

Successful treatment of immune checkpoint inhibitor-related periaortitis

Elias D. Bühler^a, Ian L. Alberts^b, Lisa Christ^a, Berna C. Özdemir^c

^a Department of Rheumatology and Immunology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

^b Department of Nuclear Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

^c Department of Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Summary

We report a 64-year-old patient with melanoma receiving ipilimumab and nivolumab therapy who presented with a periaortic soft tissue mass around the abdominal aorta on restaging fluorodeoxyglucose positron emission tomography/computed tomography imaging. Clinical, laboratory, and radiologic findings resulted in a diagnosis of immune checkpoint inhibitor-related periaortitis. Periaortitis is a rare disease presenting with fibro-inflammatory tissue around the aorta and may lead to serious complications. Immune checkpoint inhibitors were discontinued, and the patient was treated with glucocorticoids, leading to a complete resolution of the periaortitis. To our knowledge, this is only the third reported case of immune checkpoint inhibitor-related periaortitis.

Case report

Chronic periaortitis is a rare disease characterised by fibro-inflammatory tissue around the aorta that is more common in males and those aged 40–60 years. It commonly involves the abdominal aorta. Because of its nonspecific symptoms, such as lower back or abdominal pain, and rarity, its diagnosis is frequently delayed, and patients might present with complications such as urethral obstruction, vascular stenosis or aneurysm. Periaortitis may be idiopathic or secondary to infections, drugs, or malignancies [1]. Furthermore, immunoglobulin G4 (IgG4)-related disease can present as periaortitis [2].

Immune checkpoint inhibitors have revolutionised cancer treatment and can lead to long-lasting remission, even in patients with metastatic disease [3]. However, immune-related adverse events might limit their use. The most common immune-related adverse events include dermatitis, colitis, hepatitis and thyroiditis. Cancer patients routinely receive follow-up imaging to determine treatment response. Consequently, treatment-related side effects, such as periaortitis, can be detected early. To our knowledge, only two cases of immune checkpoint inhibitor-related periaortitis have been previously reported [4, 5]. Herein, we report a case of immune checkpoint inhibitor-related periaortitis.

A 64-year-old Caucasian male was diagnosed with local melanoma on the left flank (Breslow thickness = 2.5 mm) in 2015. Five years later, he was diagnosed with metastatic

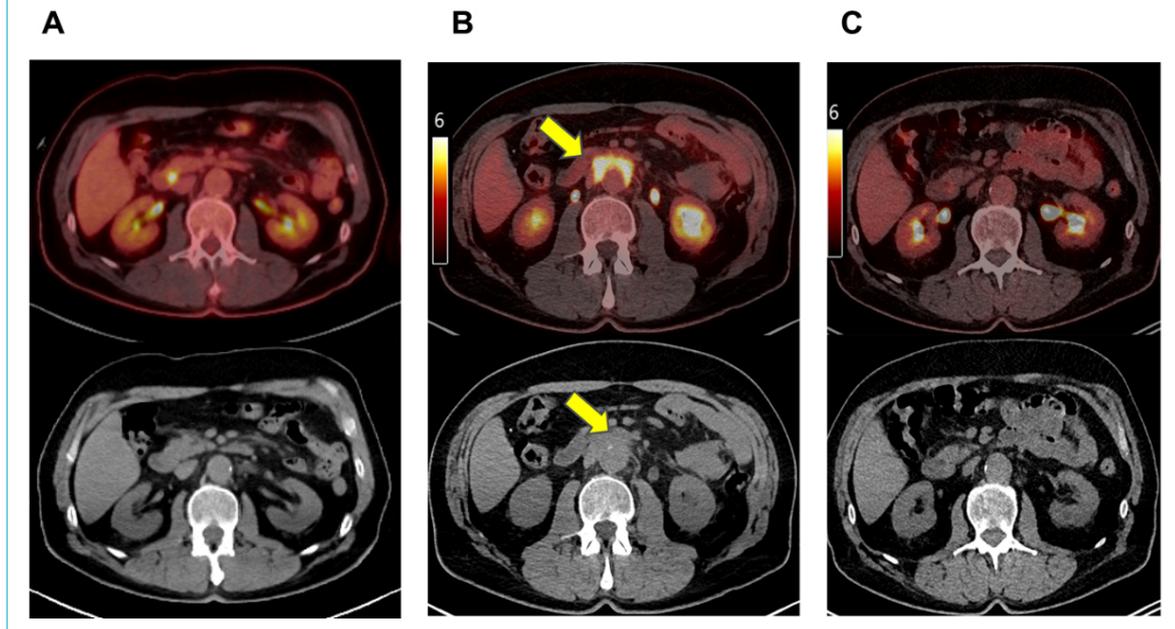
disease (B-Raf proto-oncogene serine/threonine kinase [BRAF] V600E-mutated, CD274 molecule [CD274/PD-L1] combined positive score = 80) and began combination immunotherapy with ipilimumab and nivolumab. After the onset of immune checkpoint inhibitor-associated colitis and hepatitis (no histological analysis was performed), which resolved with glucocorticoid treatment, maintenance therapy with nivolumab was continued during a partial remission with two small brain metastases, one lung, two intramuscular, and one bone lesion. After 32 cycles of nivolumab (i.e. 16 months of treatment), restaging 2-deoxy-2-[fluorine-18]fluoro-D-glucose (2-[¹⁸F]FDG) positron emission tomography (PET) / computed tomography (CT) imaging revealed a new periaortic soft tissue mass (10 × 5 cm) with intensive FDG uptake (max standardised uptake value [SUV] = 8.3) along the distal abdominal aorta (figure 1A, B).

Clinically, the patient was asymptomatic except for an unspecified dermatitis treated with topical glucocorticoids. Histology of the exanthema revealed infiltration by plasma cells (no increased IgG4 positivity) and eosinophils without evidence of a sarcoid-like reaction. His current medications were levothyroxine, amlodipine, and valsartan, which are not known to induce periaortitis [6]. Laboratory work-up revealed an elevated C-reactive protein (CRP) level of 40 mg/l (normal: <5 mg/l), an elevated erythrocyte sedimentation rate (ESR) of 81 mm/hour (normal: 0–20 mm/hour), increased serum IgG4 concentration of 3.32 g/l (normal: 0.08–1.4 g/l), and mildly reduced kidney function (creatinine = 110 μmol/l [normal: <104 μmol/l]). The antinuclear antibody (ANA) titer was 1:80 (nuclear speckled) without specific autoantibodies corresponding to the staining pattern (e.g. anti-Sjögren's syndrome [SS]-A, SS-B, myositis-associated antibodies, or Smith antigen [Sm]) in additional enzyme-linked immunosorbent assays. The antineutrophil cytoplasmic antibodies (ANCA) test, infectious serologies (hepatitis B and C, HIV, and syphilis), and QuantiFERON test were negative.

Radiological, molecular imaging, and biological findings led us to suspect nivolumab-induced periaortitis. A sarcoid-like reaction was unlikely given the atypical periaortic location [7]. A biopsy was not obtained from this patient due to potential complication risks. After a multidisciplinary discussion, nivolumab was discontinued, and systemic glucocorticoid treatment (prednisolone

Berna C. Özdemir
 Freiburgstrasse 18
 CH-3011 Bern
 berna.oezdemir[at]insel.ch

Figure 1: 2-[18F]FDG PET/CT imaging findings. (A) A co-registered PET/CT and non-contrast-enhanced CT show the aorta without periaortic soft tissue abnormality before immune checkpoint inhibitor (ICI) therapy. (B) A co-registered PET/CT and non-contrast-enhanced CT show an intensively FDG-enhanced (max SUV = 8.3) periaortic soft tissue mass (10 × 5 cm) after ICI therapy. (C) Post-glucocorticoid treatment PET/CT and non-contrast-enhanced CT show total regression of the periaortic soft tissue mass and FDG avidity.



equivalent: 1 mg/kg body weight) resulted in complete imaging remission of the soft tissue density within three months (figure 1C). After glucocorticoid treatment, the patient remained in partial remission from melanoma without new lesions. B-cell targeting approaches (e.g. rituximab) have shown efficacy in IgG4-related disease [8] and may be used as a treatment option for periaortitis in cases with relapsing disease after glucocorticoid taper.

The two previously reported cases of immune checkpoint inhibitor-induced periaortitis occurred in male patients with lung cancer (aged 57 and 66 years) and a history of aortic aneurysm and were related to nivolumab [4, 5]. In both patients, nivolumab was discontinued, and the periaortitis regressed within eight weeks, suggesting a drug-related process. Glucocorticoid treatment was added for one case. IgG4 levels were reported for one case and appeared within the normal range. Our case's IgG4 levels were elevated, possibly implicating an IgG4-related process [2]. However, the temporal relationship with immune checkpoint inhibitor treatment and previous immune-related adverse events (colitis and hepatitis) led us to suspect a diagnosis of immune checkpoint inhibitor-associated periaortitis. A biopsy would be needed to definitively rule out IgG4-related disease. Immune checkpoint inhibitor-induced IgG4-related disease has been previously reported, but none of the cases were associated with periaortitis [9, 10].

Our patient had a known history of atherosclerotic disease of the aorta with infrarenal ectasia. Aortic aneurysms and atherosclerosis are associated with chronic inflammation and might trigger chronic periaortitis [11, 12]. The immune responses induced by immune checkpoint inhibitors can facilitate periaortitis development.

In conclusion, periaortitis can be a late immune-related adverse event. Patients with a history of aortic ectasia or aneurysm might be more susceptible to this immune-re-

lated adverse event. Treatment options vary depending on the clinical presentation and include discontinuation of immune checkpoint inhibitor treatment and additional corticosteroid treatment.

Acknowledgments

An Informed consent has been obtained from the patient.

Financial disclosure

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. LC reports research/non-financial support, advisory fee and stock ownership from Gilead Sciences, F. Hoffmann-La Roche, Novartis, Pfizer, Bristol-Myers Squibb, and Sanofi. BCÖ reports receiving institutional honoraria for lectures and advisory boards from BMS, MSD, Merck, Ipsen, F. Hoffmann-La Roche, Pfizer, Novartis, Janssen, and Sanofi. EDB and ILA do not have any disclosures.

References

- Marvisi C, Accorsi Buttini E, Vaglio A. Aortitis and periaortitis: the puzzling spectrum of inflammatory aortic diseases. *Presse Med.* 2020 Apr;49(1):104018. <http://dx.doi.org/10.1016/j.lpm.2020.104018>.
- Mizushima I, Kasashima S, Fujinaga Y, Kawano M, Ishizaka N. IgG4-related periaortitis/periarteritis: an under-recognized condition that is potentially life-threatening. *Mod Rheumatol.* 2019 Mar;29(2):240–50. <http://dx.doi.org/10.1080/14397595.2018.1546367>.
- Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun.* 2020 Jul;11(1):3801. <http://dx.doi.org/10.1038/s41467-020-17670-y>.
- Roy AK, Tathireddy HR, Roy M. Aftermath of induced inflammation: acute periaortitis due to nivolumab therapy. *BMJ Case Rep* 2017/ber-2017-221852. <http://dx.doi.org/10.1136/ber-2017-221852>.
- Hotta M, Naka G, Minamimoto R, Takeda Y, Hojo M. Nivolumab-induced periaortitis demonstrated by FDG PET/CT. *Clin Nucl Med.* 2020 Nov;45(11):910–2. <http://dx.doi.org/10.1097/RLU.0000000000003215>.

6. Gianfreda D, Superchi E, Peyronel F, Mazzariol M, Vaglio A. Chronic periaortitis: A clinical approach. *Rev Med Interne*. 2023 Feb;44(2):79–84. <http://dx.doi.org/10.1016/j.revmed.2022.11.009>.
7. Gkiozos I, Kopitopoulou A, Kalkanis A, Vamvakaris IN, Judson MA, Syrigos KN. Sarcooidosis-like reactions induced by checkpoint inhibitors. *J Thorac Oncol*. 2018 Aug;13(8):1076–82. <http://dx.doi.org/10.1016/j.jtho.2018.04.031>.
8. Carruthers MN, Topazian MD, Khosroshahi A, Witzig TE, Wallace ZS, Hart PA, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. *Ann Rheum Dis*. 2015 Jun;74(6):1171–7. <http://dx.doi.org/10.1136/annrheumdis-2014-206605>.
9. Joob B, Wiwanitkit V. Immunoglobulin G4 associated autoimmune cholangitis and pancreatitis and nivolumab. *World J Clin Cases*. 2022 Dec;10(35):13146–7. <http://dx.doi.org/10.12998/wjcc.v10.i35.13146>.
10. Terashima T, Iwami E, Shimada T, Kuroda A, Matsuzaki T, Nakajima T, et al. IgG4-related pleural disease in a patient with pulmonary adenocarcinoma under durvalumab treatment: a case report. *BMC Pulm Med*. 2020 Apr;20(1):104. <http://dx.doi.org/10.1186/s12890-020-1150-x>.
11. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2012 Sep;32(9):2045–51. <http://dx.doi.org/10.1161/ATVBAHA.108.179705>.
12. Jois RN, Gaffney K, Marshall T, Scott DG. Chronic periaortitis. *Rheumatology (Oxford)*. 2004 Nov;43(11):1441–6. <http://dx.doi.org/10.1093/rheumatology/keh326>.