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EDİTÖRE MEKTUP
LETTER TO THE EDITOR

Immuno-checkpoint inhibitor-associated hyper-eosinophilia and tumor shrinkage

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To the Editor,

Hyper-eosinophilia is defined as an absolute eosinophil count of more than 1500/mm3 (1). Drug-induced hyper-eosinophilia can develop within a few weeks of the start of therapy and is associated with potentially lethal clinical complications, mainly cardiac, cutaneous, neurologic or pulmonary (2). Hyper-eosinophilia associated with cancer chemotherapy seems to be very rare. With regard to drug-induced eosinophilia by immune-checkpoint inhibitors, there have been only three reports with nivolumab therapy (3-5). In these reports, eosinophilia was evaluated as an adverse event (AE), and might be an early indicator before the onset of symptoms of adrenal insufficiency or eosinophilia and systemic symptom syndrome (3-5). We report herein a case of hyper-eosinophilia due to nivolumab therapy for an advanced lung adenocarcinoma. Of particular interest is in the patient, that, the occurrence of hyper-eosinophilia was observed at the same time of shrinkage of the primary lesion of the disease. We discuss that hyper-eosinophilia caused by nivolumab therapy may be an immune reaction associated with favorable immune response.

A 61-year-old male was referred to our hospital due to incidentally detected abnormal nodule on chest radiograph. He was diagnosed as having lung adenocarcinoma pathologically, however, neither epidermal growth factor receptor mutation nor anaplastic lymphoma kinase fusion gene was identified. Due to small but multiple metastases in brain, he received gamma-knife therapy for the metastatic cites, and two lines of systemic chemotherapy, carboplatin + pemetrexed + bevacizumab, docetaxel + bevacizumab. But the primary tumor and mediastinal lymphadenopathy did not respond and enlarged (Figure 1A). Therefore, the patient received nivolumab therapy (15 mg/kg, q14 days) as the third-line therapy, although immunostaining was evaluated as negative for PD-L1. Six weeks after the initiation of nivolumab therapy, the patient noted to have an eczema-like skin eruption over back, neck and upper thorax.

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Twelve weeks after the initiation of the therapy, eosinophilia appeared and continued for several weeks (Figure 2). On the other hand, chest CT scan taken at 6 weeks after the initiation of the therapy, primary lesion began to shrink (Figure 1B) and the shrinkage continued for 18 weeks (Figure 1C). Mediastinal lymphadenopathy also shrank and nivolumab therapy achieved as having "partial response (PR)". Adrenocorticotropic hormone (25.9 pg/mL, normal range: 7.2-63.6 pg/mL) and cortisol (14.0 μg/dL, normal range: 6.24-18.0 μg/dL) were normal. Serum total IgE level was 82.1 IU/mL (normal range: 0-173IU/mL). Parasitic eggs were not detected in fecal examination. As blood eosinophil count increased up to 6200/mm^3 and dyshidrosis was found in the left sol at the 22 weeks after initiation of nivolumab therapy, oral prednisolone (20 mg/day) was started, although the patient did not develop cardiac, respiratory, liver or renal complications. Soon after the initiation of the systemic corticosteroid therapy, normalization of blood eosinophil count and a dramatic improvement in eczema-like skin eruption and dyshidrosis in the left sole were observed. Because of achievement of the prompt response and disagree with the skin biopsy of the patient, no pathological specimens of the skin lesions were obtained. Shrinkage of the primary tumor is maintained for 12 weeks despite administration of systemic corticosteroid therapy (Figure 3-A, B, C). The patient is now well, and Nivolumab therapy is continued.

Nivolumab, an immune-checkpoint inhibitor, is now approved for the treatment of non-small cell lung cancer, melanoma, and renal cell carcinoma (6). Despite the impressive benefits of the immune checkpoint blockade, its use can be hampered by the occurrence of serious adverse events which can affect multiple organs of the body (7-11). Since our patient had neither bronchial asthma nor parasitic disease, and since the patient did not develop nivolumab-induced adrenal insufficiency, we evaluated that the hyper-eosinophilia was related to a nivolumab-induced drug reaction, as the patient had good response at the same time of hyper-eosinophilia. Six weeks after the initiation of nivolumab therapy, the patient noted to have an eczema-like skin eruption, ad 12 weeks after the initiation of the therapy, hyper-eosinophilia appeared and continued. At the same time, favorable response was observed in our case. Whether hyper-eosinophilia and skin eruption were reactions related to a favorable effect or reactions related to AEs, therefore, there can be room for discussion on this point.

Pathophysiologically, the etiologies of hyper-eosinophilia and that of eczema-like skin eruption are heterogeneous and autoimmune reaction is thought to be one of the causes of such blood change and systemic skin eruption (12). We speculate that nivolumab-induced cancer cell destruction might cause reconstruction of the immune system, which somewhat resembles graft versus host disease. Immune checkpoint inhibitors are currently available and there have been three reports who developed eosinophilia during nivolumab therapy without any good response to the drug; two had adrenal insufficiency (4,5), and one had "eosinophilia and systemic symptom syndrome" (3). Therefore, this

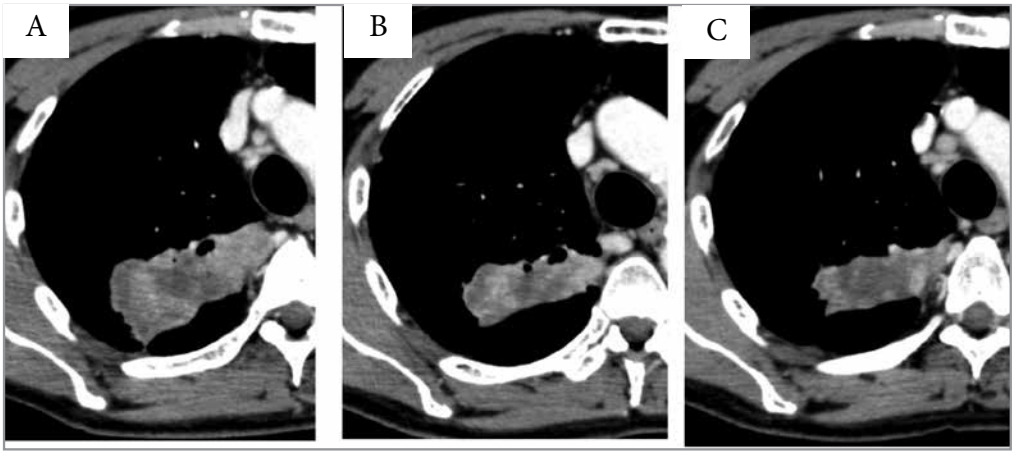

Figure 1. Chest CT scan before the nivolumab therapy **(A)**, chest CT scan at 9 weeks **(B)**, and chest CT scan at 22 weeks after the initiation of the therapy **(C)**.

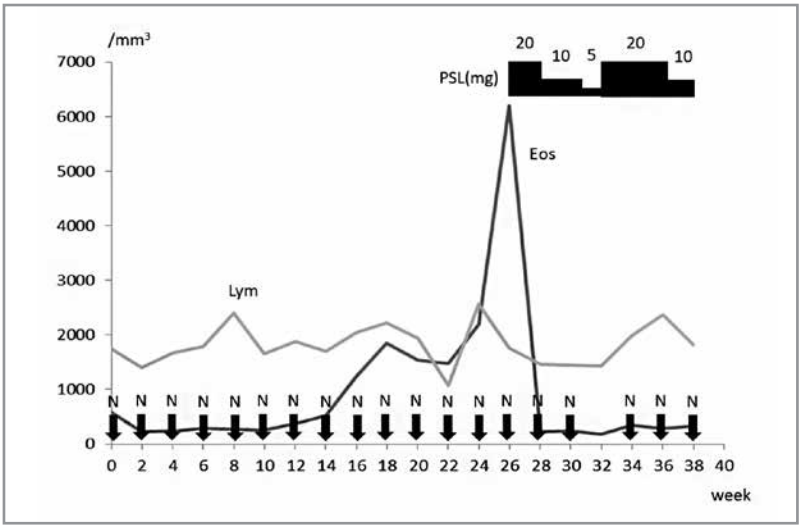

Figure 2. Clinical course of the patient. N: administration of nivolumab, Lyn: number of lymphocytes, Eos; number of eosinophils, and PSL: prednisolone.

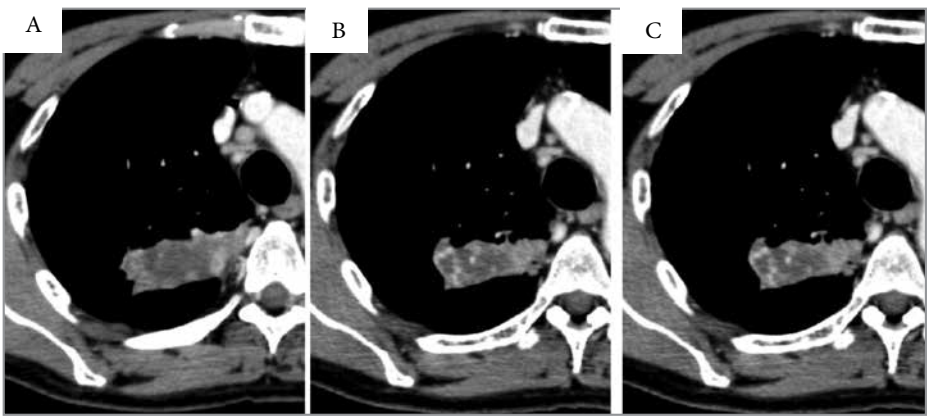

Figure 3. Chest CT scan 22 weeks after the initiation of nivolumab therapy (before systemic corticosteroid therapy) **(A)**. Chest CT scan at 6 weeks after the initiation of systemic corticosteroid therapy (30 weeks after initiation of nivolumab therapy) **(B)**. Chest CT scan at 10 weeks after the initiation of systemic corticosteroid therapy (34 weeks after initiation of nivolumab therapy) **(C)**.

patient was first case report with both hyper-eosinophilia and "effective response" nivolumab in nivolumab therapy.

We here report a case of immuno-checkpoint inhibitor-associated hyper-eosinophilia and tumor shrinkage. While this condition is very rare, it is important to recognize it, since it requires the decision whether the drug to be discontinued or not, and whether it requires systemic corticosteroid therapy. Since hyper-eosinophilia over 1500/mm^3 and lasting more than one month increases a risk of severe organ dysfunction (1,13), including death from cardiac failure (14). Discontinuation of the therapy can be recommended if these conditions are observed if any favorable response of the cancer lesion. It is more difficult to judge the continuity of nivolumab in patients where tumor shrinkage was confirmed as in the present case. In addition, it is not clear whether systemic corticosteroid therapy will attenuate the effect of nivolumab. In our patient, however, normalization of eosinophilia and improvement of skin reaction were achieved by systemic corticosteroid therapy without impairing the effect of nivolumab. If continuation of this immune checkpoint inhibitor is needed, a close observation and collaboration among oncologists, chest

physicians and allergologists will be required. Accumulation of knowledge on reconstruction of immune mechanisms associated with immune checkpoint inhibitors is awaited.

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