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Case Report

Fulminant Marginal Keratitis Induced by Atezolizumab, a Programmed Death Ligand 1 Inhibitor for Lung Cancer

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Keywords
Corneal inflammation · Drug-related side effects and adverse events · Immune checkpoint inhibitors · Keratitis · Lung neoplasms

Abstract
Introduction: With the increasing use of immune checkpoint inhibitors, ocular adverse events have gained attention. We describe a case of atypical keratitis presumably induced by atezolizumab, a programmed cell death ligand 1 inhibitor. ***Case Presentation:*** A 73-year-old Japanese woman developed ring-shaped marginal infiltrations with epithelial breakdown of the corneas in both eyes. The patient had advanced small cell lung cancer and had received intravenous carboplatin, etoposide, and atezolizumab. She was treated with topical administration of 0.1% sodium phosphate betamethasone and 0.5% moxifloxacin six times daily. On day 14 following initial presentation, marked reduction of bilateral corneal infiltration was observed. During the succeeding cycles of chemotherapy, marginal keratitis did not recur, and then, the topical steroid was gradually tapered. ***Conclusions:*** Cancer immunotherapy, including atezolizumab, may lead to active T-cell recruitment into the cornea, which result in autoimmune corneal keratitis. We believe that this report is informative to both ophthalmologists and oncologists involved in the treatment of patients receiving cancer immunotherapy.

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Introduction

Immune checkpoint inhibitors (ICIs) are a new class of anticancer drugs [1, 2]. Several ICIs, including monoclonal antibodies for cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and PD-ligand 1 (PD-L1), have been approved for clinical use to treat various cancers. ICIs exert antitumor T cell responses by breaking immune quiescence. Subsequently, ICIs cause systemic immune-related adverse events (AEs) due to their non-specific immune activation. Common AEs of ICIs include pneumonitis, colitis, and hepatitis. The frequency of systemic AEs is considerably high, ranging between 54% and 96%, whereas ocular AEs are relatively rare [3, 4].

With the increasing use of ICIs, however, ocular AEs have gained attention. Some observational studies and case series have shown that ICIs cause various inflammatory eye diseases such as uveitis, scleritis, dry eye, optic neuropathy, and ophthalmoplegia [2–6]. Concerning ocular surface disorders, some severe conditions, such as granulomatous conjunctivitis, cicatrizing conjunctivitis, and autoimmune keratitis, have been reported [3, 7, 8]. Herein, we report a case of atypical keratitis presumably induced by atezolizumab, a PD-L1 inhibitor.

Case Presentation

A 73-year-old Japanese woman was referred to our ophthalmological clinic due to sudden onset of blurred vision in both eyes 1 week after receiving a second course of carboplatin, etoposide, and atezolizumab (CBDCA + ETP + atezolizumab) for advanced small cell lung cancer. She had noted ocular pain in both eyes 3 days before the sudden visual disturbance. Upon initial visit, her best-corrected visual acuity was 20/40 in the right eye and 20/200 in the left eye. Intraocular pressure in both eyes was normal. Slit-lamp examination revealed bilateral ring-shaped marginal infiltrations of the cornea with marked conjunctival hyperemia (Fig. 1a, b). Stromal edema with Descemet membrane folds and anterior chamber cells were also seen in the left eye. Sites of infiltration were stained with fluorescein sodium, which suggested epithelium breakdown. Anterior segment optical coherence tomography revealed that the affected lesions were thickened, possibly because of stromal edema (Fig. 1c–f).

There were no signs of blepharitis or meibomian gland dysfunction. The results of microbial culture from conjunctival swabs were negative. The patient had no previous history of inflammatory ocular disease including marginal keratitis, and reported that there was nothing unusual at the first course of CBDCA + ETP + atezolizumab. Autoantibody tests for anti-nuclear antibody, rheumatoid factor, SS-A/Ro, SS-B/La, PR3-ANCA, and MPO-ANCA were negative. Hence, a diagnosis of bilateral marginal keratitis presumably due to atezolizumab was made.

She was prescribed with 0.1% sodium phosphate betamethasone eye drops and 0.5% moxifloxacin eye drops six times daily. An ophthalmological examination conducted on day 14 following her initial presentation revealed an improved best-corrected visual acuity (20/30 for both eyes) and marked reduction of bilateral corneal infiltration (Fig. 2a–d). Anterior chamber cells and Descemet membrane folds in the left eye also disappeared. Anterior segment optical coherence tomography showed thinning of the peripheral stroma of both eyes (Fig. 2e, f). Topical administration of 0.1% betamethasone four times daily was continued during the third and the fourth cycles of CBDCA + ETP + Atezolizumab treatment. Marginal keratitis did not recur the rest of the chemotherapy duration, and then topical steroid was gradually tapered.

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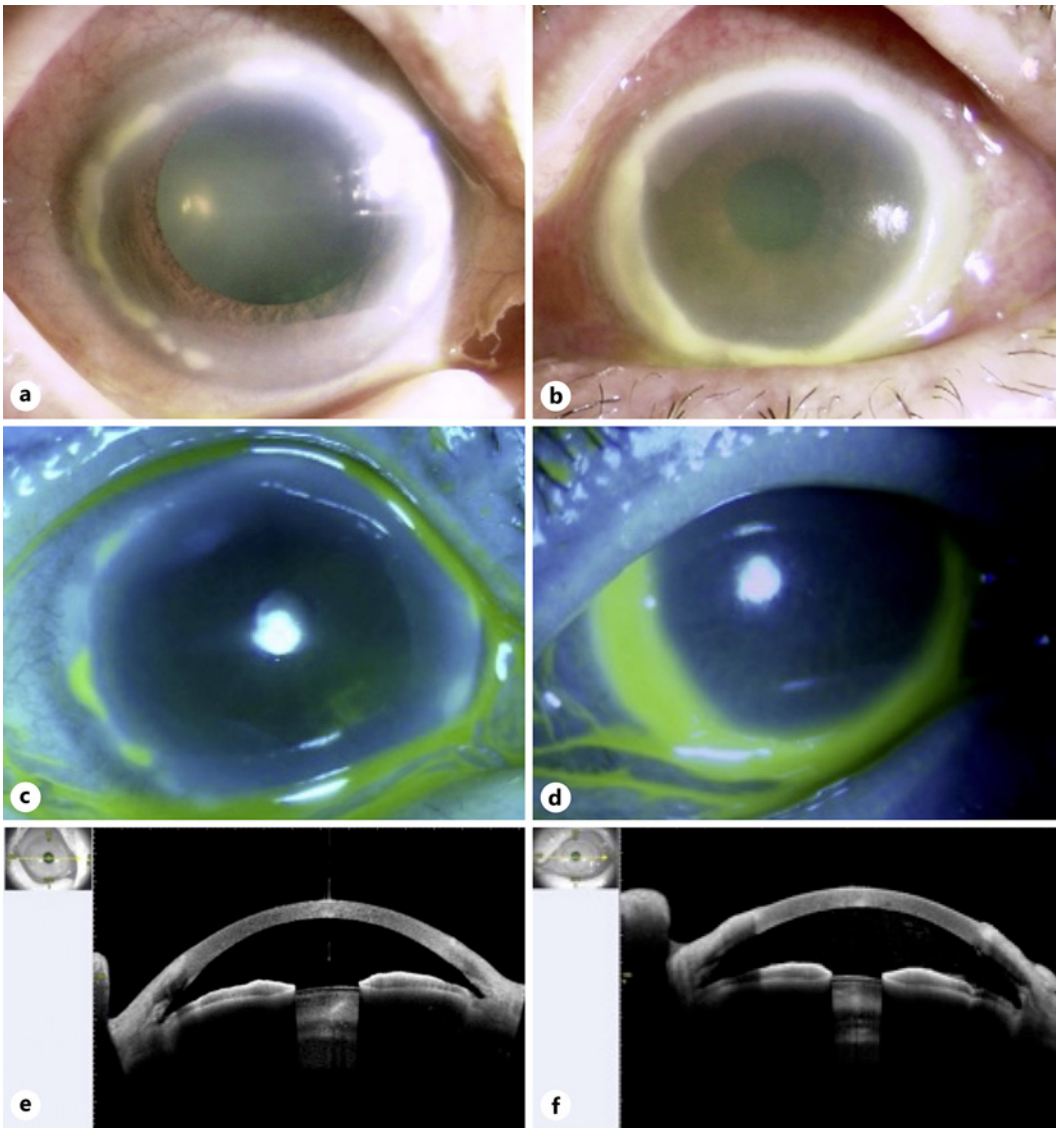

Fig. 1. Slit-lamp examination and anterior segment optical coherence tomography (AS-OCT) at initial presentation (**a**, **c**, **e** for the right eye. **b**, **d**, **f** for the left eye) of the patient. Ring-shaped marginal infiltrations with marked conjunctival hyperemia were observed in both eyes (**a**, **b**). Sites of infiltration were stained with fluorescein sodium (**c**, **d**) and thickened possibly because of stromal edema (**e**, **f**).

Discussion

The increased association between ICIs and ocular AEs has been recognized [2–6]. Additionally, the incidence of ocular AEs appears to be different depending on the classes of ICIs used. Young et al. [6] reviewed two large AE databases and summarized AEs of inflammatory eye conditions, including keratitis (n = 5) due to PD-1 and PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab, and durvalumab). Fang et al. [2] conducted a disproportionality analysis to quantify the risk of AEs with ICIs and reported that atezolizumab might have the highest association with eye inflammation. In addition to case series and data base surveys, uncommon AEs on the ocular surface (granulomatous conjunctivitis

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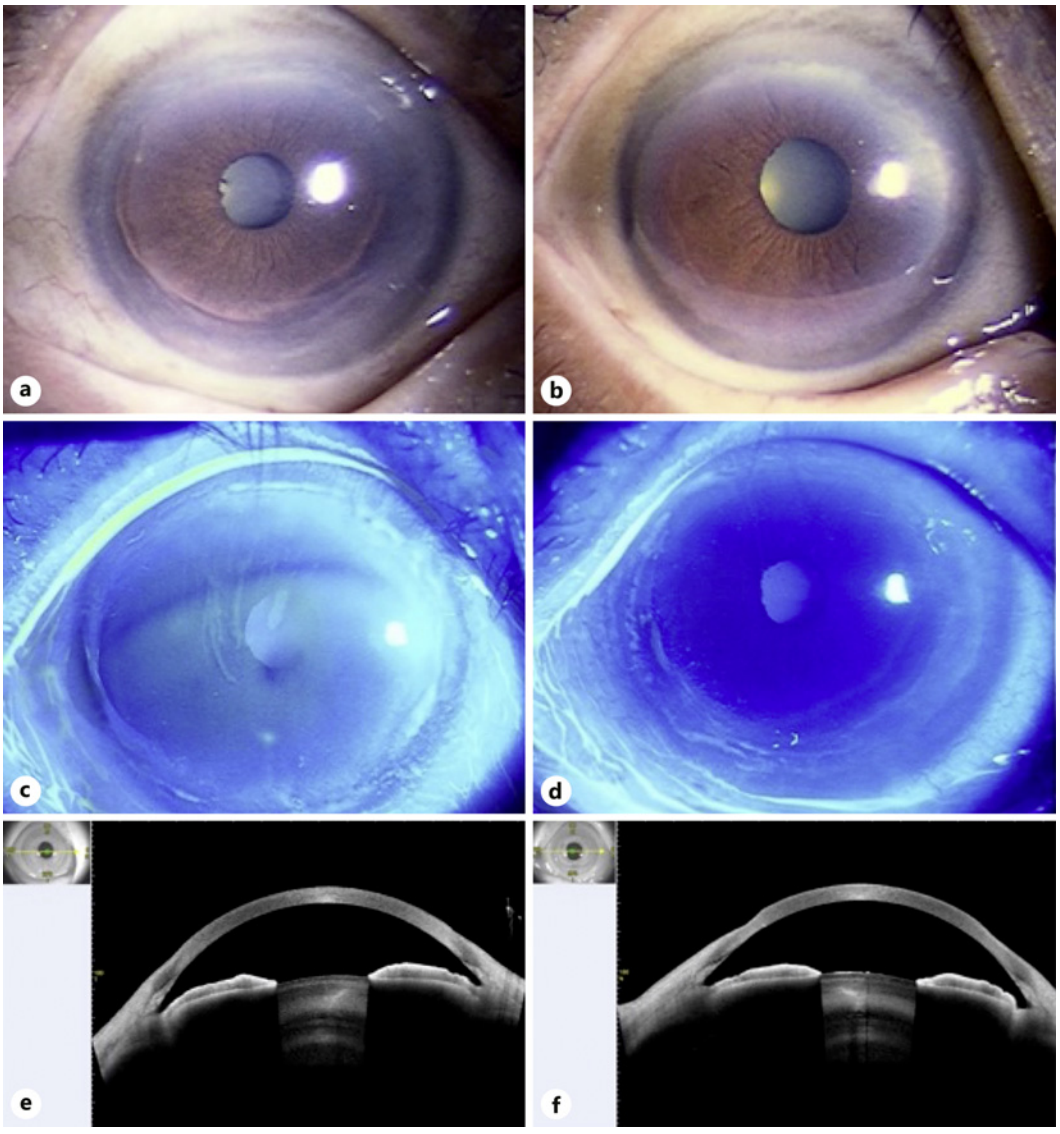

Fig. 2. Slit-lamp examination and anterior segment optical coherence tomography (AS-OCT) on day 14 following initial presentation (**a**, **c**, **e** for the right eye. **b**, **d**, **f** for the left eye) of the patient. Marked reduction of bilateral corneal infiltration was observed (**a–d**). AS-OCT showed thinning of peripheral stroma of both eyes (**e**, **f**).

and autoimmune keratitis) associated with atezolizumab have been reported as a case report [7, 8].

In our case, bilateral marginal keratitis was observed after atezolizumab administration. The differential diagnoses of this condition include catarrhal infiltrates associated with Staphylococcal blepharitis, Mooren ulcer, peripheral ulcerative keratitis associated with collagen-vascular disorders, and contact lens-induced peripheral ulcer. However, the patient did not have any history of inflammatory eye disease nor used contact lenses. Evaluation for autoimmune causes of collagen-vascular disorders was also unremarkable. We speculate that atezolizumab, a PD-L1 inhibitor, might be the cause of the corneal lesions. The corneal epithelium, stroma, and endothelium constitutively express high levels of PD-L1, contributing to the immune-privileged status of the cornea [9–11]. Under normal conditions, the

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constitutive expression of PD-L1 in the cornea downregulates antigen presenting cells located in the peripheral cornea and limits T-cell infiltration. Inhibition of PD-1/PD-L1 results in an immune-mediated response involving upregulation of antigen presenting cells and active T-cell recruitment into the cornea. Thus, considering the crucial role of PD-L1 and its ligands in the cornea, cancer immunotherapy, including atezolizumab, can be causative of autoimmune corneal inflammation. In our case, marginal keratitis responded well with topical application of steroid eye drops and did not recur during the rest of the chemotherapy duration.

The number of reported ocular AEs associated with ICIs is increasing. The incidence of ocular AEs induced by PD-1/PD-L1 inhibitors is estimated to be 3.3–7.4% [6], which is considerably higher than assumed before [3, 4]. Herein, we report a patient with lung cancer who developed bilateral marginal keratitis, which has not been known as AEs of atezolizumab administration. Ophthalmologists, however, may encounter similar cases as atezolizumab is highly associated with ocular inflammation [2]. We believe that this report is informative to both ophthalmologists and oncologists involved in the treatment of patients receiving cancer immunotherapy. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535077).

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Statement of Ethics

The authors have no ethical conflicts to disclose. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This report does not contain any personal information that could lead to the identification of the patient. Reporting and writing are all in compliance with the Declaration of Helsinki. The study protocol was reviewed and the need for approval was waived by the Institutional Review Board of Kyorin University Hospital.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Masashi Yamamoto, MD; Masakazu Yamada, MD, PhD; Yumi Kusumi, MD; Masaki Fukui, MD, PhD; and Chika Shigeyasu, MD, PhD meet the ICMJE criteria including substantial contributions to the conception of the work, drafting the work critically, final approval of the version to be published, and agreement to be accountable to all aspects of the work regarding accuracy and integrity of the manuscript. Masakazu Yamada, MD, PhD, is the corresponding author.

Data Availability Statement

All data generated or analyzed during this study are included in the article and its online supplementary material. Further enquires can be directed to the corresponding author.

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