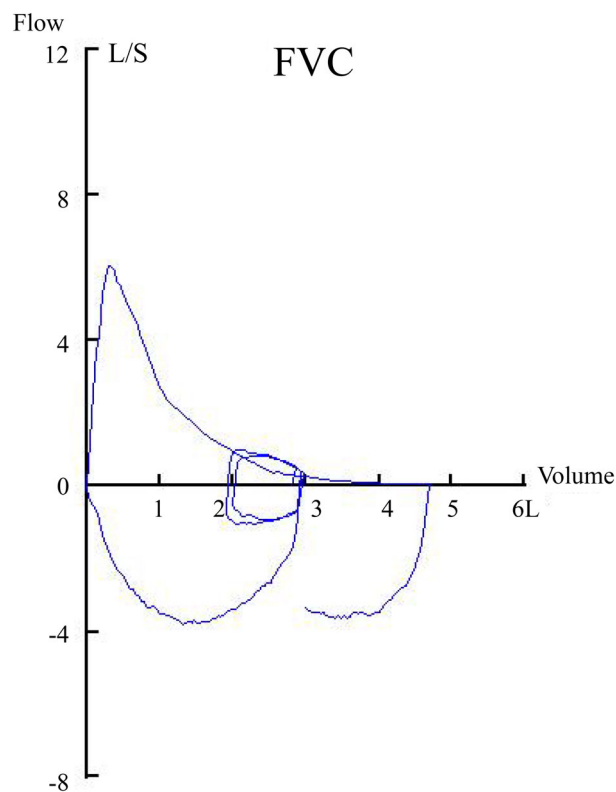


FIGURE 2 The flow–volume curve during durvalumab administration features a downward-facing convex, suggesting the presence of asthma. FVC, forced vital capacity

we clinically diagnosed him with asthma. In addition to BUD/FOR inhalation, we administered oral prednisolone (30 mg/day). His severe cough rapidly improved over the next few days. The patient has continued treatment with durvalumab every 2 weeks. At his last follow-up, he exhibited a partial response to the treatment for NSCLC. He has also continued BUD/FOR inhalation, and his cough has not relapsed.

Case 2

A 71-year-old male visited our hospital for mediastinal lymph node enlargement. He had not been diagnosed with bronchial asthma. He had a 60 pack-year history of smoking. Bronchoscopic examination revealed a tumour in the right upper bronchus. Based on the results of biopsy, we diagnosed the patient with stage IIIB lung adenocarcinoma (*EGFR*- and *ALK*-negative; tumour proportion score using 22C3 antibody, 0%). We initiated chemoradiotherapy with cisplatin and vinorelbine. After completing chemoradiotherapy, we administered durvalumab (10 mg/kg every 2 weeks) as maintenance therapy. After 6 months, his dry cough was noticed to involve wheezing. The bulky mediastinal lymph nodes had shrank, and pneumonitis was not observed in the irradiation field. His spirometric values at that time were as follows (Figure 2): FVC, 5080 ml (134.4% of predicted); FEV₁, 2270 ml (74.2% of predicted); and FEV₁/FVC, 44.7%. FEV₁ increased by

470 ml (20.7% increase) relative to the absolute volume following β 2-agonist inhalation, suggestive of reversible airflow obstruction. The fraction of exhaled nitric oxide was elevated at 39.1 ppb, indicative of eosinophilic airway inflammation. Based on these findings, a clinical diagnosis of asthma was established. We administered BUD/FOR as two inhalations twice daily, and his severe cough rapidly improved over the subsequent few days. The patient has continued treatment with durvalumab every 2 weeks. At his last follow-up, he exhibited a complete response to the treatment for NSCLC. He is currently using BUD/FOR inhalation continuously, and his cough has not relapsed.

DISCUSSION

Our report is the first to present two cases of asthma caused by treatment with an anti-PD-L1 antibody after chemoradiotherapy. The side effects of radiotherapy are classified as either early or late. Early side effects, including skin erythema, dry or moist desquamation of the skin, mucositis, nausea and diarrhoea, manifest within a few weeks after completing a course of fractionated radiotherapy. Late side effects, including radiation-induced fibrosis, atrophy, vascular damage, neural damage and a range of endocrine- and growth-related effects, are typically noticed after latent periods of months to years after the completion of treatment. The early phases of fibrogenesis after radiotherapy can be observed as a wound-healing response characterized by the almost immediate upregulation of pro-inflammatory cytokines such as tumour necrosis factor- α , interleukin 1 (IL1), IL6 and several other growth factors in the irradiated tissue.

Although asthma is not usually caused by radiotherapy and it is not listed as a general side effect, durvalumab may enhance the effects of these radiation-induced cytokines. Asthma induced by the programmed cell death-1 (PD-1) inhibitor nivolumab has already been reported,² and a similar mechanism may be involved in the pathogenesis of asthma attributable to PD-L1 blockade. Asthma is defined as a chronic inflammatory disease involving airway hyperreactivity (AHR) and reversible bronchoconstriction. PD-L1 and PD-L2 reportedly have opposing roles in the pathogenesis of asthma in mice. Specifically, absent PD-L1 expression leads to reduced AHR, whereas absent PD-L2 expression results in increased AHR.³ Conversely, increased PD-L2 expression in the inflamed lungs of mice permits the development of more severe AHR.

Occasionally, we experience eosinophilia in patients treated with anti-PD-1 or anti-PD-L1 antibody. A recent study demonstrated that eosinophils are important in anti-cancer immunity. Tumour-homing eosinophils secrete chemoattractants that guide T-cells to the tumour, resulting in tumour eradication and patient survival.⁴ Furthermore, the co-transfer of eosinophils and T-cells also led to considerable changes in the tumour microenvironment, including normalization of the tumour vasculature and macrophage

polarization. These processes support the infiltration and activity of T-cells. Indeed, the eosinophil count was positively correlated with disease outcome in metastatic melanoma and classical Hodgkin lymphoma treated with anti-PD-1 antibodies. Radiotherapy-induced regression of metastatic cancer at a distance from the irradiated site, which is called the abscopal effect, may be mediated by immunologic mechanisms because it has been revealed to increase the presentation of neoantigen by myeloid cells within the tumour stroma and thereby enhance the T-cell-mediated killing of tumour cells.⁵ It was suspected that radiation therapy also increases neoantigen release, suggesting that asthma develops from the introduction of eosinophils and T-cells.

The association of asthma with PD-1, PD-L1 and PD-L2 in our patients remains unknown, and further investigations are needed for elucidation. In these cases, we observed the development of asthma attributable to durvalumab administration after chemoradiotherapy. Asthma should be considered a possible side effect when immune checkpoint inhibitors are used in cancer treatment.

CONFLICT OF INTEREST

Akio Niimi has received personal fees and grants from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Kyorin Pharmaceutical, Kyowa Hakko Kirin, MSD, Novartis Pharma, ONO Pharmaceutical Industries, Sanofi and Taiho Pharmaceutical. Toyooki Hida has received personal fees and grants from AbbVie, Astellas, AstraZeneca, Bristol-Meyers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Ignyta, Janssen Pharmaceutical, Kissei, Merck Serono, MSD, Nippon Boehringer Ingelheim, Novartis, ONO Pharmaceutical Industries, Pfizer, Taiho Pharmaceutical and Takeda Pharmaceutical. All other authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

Conceptualization: Takehiro Uemura. Supervision: Tetsuya Oguri, Akio Niimi, Toyooki Hida. Literature search: Takehiro Uemura, Tomohiro Onuki, Satoshi Fukuda. Data curation: Kensuke Fukumitsu, Yoshihiro Kanemitsu. Writing manuscript: Takehiro Uemura. Final review and editing of manuscript: Ken Meano, Tetsuya Oguri, Akio Niimi, Toyooki Hida.

ETHICS STATEMENT

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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