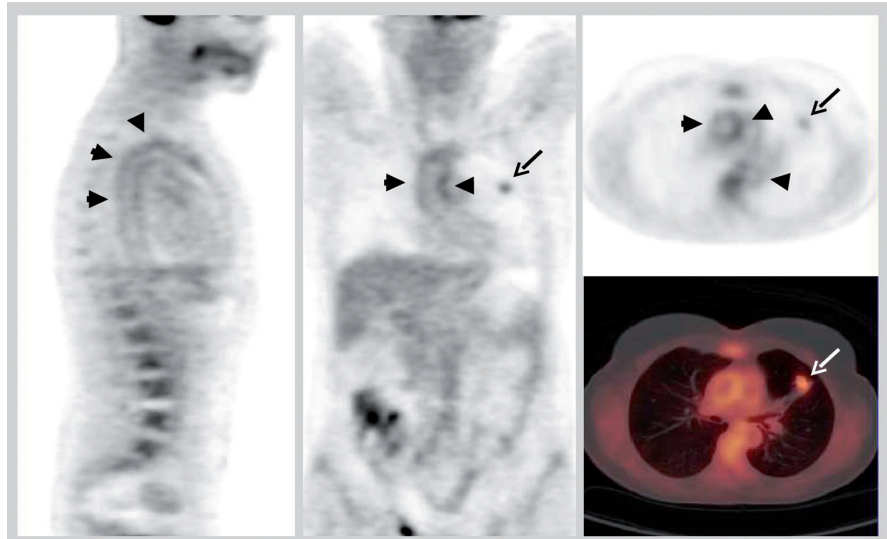


**Subclinal aortitis after starting nivolumab in a patient with metastatic melanoma. A case of drug-associated aortitis?**

Sirs,  
 Melanoma is the most severe skin malignancy and entails a higher metastatic potential. Nivolumab, a monoclonal antibody with high affinity for programmed cell death 1 (PD-1), has been approved for the treatment of unresectable or metastatic melanoma (1-3). Aortitis is an inflammation of aortic wall that can be idiopathic or secondary to other conditions (4-6).  
 Herein, we report a 48-year-old female with aortitis diagnosed by a PET/CT scan. Seven years earlier, she was diagnosed with malignant melanoma with superficial extension from a skin lesion on her back. She underwent a wide excision with negative axillary sentinel lymph node biopsy. Pathologic staging was pT2a N0 M0 (Breslow thickness: 1.17 mm; Clark level III). In September 2015, the patient complained of gait instability, aphasia and right facial palsy. A brain MRI disclosed a right precentral cortical-subcortical nodular lesion. A fully resection of the cerebral lesion was performed confirming the diagnosis of metastasis from melanoma without BRAF mutation. She also received adjuvant treatment with radiosurgery in the surgical bed. Nonetheless, in February 2016, the patient suffered an episode of disconnection and tremor in the upper right limb. A new cranial CT scan showed three metastatic lesions. A brain MRI disclosed several supratentorial metastatic focal intraparenchymal lesions. The patient received palliative holocranial radiation therapy. A PET/CT scan confirmed these findings, and showed a subcutaneous hypermetabolic nodule in the right pelvis. Three months later, a new PET/CT showed a significant progression of the known metastatic lesions, and new muscular, subcutaneous and visceral nodular tumoral implants. Treatment with intravenous nivolumab (3 mg/kg every other week) was started. Two months later, a PET/CT scan showed an excellent response with FDG-uptake persistence only in the nodule located in the upper lobe of the left lung. In February 2017, a new PET/CT scan disclosed the same metabolic pattern in the known pulmonary nodule but also FDG-uptake in the thoracic aortic wall consistent with aortitis (Fig. 1). No evidence of giant cell arteritis or polymyalgia rheumatica was found. Acute phase reactants were within normal limits, as well as the immunologic determinations. Nivolumab and pembrolizumab, two IgG4 PD-1 inhibitors, as well as ipilimumab, a biologic monoclonal antibody directed against CTLA-4 expressed on the surface of activated T cells, have become the first-line therapies for this neoplasm (1-3). PD-1 is a cell surface receptor expressed on



**Fig. 1.** PET and fused PET/CT images showed increased focal 18F-FDG uptake at the left lung nodule metastasis (arrows). Lineal uptake along the thoracic aortic wall (arrowheads) was also seen suggesting vascular inflammation.

T cells, B cells, macrophages and NK cells. It is an inhibitory molecule which may bind to PD-ligand 1 (PD-L1) and PD-L2. The binding between PD-1 and its ligands inhibits apoptosis of the cancer cells and promotes conversion of T effector cells to Treg cells. Moreover, PD-1 seems to prevent excessive immune reactions by negatively regulating the functions of autoreactive T cells.  
 To our knowledge, the affection of the aortic wall has never been published to date. Noteworthy, the development of giant cell arteritis in patients treated with ipilimumab has been previously reported (7, 8).  
 In our patient, aortitis was diagnosed by PET/CT scan, and there was no symptoms or raised acute phase reactants, indicating a subclinical form of the disorder. We cannot totally assure that aortitis was caused by nivolumab; however, the temporal relationship between exposure to nivolumab and the development of aortitis is suggestive of a drug-associated effect (possible association according to the Naranjo scale (9)).  
 PD-1 seems to be an important inhibitory co-receptor expressed by T cells. Moreover, the T cell is the critical cellular player in the vasculitic lesion in large-vessel vasculitis (10). Thus, we are tempted to speculate that nivolumab might incite aortitis by inducing a permanent activation of T cells.

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