

Letter to the editor

Nivolumab-induced asthma in a patient with non-small-cell lung cancer

The programmed cell death-1 (PD-1) inhibitor nivolumab has now become standard in the management of patients with previously treated non-small-cell lung cancer; however, nivolumab treatment has been associated with various immune-related adverse events [1]. Herein, we report the case of a patient who suffered from asthma during treatment with nivolumab.

A 50-year-old man with no prior medical history was diagnosed with stage IV lung adenocarcinoma (*EGFR* wild-type, *ALK*-negative status) in January 2016. He was treated with four cycles of pemetrexed and carboplatin, followed by one cycle of docetaxel. Subsequently, third-line treatment with nivolumab (3 mg/kg every 2 weeks) was initiated in August 2016 due to enlargement of the primary tumor accompanied by carcinomatous lymphangiosis. Six weeks after the initiation of nivolumab treatment, radiological evaluation revealed partial response without any obvious adverse events. In May 2017, however, he presented with cough and wheezing, which worsened at night and in the early morning. He had no personal or family history of asthma and atopy, had not begun taking any new medications, and exhibited no clinical signs of heart failure, infection, or acid reflux. Chest computed tomography images revealed no changes since the previous evaluation. On laboratory testing, a complete blood count was unremarkable aside from peripheral blood eosinophilia (11%, $8.14 \times 10^8/l$) since the previous evaluation. Serum levels of total immunoglobulin E were elevated (863 IU/ml) relative to values obtained in May 2016 (238 IU/ml). Spirometric values were as follows: forced vital capacity (FVC): 4460 ml (103.7% of predicted), forced expiratory volume in 1 second (FEV_1): 2490 ml (67.8% of predicted), FEV_1/FVC : 55.8%. FEV_1 increased by 260 ml of the absolute volume following β_2 -agonist inhalation, suggestive of reversible airflow obstruction. The fraction of exhaled nitric oxide was markedly elevated at 113.0 ppb, indicative of eosinophilic airway inflammation. Based on the above findings, a clinical diagnosis of asthma was established. Besides oral prednisolone, he was treated with daily inhalation of fluticasone propionate/formoterol fumarate dehydrate (FP/FOR, 500/20 μ g). His symptoms had rapidly improved by the following day. No signs of lung cancer recurrence or worsening of asthma symptoms have been observed since the initiation of treatment with nivolumab and FP/FOR.

Asthma is a chronic inflammatory disease of the airways characterized by airflow obstruction and airway hyperresponsiveness (AHR). In a murine model of asthma, the severity of AHR and

airway inflammation was significantly greater in PD-L2^{-/-} mice than in wild-type mice [2]. However, another research group reported that PD-1/PD-L1 blockade enhances AHR [3]. Given that the relative contribution of PD-1/PD-L1/PD-L2 signaling to the development and regulation of asthma has been widely recognized, asthma induced by nivolumab is theoretically possible, although the precise mechanisms underlying this effect remain controversial. To our knowledge, the present report is the first to discuss a case of asthma associated with anti-PD-1 antibody treatment. Clinicians must therefore be cautious not to misconceive symptoms of asthma as those of pulmonary lesion of cancer, when patients are on cancer immunotherapy.

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