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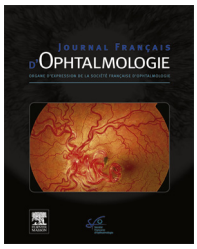

Formation médicale continue

ORIGINAL ARTICLE

Bilateral uveitis associated with nivolumab therapy

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Summary New anticancer therapies, immune pathway inhibitors, may cause immune-related adverse events (IRAE). Immune-related ocular toxicities are rare but are potentially serious adverse events. The purpose of this article is to report a case of ocular inflammatory involvement potentially related to the immune response and the use of nivolumab, a new immunologic agent used for the treatment of a solid tumor. Despite the implication of this therapy in the occurrence of inflammation, other causes must always be ruled out. It is possible to continue this therapy in consideration of the risk/benefit ratio for each patient. Close collaboration between oncologists and ophthalmologists is necessary in the diagnosis and timely management of IRAE related to these new emerging therapies.

Introduction and purpose

Immune-related ocular toxicities are rare but are serious adverse events, which may be associated with inhibitors of certain points in the immune system. Nivolumab — Opdivo® is a human monoclonal antibody (HuMAb) of the G4 immunoglobulin type (IgG4), which, by binding to the PD receptor on the surface of T lymphocytes, blocks its interaction with PD-L1 and PD-L2, and permits activation and proliferation of T lymphocytes.

The purpose of this article is to report a case of ocular inflammatory involvement potentially related to the immune system and the use of nivolumab for the treatment of a solid tumor.

Clinical case

A 63-year-old woman was referred to the ophthalmology service of la Pitié-Salpêtrière in December 2016, for the sensation of a bilateral veil, progressing since November 2016.

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This patient happened to be on chemotherapy (12th line) for a KRAS mutation bronchial adenocarcinoma, T3 N3 M1b (carcinomatous lymphatic and peritoneal involvement). The treatment consisted of nivolumab — Opdivo® (type IgG4 monoclonal antibody) since June 2015 (36th course). Bevacizumab — Avastin® was added in January 2017.

The initial ophthalmologic examination revealed: visual acuity of 0.5/10 in the right eye and 5/10 in the left eye; bilateral anterior chamber inflammation (with cyclitic membrane, Descemet's folds, 3+ flare and posterior synechiae in the right eye; 1+ flare in the left eye). Intraocular pressure was normal. The posterior segment examination revealed no inflammatory signs but was very limited in the right eye.

For this asymmetric bilateral non-granulomatous anterior uveitis with synechiae, the patient received local anti-inflammatory treatment (dexamethasone-Dexafree®: 1 drop eight times per day, and dexamethasone-oxytetracycline ointment — Sterdex®: one application at bedtime, along with mydriatic drops to prevent and treat synechiae), and local/regional treatment (5 subconjunctival injections of dexamethasone in the right eye: one injection per day for 5 days). Treatment with valacyclovir — Zelitrex® (500 mg: 2 tablets three times per day, i.e. 3 g/day) was also used under the assumption of a viral etiology, despite the bilaterality, due to her general status.

A work-up found no etiology for this inflammation. Serologies (HIV; HCV; Lyme; TPHA-VDRL; Brucella; HBV: vaccine panel) were negative. Toxoplasma serology showed established immunity. Herpetic serologies were positive for VZV and HSV1 and negative for HSV2 and CMV. ACE was normal, and lysozyme mildly elevated (16; N < 10). Quantiferon and RDI were negative.

She was seen again in the ophthalmology service 1 month later. The clinical course was favorable, with visual acuity 9/10 in both eyes and almost total disappearance of active anterior chamber inflammatory signs (persistent 1+ flare in both eyes). Intraocular pressure was still normal. The posterior segment examination, now easier, revealed 1+ bilateral vitritis. Fluorescein and indocyanine green angiography (Fig. 1) revealed vitritis, bilateral papillitis, a drusenoid PED in the inferior macula of the left eye, and multiple small bilateral choroidal infiltrates.

This was thus a bilateral granulomatous panuveitis with synechiae and no intraocular pressure elevation in a woman treated with nivolumab for metastatic adenocarcinoma of the lung.

Discussion

Certain medications have long been known to cause ocular inflammation, such as cidofovir — Vistide®, beta-blockers, and etanercept — Enbrel®.

Immune cells, particularly T lymphocytes, are directed by a series of feedback points, which carefully regulate the equilibrium of the immune system. The balance between activation and inhibition signals allows for the maintenance of immune tolerance and the effectiveness of the reaction of the system to intruders such as infections or tumors. Certain tumors have the ability to modify expression of proteins involved in the immune pathways, allowing the tumor to escape the immune system [1]. The inhibitors of immune pathways are antibodies, which in turn block these pathways so as to allow the immune system to combat these tumor cells. Antigen 4 (CTLA-4), associated with cytotoxic T lymphocytes, and protein 1 of programmed cell death (PD1) are the two main pathways used in cancer therapy (they allow activation of the specific response of antitumor T lymphocytes). This is a very promising new therapy given its initial success in metastatic melanoma. Ipilimumab — Yervoy® is an immunoglobulin G1 (IgG1) type human monoclonal antibody, a CTLA-4 antagonist, approved in 2011 for the treatment of non-resectable or metastatic melanoma. Pembrolizumab — Keytruda® is humanized monoclonal antibody which blocks the interaction between PD1 and its ligand PDL1, approved in 2014 for the treatment of non-resectable or metastatic melanoma. Nivolumab — Opdivo® is an immunoglobulin G4 (IgG4) type human monoclonal antibody (HuMAb) which binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2. It is currently used in the treatment of melanoma, small cell bronchial cancer, renal carcinoma and Hodgkin's lymphoma, of advanced stage after previous treatment.

Patients receiving immune pathway inhibitors develop numerous immune-related adverse events (IRAE). Ophthalmologic IRAE are rare and are reported in less than 1 % of patients (incidence of ocular IRAE in the phase II and III trials of ipilimumab of 1.3 %, with 0,4 % described as severe). Several studies have shown that patients developing ophthalmologic IRAE were also susceptible to other IRAE — dermatologic, gastrointestinal, hepatic and endocrine. An IRAE may occur from 1 week after the first injection up to 3 weeks after the fourth dose, with a cumulative frequency at 2 months after starting immune pathway inhibitors. Reported ocular side effects are peripheral ulcerative keratitis (PUK) with ipilimumab, corneal graft rejection with nivolumab [2], bilateral anterior uveitis with nivolumab [3], and with ipilimumab [4], Vogt-Koyanagi-Harada syndrome [5], bilateral uveitis with papillitis with pembrolizumab [6], choroidal neovascularization, melanoma associated retinopathy or MAR syndrome, thyroid orbitopathy and idiopathic orbital inflammatory disease, in association with ipilimumab [1].

The treatment of IRAE depends on the severity and the type of symptoms. Anti-inflammatory treatment with steroids may be local or local-regional in mild to moderate involvement (anterior uveitis and episcleritis). Systemic treatment is indicated for more severe ocular inflammation such as intermediate or posterior uveitis, VKH syndrome, and orbital inflammatory disease. Definitive discontinuation of the therapy must be considered in the case of severe inflammation or choroidal neovascularization. In general, reinstitution of the therapy may be considered in patients with mild IRAE, upon regression of the symptoms.

It is difficult to definitely attribute this case of uveitis to the use of nivolumab. The criteria of chronologic imputability are difficult to verify. Given the efficacy of this therapy on the patient's systemic pathology, it did not seem ethically possible to suggest discontinuing and reinstituting the therapy. In addition, since the ocular inflammation was not very severe, it alone did not justify discontinuation of the suspect therapy (individual risk/benefit ratio). The criteria of etiologic imputability were also difficult to establish (little known characteristics of induced ocular inflammation).

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