Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8688-21
Intern Med 61: 2339-2341, 2022
http://internmed.jp

【 CASE REPORT 】

Inflammatory Thoracic Aortic Aneurysm in a Patient with Advanced Lung Adenocarcinoma Treated with Pembrolizumab

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Abstract:
A 57-year-old man with lung adenocarcinoma was treated with chemotherapy and immune checkpoint blockade. After two cycles of carboplatin, pemetrexed, and pembrolizumab, he developed a persistent fever. Chest computed tomography (CT) suggested inflammation of the aortic wall. We treated the patient with corticosteroids. After four cycles of carboplatin, pemetrexed, and pembrolizumab, chest CT showed an aneurysm in the ascending aorta. We diagnosed him with inflammatory thoracic aortic aneurysm induced by pembrolizumab and performed surgical replacement of the ascending aorta. Although this might be a very rare case, we should be aware of aortitis as a potential adverse effect of pembrolizumab.

Key words: aortitis, inflammatory thoracic aortic aneurysm, immune-related adverse events, pembrolizumab

(Intern Med 61: 2339-2341, 2022)
(DOI: 10.2169/internalmedicine.8688-21)

Introduction

The development of immune checkpoint blockade (ICB) therapy has led to dramatic progress in the treatment of advanced non-small-cell lung cancer (NSCLC). Monoclonal antibodies (mAbs) against programmed cell death 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4), such as nivolumab and pembrolizumab, atezolizumab and durvalumab, and ipilimumab, respectively, counteract molecule-mediated immunosuppressive signals. The addition of these key immune checkpoint inhibitors (ICIs) (1-3) to standard chemotherapy has resulted in a significantly longer overall survival and progression-free survival than with chemotherapy alone in patients with previously untreated metastatic NSCLC (5-8).

However, despite its benefits, ICB therapy is associated with immune-related adverse events (irAEs) that are different from those of conventional chemotherapy. Aortitis is a very rare irAE. To date, only three cases of aortitis and aortic aneurysm have been reported, and all three cases were in patients with melanoma who received an anti-CTLA-4 antibody.

We herein report a patient with lung adenocarcinoma who developed aortitis induced by an anti-PD-1 mAb.

Case Report

A 57-year-old man was diagnosed with adenocarcinoma of the lung in June 2019. His tumor was at stage IVB (T2N 2M1c). The tumor did not express PD-L1 (tumor proportion score, 0%). There were no mutations in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS-1), v-raf murine viral oncogene homolog B1 (BRAF), or mesenchymal-epithelial transition factor (MET). Anti-cancer treatment with carboplatin, pemetrexed, and pembrolizumab was started in July 2019. After two cycles, the patient developed a persistent fever and elevated C-reactive protein (CRP). Chest computed tomography (CT) showed thickening of vessels in the aortic arch and higher density around vessels in the aortic arch, which suggested inflammation of the aortic wall (Fig. 1).

He was treated with oral prednisolone (25 mg/day), which

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Received: September 21, 2021; Accepted: October 24, 2021; Advance Publication by J-STAGE: January 13, 2022
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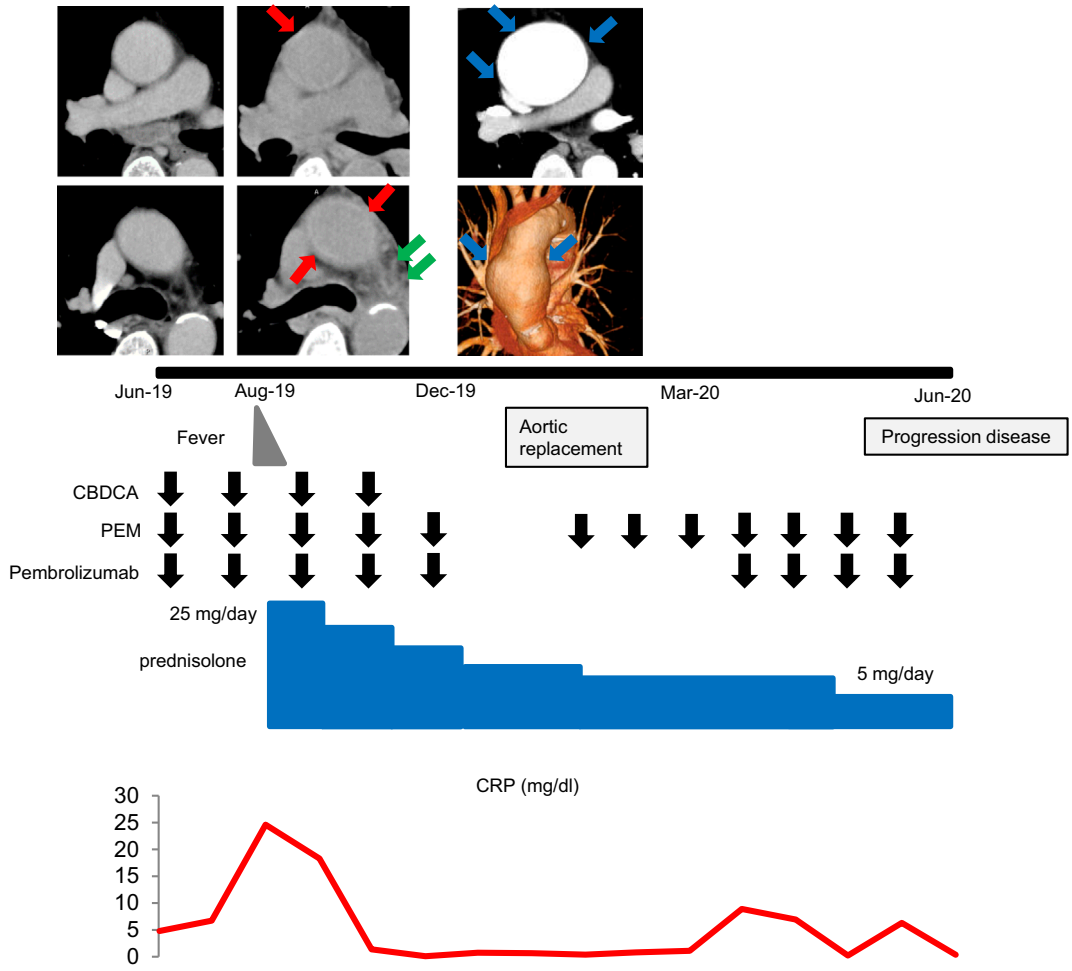

Figure 1. **Clinical course. The red and green arrows indicate inflammatory thickening of the vessels in the aortic arch and increased density around the vessels in the aortic arch. The blue arrows indicate the aneurysm. CBDCA: carboplatin, PEM: pemetrexed, CRP: C-reactive protein**

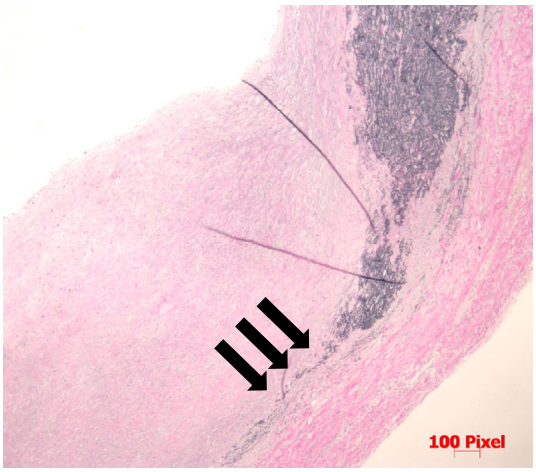

Figure 2. **Elastica van Gieson stain. The arrows indicate the disruption of elastic fibers in the media of the aorta.**

was gradually tapered. The fever resolved, and the anticancer regimen was restarted. After four cycles of induction with carboplatin, pemetrexed, and pembrolizumab and one cycle of maintenance therapy with pemetrexed and pembrolizumab, an aneurysm in the ascending aorta was detected on chest CT. We performed repair of the aortic aneurysm and analyzed the resected aortic wall with Elastica van Gieson stain. The stain showed disruption of the elastic fibers in the media of the aorta (Fig. 2).

Diseases leading to aortitis in the differential diagnosis, such as arteriosclerosis, inflammatory abdominal aortic aneurysm, vascular Behcet's disease, syphilitic mediastinitis, congenital vascular abnormalities, and bacterial aneurysm, were excluded; thus, we presumed that the inflammatory thoracic aortic aneurysm was an irAE related to pembrolizumab. We explained to the patient that there was still a risk of recurrence of aortitis if pembrolizumab was readministered, although surgical replacement had been performed and oral prednisolone was maintained. The patient agreed and received more treatment with 3 cycles of pemetrexed and 4 cycles of pemetrexed and pembrolizumab with oral prednisolone maintenance therapy (5-7.5 mg/day) (Fig. 1).

He is currently receiving a different regimen of chemotherapy without any relapse of aortitis or aortic aneurysm.

Discussion

Diagnostic criteria for aortitis syndrome have been estab-

lished. First, occlusive or dilated lesions are present in the aorta or its major branches and pulmonary arteries on imaging examinations, such as digital subtraction angiography, CT, or magnetic resonance angiography. Second, at least one of the following findings are present: 1) pulse deficiency or intermittent claudication; 2) blood pressure difference between the left and right upper (or lower) limbs or between the upper and lower limbs; 3) a bruit in the neck, back, or abdomen; 4) high blood pressure; and 5) elevated inflammatory response. Third, arteriosclerosis, inflammatory abdominal aortic aneurysm, vascular Behcet's disease, syphilitic mediastinitis, congenital vascular abnormalities, and bacterial aneurysm should be excluded (9). Our patient had an inflammatory response with a sustained fever and elevated CRP level, and CT showed dilated lesions in the thoracic aorta. Thus, our patient met the criteria described above, and we diagnosed him with aortitis and aortic aneurysm.

PD-1, a cell surface receptor expressed on T cells, macrophages, and natural killer cells, inhibits the immune response. Binding between PD-1 and its ligands, PD-L1 and PD-L2, inhibits apoptosis in cancer cells and promotes conversion of Th1 cells into Treg cells. Furthermore, PD-1 is reported to prevent excessive immune reactions by negatively regulating the function of autoreactive T cells (10). Because T cells play a critical role in large-vessel vasculitis (11, 12), we speculated that pembrolizumab might have induced aortitis by continuous activation of T cells in our patient.

While arthralgias, myalgias, and inflammatory arthritis frequently occur as irAEs, vasculitis has been uncommonly reported in the literature. There are only three reported cases of ICI-induced aortitis (13-15). All these cases occurred in patients with melanoma and were caused by the CTLA-4 inhibitor ipilimumab. There have been no reports of arteritis in patients with lung cancer that were caused by PD-1 or PD-L 1 inhibitors, including pembrolizumab. The inhibition of the CTLA4-CD80/86 axis and the anti-PD-1-PD-L1 axis can cause arteritis via similar immune-activating mechanisms.

At present, there are no established guidelines to predict and treat vasculitis associated with ICB therapy. Whether or not corticosteroid treatment alone is sufficient for aortitis induced by ICIs and whether or not ICIs can be resumed after treatment remain unclear. Both responders and non-responders to corticosteroids have been reported thus far (13-15). In the present case, there was a risk of recurrence of other aortitis induced by re-administration of pembrolizumab, but surgical replacement has performed at previous aortitis part. The patient agreed to receive re-administration of pembrolizumab with this risk in mind, but there was no recurrence of aortitis. Further studies are required to evaluate the clinical course and treatment of aortitis induced by ICIs.

Conclusion

Aortitis is an irAE that can be caused by ICB therapy. This is the first case of inflammatory thoracic aortic aneurysm as an irAE in lung cancer and the first case associated with an anti-PD-1 mAb. It is necessary to keep this irAE in mind during ICI treatment.

The authors state that they have no Conflict of Interest (COI).

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