

A case of immune checkpoint inhibitor-related conjunctivitis controlled by tacrolimus eye drops

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ABSTRACT

Purpose: We report a case where tacrolimus eye drops may have alleviated immune checkpoint inhibitor (ICI)-related conjunctivitis attributed to nivolumab.

Observations: A 61-year-old female complained of conjunctival hyperemia and eyelid swelling in both eyes. The patient was previously undergoing treatment for gastric cancer with nivolumab, with the final dose administered one week before the first ophthalmology visit. Initially, the patient was diagnosed with allergic conjunctivitis, managed with 0.1 % fluorometholone eye drops, 4 times daily in both eyes, but the symptoms did not improve despite 27 weeks of treatment, ICI-related conjunctivitis was considered, and the patient was prescribed with 0.1 % tacrolimus eye drops twice daily in both eyes. One week later, there was a remarkable improvement in the conjunctival symptoms. Three months after, the conjunctival hyperemia reduced and swelling disappeared in both eyes, and, the frequency of instillation was reduced to once daily. The condition remains in remission with 0.1 % tacrolimus eye drops applied once daily in both eyes.

Conclusions: Tacrolimus eye drops may have played a role to suppress ICI-related conjunctivitis.

1. Introduction

Immune-related adverse events are side effects that occur when using immune checkpoint inhibitors (ICIs), such as programmed cell death-1 (PD-1) inhibitors or cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors, in cancer treatment. ICIs activate T-cells that attack cancer cells as well as autoreactive T-cells that induce autoimmune reactions; these can sometimes increase autoimmune reactions in normal tissues. These adverse events can affect various organs throughout the body, causing skin symptoms, gastrointestinal symptoms, liver dysfunction, pneumonia or bronchitis, and endocrine abnormalities. Although the onset often occurs several months after ICI administration, there can be significant variability in the timing.

ICI-related conjunctivitis can occur as a side effect of ICI therapy,¹ with common symptoms including redness, itching, foreign body sensation, tearing, photophobia, and visual disturbances. In severe cases, complications such as keratitis or visual impairment may occur. The treatment for ICI-related conjunctivitis typically involves ophthalmic procedures such as eye irrigation and steroid eye drops to suppress inflammation. Additionally, it may be necessary to adjust the

dose, temporarily discontinue ICIs, or switch to other treatment modalities.

In this paper, we report a case of nivolumab-related conjunctivitis that was resistant to fluorometholone treatment but resolved with tacrolimus eye drops.

2. Case report

A 61-year-old female with a history of retinitis pigmentosa underwent treatment for gastric cancer using nivolumab, an anti-PD-1 antibody. The patient underwent 6 doses of nivolumab intravenous administration. Afterwards, the patient developed cholangitis and the treatment was stopped. Four days after the sixth dose of nivolumab, the patient developed conjunctival hyperemia and eyelid swelling in both eyes. Treatment with 0.1 % fluorometholone eye drops 4 times daily in both eyes was initiated. The patient continued fluorometholone for 27 weeks, but the conjunctival hyperemia and swelling gradually worsened, primarily affecting the palpebral conjunctiva. Conjunctival scraping samples revealed an abundance of polymorphonuclear white blood cells, with no bacteria or fungi detected. Allergen-specific

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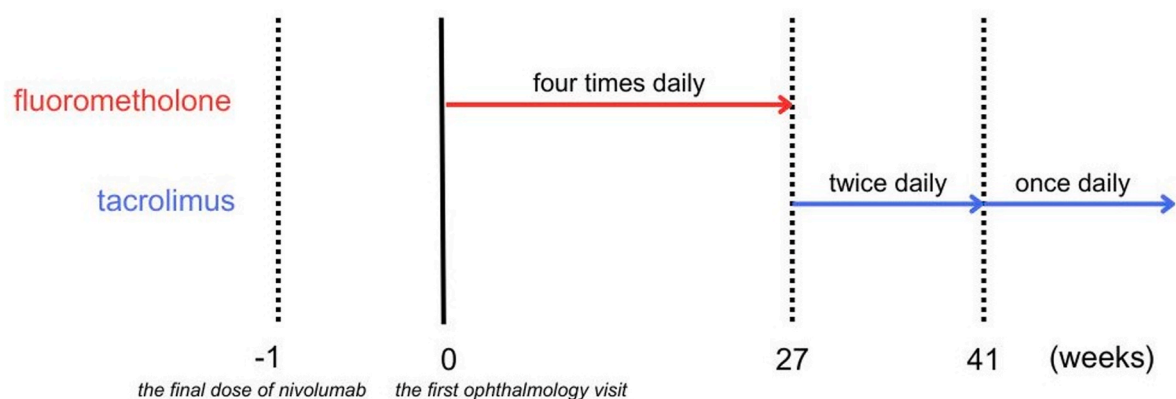


Fig. 1. Treatment timeline of 0.1 % fluorometholone eye drops and 0.1 % tacrolimus eye drops. Week 0 marks the first ophthalmology visit consult.

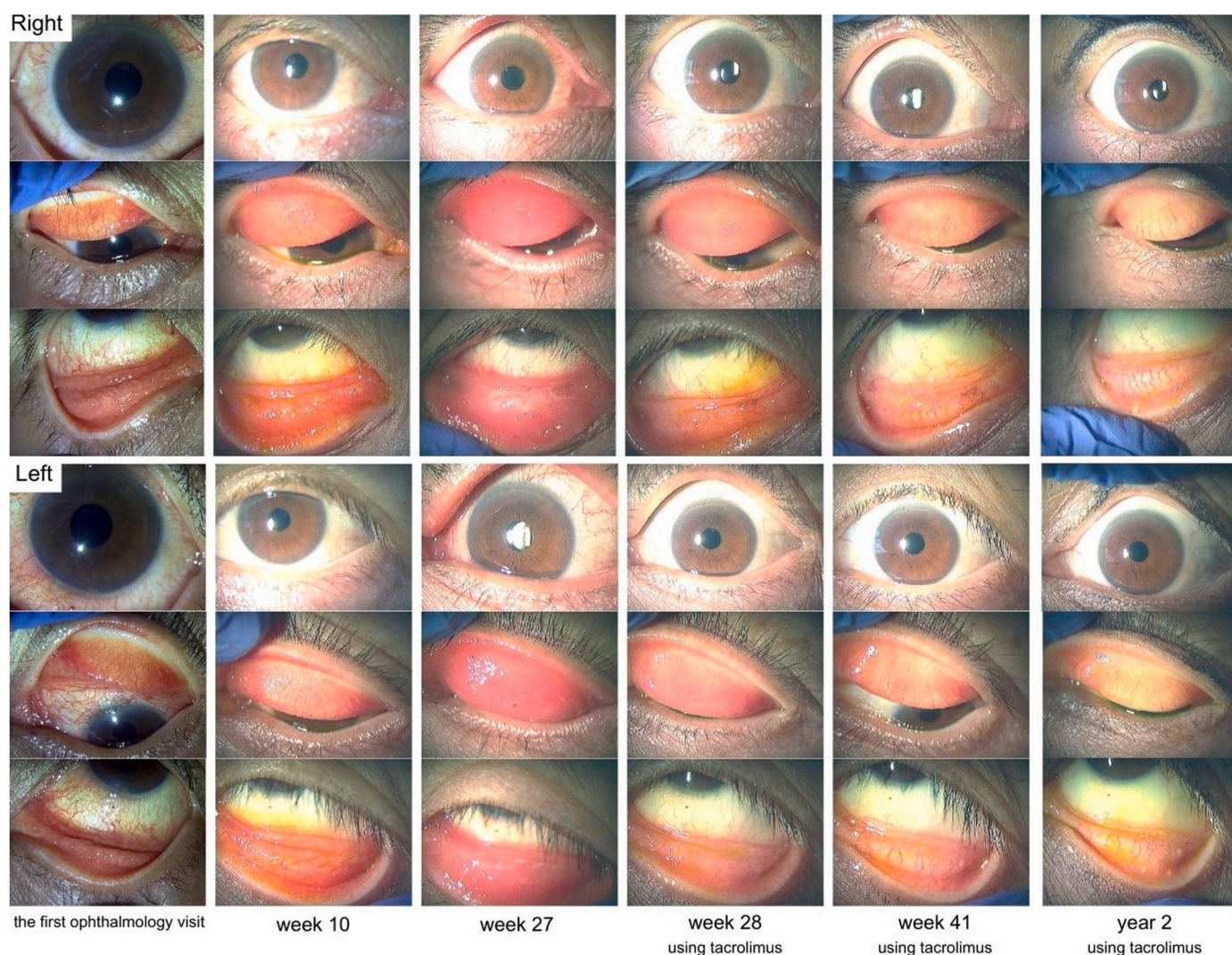


Fig. 2. Slit-lamp microscopy images of the patient who developed bilateral conjunctivitis following treatment with nivolumab for gastric cancer. Each photograph represents the weeks elapsed since the first ophthalmology visit. At the first ophthalmology visit (week 0), 0.1 % fluorometholone eye drops were started in both eyes. At week 27, treatment was switched to 0.1 % tacrolimus eye drops in both eyes.

immunoglobulin E was not detected in the serum despite multiple allergen screening tests. Furthermore, Chlamydia trachomatis Deoxy-ribonucleic Acid was not detected on polymerase chain reaction of the conjunctival scraping samples. Collectively, we speculated that the

conjunctival changes may be due to autoimmune reactions associated with anti-PD-1 antibodies. In the 27th week after the first ophthalmology visit, 0.1 % Tacrolimus eye drops were administered in both eyes twice daily instead of using more potent steroid eye drops. All other

eye drops were discontinued. One week later, a remarkable improvement was noted in the conjunctival symptoms. Three months after starting 0.1 % tacrolimus eye drops, the conjunctival hyperemia lessened and the swelling disappeared in both eyes. The frequency of installation was reduced to once daily. The condition remains in remission by using 0.1 % tacrolimus eye drops once daily for 3 months (Figs. 1 and 2).

3. Discussion

Nivolumab-associated conjunctivitis is presumably induced by the disturbance of immunosuppression induced by the interaction between PD-1 and PD-L1. Hori et al.^{2,3} investigated the role of PD-1 and PD-L1 interaction in corneal transplantation using *in vitro* culture systems of corneal tissue and T-cells, reporting that PD-L1 expression on cornea induces T-cell apoptosis and protects corneal endothelial cells from killing by T-cells. Nivolumab-related dry eye is suspected to be due to PD-1 blockade, which weakens corneal immunity and allows T-cell infiltration into the ocular surface. Similar to corneal transplantation and dry eye, PD-L1 blockade can theoretically activate T-cells that attack the conjunctiva. Park et al.¹ reported cases of nivolumab and pembrolizumab-related conjunctivitis that were controlled by topical steroids, which suppress immunocompetent cells in the conjunctiva.

Previous reports have suggested the efficacy of calcineurin inhibitors in ICI-related dry eye and immune-related adverse events in other organs. Nguyen et al.⁴ reported two cases of nivolumab-associated dry eye, with one case progressing to corneal perforation, which improved with eye drop regimens including topical cyclosporine. This report supports our notion that tacrolimus eye drops would also be effective against ICI-related conjunctivitis. The effectiveness of treatment with tacrolimus eye drops is reasonable because the calcineurin inhibitor downregulates T-cell activity, which is activated by the blockade of PD-1 and PD-L1 interaction. Additionally, systemic treatment with tacrolimus was also reported to control refractory immune-related hepatitis.⁵

In our case, improvement occurred just one week after switching from fluorometholone to tacrolimus eye drops at 29 weeks after discontinuing nivolumab. Osa et al.⁶ reported that the T-cell activating effects of nivolumab last at least 20 weeks; however, the duration of its effects can vary among individuals. Thus, it cannot be completely ruled out that the improvement in symptoms was due to the waning effect of nivolumab. Nevertheless, the drastic improvement in conjunctivitis was observed after switching medications which increases our suspicion that the improvement was due to tacrolimus itself rather than natural waning.

It can be argued that switching from fluorometholone to more potent steroid eye drops such as dexamethasone and betamethasone should have been attempted, prior to using tacrolimus. Dexamethasone and betamethasone eye drops have high corneal permeability and can easily penetrate the eye, resulting in a shorter duration of action on the ocular surface.⁷ Therefore, fluorometholone was selected for treating the conjunctivitis in this case. More importantly, the fact that T cells are predominantly involved in the development of irAEs^{2,3,5} led us to use tacrolimus eye drops which selectively suppress T cells, rather than strong steroid eye drops.

4. Conclusion

Tacrolimus eye drops may have played a role to suppress ICI-related conjunctivitis.

CRedit authorship contribution statement

Ayaka Kawaguchi: Writing – review & editing, Writing – original draft. **Hayato Tanaka:** Writing – review & editing. **Hitoshi Tabuchi:** Supervision. **Kei Nakai:** Supervision. **Atsuki Fukushima:** Writing – review & editing, Supervision, Conceptualization.

Patient consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. This report does not contain any personal identifying information.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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