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SHORT REPORT

Long-term adverse event: inflammatory orbitopathy induced by pembrolizumab in a patient with metastatic melanoma

Charlée Nardin[1,2] · Sophie Borot[3] · Marie-Astride Beaudoin[3] · Françoise Cattin[4] · Eve Puzenat[1,2] · Anne-Sophie Gauthier[5] · Franck Schillo[3] · Christophe Borg[6] · François Aubin[1,2]

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Summary
The recent advent of immune checkpoint inhibitors (ICI), including anti-programmed cell death 1 protein (anti-PD-1) agents has revolutionized the therapeutic approach of metastatic malignancies. Yet, ICI can disrupt immune tolerance resulting in enhanced immune activation in normal tissues with significant toxicity. A dysregulated activation of T-cells directed to normal tissues stands as the main mechanism of immune-related adverse events (irAE). To date, only two cases of immune-related inflammatory orbitopathy related to anti-PD-1 agents have been reported. This rare immune adverse event usually occurred early after ICI initiation. Here, we report the first case of late inflammatory orbitopathy occurring in a melanoma patient treated with pembrolizumab. Consequently, the occurrence of irAE under ICI should be monitored, even late after treatment instauration.

Keywords Orbitopathy · Pembrolizumab · Immune adverse event · Melanoma

Introduction

The recent advent of immune checkpoint inhibitors (ICI), including anti-programmed cell death 1 protein (anti-PD-1) agents has revolutionized the therapeutic approach of metastatic malignancies. Their efficacy relies on enhancing anti-tumour immunity through the inhibition of negative regulatory signalling in T cells. Yet, the inhibition of immune checkpoint receptors can disrupt immune tolerance resulting in enhanced immune activation in normal tissues with significant toxicity. A dysregulated activation of T-cells directed to normal tissues stands as the main mechanism of immune-related inflammatory adverse events (irAE). Among anti-PD-1 agents, pembrolizumab has been associated with various irAEs that are most frequently thyroid dysfunction [1]. We report herein the first case of late inflammatory orbitopathy occurring in a melanoma patient treated with pembrolizumab.

Case report

A 68-year-old male with no past history of ophthalmologic disorder or smoking had a BRAF wild-type primary cutaneous melanoma of the left thigh in 2000. He developed BRAF wild-type lymph node metastases in 2010 and 2012 and lung metastases in 2012 treated with surgery. After further progression in 2014, he was treated with infusions of ipilimumab (3 mg/kg every 3 weeks) for AJCC stage IV metastatic melanoma. After 3 cycles of ipilimumab, he developed hyperthyroidism due to Graves' disease treated with anti-thyroid medications, radioactive iodine leading to subsequent thyroid hormone supplementation. Ipilimumab was subsequently resumed. Two months later, further disease progression to the brain required gamma-knife stereotactic radiosurgery combined with anti-PD-1, pembrolizumab (2 mg/kg every 3 weeks). After two infusions of

✉ Charlée Nardin
charleenardin@hotmail.fr

1 Service de Dermatologie, Centre Hospitalier Universitaire, 3 Boulevard Alexandre Fleming, 25030 Besançon cedex, France

2 EA 3181 Université de Franche Comté, Besançon cedex, France

3 Service d'Endocrinologie, Centre Hospitalier Universitaire, Besançon, France

4 Service de Radiologie, Centre Hospitalier Universitaire, Besançon, France

5 Service d'Ophtalmologie, Centre Hospitalier Universitaire, Besançon, France

6 Service d'Oncologie, Centre Hospitalier Universitaire, Besançon, France

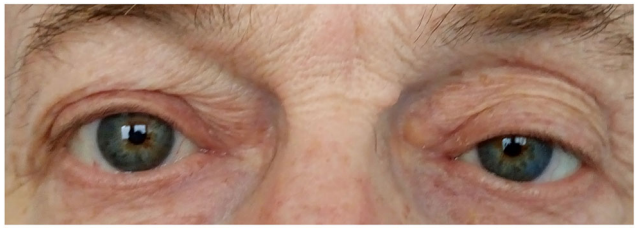

Fig. 1 External photos. External photos of the subject taken at presentation, with periorbital swelling, upper eyelid retraction, and proptosis with an elevation of the right eye in primary position

pembrolizumab, type 1 diabetes with positive anti-GAD antibodies was diagnosed and insulinotherapy was required. Further follow-up showed initial partial response according to RECIST criteria and irRECIST criteria. While deemed in complete remission after 3 years of treatment with pembrolizumab (51 cycles), he presented with acute redness and retro-orbital pain of the right eye. Clinical examination found binocular vertical diplopia, upper and lower eyelid swelling, upper eyelid retraction with lateral flare, proptosis and limited vertical eye movements without lagophtalmus of the right eye (Fig. 1). Slit lamp examination revealed conjunctival chemosis and injection. Intraocular pressures and fundus exam were normal in both eyes. There was no sign of uveitis. Thyroid examination was negative for goitre, nodules, or tenderness over the gland. Laboratory tests found the patient to be euthyroid: Thyroid stimulating hormone (TSH) 0.47 mIU/L (normal range 0.3–4.0 mIU/L) and normal free thyroxine (T4) under hormonal supplementation. Antithyroid antibodies (TSH receptor antibody, thyroid stimulating immunoglobulin antibody and anti-thyroid peroxidase antibody), and anti-neutrophil cytoplasmic antibody were not detected. Creatine kinase, IgG4 and complement levels were normal. Acetylcholine receptor antibody level, the edrophonium test and the ice pack test were negative for myasthenia gravis. Orbital MRI revealed thickening of all extra-ocular muscles involving mainly the medial, lateral and inferior rectus muscles of the right eye suggestive of inflammatory orbitopathy (Fig. 2).

Based on the orbital symptoms and laboratory tests ruling out thyroid-associated orbitopathy and myasthenia gravis, the diagnosis of inflammatory orbitopathy (IO) associated with anti-PD-1 treatment was made.

Management consisted first in intravenous methylprednisolone, 500 mg every week for 3 months, followed by radiation treatment (20 Grays, 2 Grays per fraction) in association with 1 mg/kg/day oral prednisone. Symptoms gradually resolved and MRI showed IO decrease. Anti-PD-1 treatment was definitively interrupted. However, intermittent diplopia still persisted and fully resolved 10 months after pembrolizumab interruption.

Discussion

Ocular toxicity is a rare irAE reported with immune checkpoint inhibitors (ICI) [2]. To date, the current observation is the first to report late ICI-related inflammatory orbitopathy.

The patient had symptoms that resemble those of thyroid-associated orbitopathy (TAO) but was euthyroid. TAO is an IO which is related to systemic autoimmune thyroid dysfunction. Various orbital lesions ranging from myositis in euthyroid patients to thyroid associated orbitopathy (TAO) have been reported in association with anti-CTLA-4 [3–7]. More recently, one case of IO mimicking TAO involving the orbital adipose tissue has been reported with nivolumab and two cases of panmyositis with ophtalmoplegia have been reported with pembrolizumab and the association of nivolumab and ipilimumab [8–10].

In the current observation, IO is fully imputed to pembrolizumab. Even though the role of ipilimumab

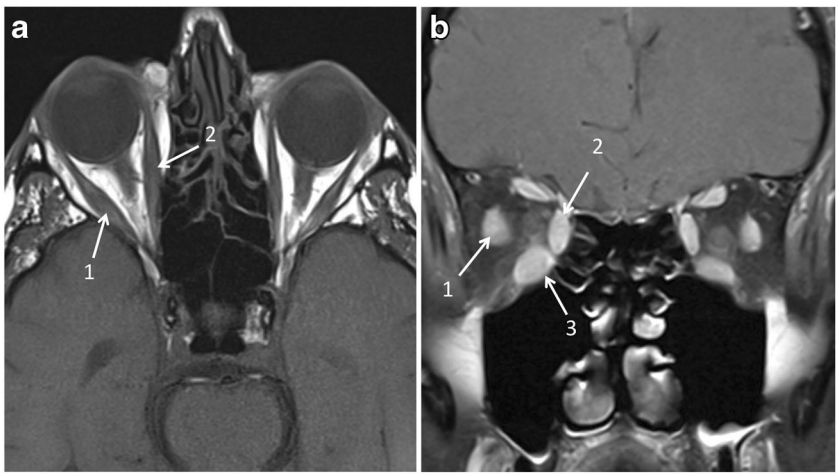

Fig. 2 Magnetic resonance imaging of the orbits. Axial contrast-enhanced spin echo T1-weighted images (**a**) and coronal spin echo T2-weighted images (**b**) revealed the presence of thickening of all extra-ocular muscles of the right eye. Enlargement of the lateral (arrow 1), medical (arrow 2) and inferior (arrow 3) rectus muscles of the right eye are shown with arrows

cannot be excluded, the long interval between ipilimumab treatment and IO diagnosis is poorly compatible with the imputability of ipilimumab [4, 7]. Indeed, the patient had presented Grave's disease under ipilimumab without eye involvement and later developed an IO more than 3 years after the last ipilimumab infusion.

The first relevant point of the current case is the interval of 3 years between the instauration of pembrolizumab to the development of IO. In the previous reports, IO occurred earlier, generally within 3 months after ICI instauration [3–10]. This case illustrates the risk of late irAE associated with the use of anti-PD-1 agents. Although there is no recommendation regarding the duration of anti-PD-1 therapy in case of remission, the risk of late irAE should be weighed in decision making.

Second, the current case shows the use of radiation therapy in case of ICI-related IO. There is no recommendation for the treatment of IO associated with ICI. In case of resistance to steroids, second line treatment such as immunoglobulins, infliximab, methotrexate, plasmapheresis have been reported as not efficient [8, 10]. Radiation therapy is known to be efficient in case of TAO and orbital myositis [11, 12]. In the current case, radiation therapy was partially efficient but symptoms fully resolved 10 months after pembrolizumab interruption.

While mechanisms of ICI-associated IO remain unclear, the fact that the patient had developed Grave's disease and a type 1 diabetes under ICI prior to IO may suggest a genetic susceptibility to irAE reported with cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) polymorphism [13]. CTLA-4 gene polymorphisms have been associated with autoimmune thyroid disease [14], but a meta-analysis failed to find a significant association between CTLA-4 gene polymorphisms and TAO [15]. Further, a positive correlation between clinical response to ICI and the occurrence of irAE has been observed [1, 16]. In this regard, the patient experienced complete remission under pembrolizumab.

This is the first report of late IO imputed to ICI (pembrolizumab). Consequently, the occurrence of irAE under ICI should be monitored, even late after treatment instauration.

Compliance with ethical standards

Conflicts of interest The authors do not have any disclosure.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient.

References

1. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F et al (2016) Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 13(8):473–486
2. Zimmer L, Goldinger SM, Hofmann L, Loquai C, Ugurel S, Thomas I, Schmidgen MI, Gutzmer R, Utikal JS, Göppner D, Hassel JC, Meier F, Tietze JK, Forschner A, Weishaupt C, Leverkus M, Wahl R, Dietrich U, Garbe C, Kirchberger MC, Eigentler T, Berking C, Gesierich A, Krackhardt AM, Schadendorf D, Schuler G, Dummer R, Heinzerling LM (2016) Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer 60:210–225
3. Lecouflet M, Verschoore M, Giard C, Gohier P, Le Corre Y, Milea D et al (2013) Orbital myositis associated with ipilimumab. Ann Dermatol Venereol 140(6–7):448–451
4. McElnea E, Ní Mhéalóid A, Moran S, Kelly R, Fulcher T (2014) Thyroid-like ophthalmopathy in a euthyroid patient receiving Ipilimumab. Orbit Amst Neth 33(6):424–427
5. Borodic G, Hinkle DM, Cia Y (2011) Drug-induced graves disease from CTLA-4 receptor suppression. Ophthal Plast Reconstr Surg 27(4):e87–e88
6. Min L, Vaidya A, Becker C (2011) Thyroid autoimmunity and ophthalmopathy related to melanoma biological therapy. Eur J Endocrinol 164(2):303–307
7. Sheldon CA, Kharlip J, Tamhankar MA (2017) Inflammatory Orbitopathy associated with Ipilimumab. Ophthal Plast Reconstr Surg 33:S155–S158
8. Nasr F, El Rassy E, Maalouf G, Azar C, Haddad F, Helou J et al (2018) Severe ophthalmoplegia and myocarditis following the administration of pembrolizumab. Eur J Cancer Oxf Engl 1990 91:171–173
9. Campredon P, Imbert P, Mouly C, Grunenwald S, Mazières J, Caron P (2018) Severe inflammatory Ophthalmopathy in a Euthyroid patient during Nivolumab treatment. Eur Thyroid J 7(2):84–87
10. Alnabulsi R, Hussain A, DeAngelis D (2018) Complete ophthalmoplegia in Ipilmumab and Nivolumab combination treatment for metastatic melanoma. Orbit Amst Neth 30:1–4
11. Bartalena L, Marcocci C, Gorman CA, Wiersinga WM, Pinchera A (2003) Orbital radiotherapy for Graves' ophthalmopathy: useful or useless? Safe or dangerous? J Endocrinol Investig 26(1):5–16
12. Mombaerts I, Koornneef L (1997 Mar) Current status in the treatment of orbital myositis. Ophthalmology 104(3):402–408
13. Ueda H, Howson JMM, Esposito L, Heward J, Snook H, Chamberlain G et al (2003) Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature 423(6939):506–511
14. Chistiakov DA, Turakulov RI (2003) CTLA-4 and its role in autoimmune thyroid disease. J Mol Endocrinol 31(1):21–36
15. Han S, Zhang S, Zhang W, Li R, Li Y, Wang Z, Xie Y, Mao Y (2006) CTLA4 polymorphisms and ophthalmopathy in Graves' disease patients: association study and meta-analysis. Hum Immunol 67(8):618–626
16. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J et al (2017) Safety profile of Nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol Off J Am Soc Clin Oncol 35(7):785–792