Case Report

Corneal ulcer development due to sintilimab-anlotinib combination therapy-induced dry eye: a case report

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Background: Programmed cell death-1 (PD-1) inhibitors and anti-angiogenic drugs have become a hotspot in research of anti-tumor programs; however, they can also cause some rare drug-related adverse reactions. Immune checkpoint inhibitors (ICIs) cause adverse reactions in the body, collectively known as immune-related adverse events (irAEs). Ocular side effects can occur in both targeted and immunotherapy patients, including dry eye, blurred vision, uveitis, conjunctivitis, retinopathy, or thyroid eye disease. To our knowledge, this is the first case report describing corneal ulcers secondary to dry eye in a patient treated with the combination of PD-1 inhibitor sintilimab and multi-targeted receptor tyrosine kinase inhibitor (TKI) anlotinib.

Case Description: A 65-year-old woman with non-small cell lung cancer (NSCLC) and bone metastases, without pre-existing ocular conditions, experienced mild dry eye symptoms 1 month following treatment with sintilimab (200 mg q3w) in combination with anlotinib (12 mg q3w). Unrelieved dry eye symptoms occurred after the third cycle of chemotherapy, and she was diagnosed with dry eye syndrome. Subsequently, she received corneal protective lens, sodium hyaluronate eye drops, and prednisone treatment. Her corneal epithelial damage did not improve significantly, and within the following 2 months, her vision decreased in both eyes and progressed to bilateral corneal ulcers. Oral administration of sintilimab and anlotinib was interrupted, and treatments such as corticosteroids, anti-inflammatory drugs, and corneal repair were administered; however, both eyes presented with corneal subepithelial defect and corneal scarring. Due to a shortage of donors, no corneal transplantation surgery could be performed.

Conclusions: The development of corneal epithelial disorders in patients receiving target therapy and immunotherapy may not be reversed by reducing its dose. Although the condition is controlled with the use of glucocorticoids, some eye side effects cannot be cured. The timely detection and intervention of adverse effects of anti-tumor drugs by oncologists and ophthalmologists is critical for rational prescription. Ophthalmologists should be aware of eye side effects in patients using immunotherapy to ensure appropriate treatment and minimize potential eye complications such as dry eye, conjunctivitis, etc.

Keywords: Sintilimab; anlotinib; non-small cell lung cancer (NSCLC); corneal ulcer; case report

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Introduction

Lung cancer is the leading cause of cancer death worldwide. In China, lung cancer has become the malignant tumor with the highest annual morbidity and mortality. Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancer cases (1). In the past, chemotherapy was the main treatment for advanced NSCLC, but platinum-based double-drug chemotherapy has limited efficacy and a high incidence of adverse reactions (2). In recent years, the precision treatment of lung cancer has developed rapidly, with the emergence of targeted therapy, anti-angiogenic therapy and immunotherapy. In 2013, the Food and Drug Administration (FDA) granted approval for the utilization of a novel programmed cell death-1 (PD-1) antagonistic antibody as an immune checkpoint inhibitor (ICI) in the treatment of NSCLC, thereby ushering in a new era in the realm of tumor immunotherapy (3). Currently, there is a rapid global advancement in research within this domain, encompassing more than 500 targets (4). The primary approaches for tumor immunotherapy comprise cytokine therapy, tumor vaccines, cell therapy, ICIs, and specific antibodies (5). In China, research in this field mainly focuses on T-cell immune modulators and cell therapy.

PD-1 and programmed cell death ligand-1 (PD-L1) are currently widely used ICIs. Selective up-regulation of PD-L1 on the surface of tumor cells promotes the apoptosis of T cells, resulting in impaired immune activity. This approach aims to harness the body's own immune system for tumor defense by blocking the PD-1/PD-L1 signaling pathway. Currently, the clinical assessment of solid tumor treatment efficacy primarily relies on lesion size observation. Commonly employed clinical evaluation indices include overall survival (OS), progression-free survival (PFS), and objective response rate (ORR). Among them, ICIs combined with anti-angiogenic drugs have achieved gratifying results in the treatment of NSCLC, showing good efficacy and acceptable tolerance, and have certain clinical application prospects. It has become a hotspot in the research of anti-tumor programs (6-10).

However, the non-specific immune activation effect of immunosuppressants can lead to immune-related adverse events (irAEs) affecting multiple organs in the body. Common irAEs encompass dermatitis, hypertension, hematotoxicity, myocarditis, pneumonia, colitis and hepatitis. Additionally, endocrine disorders such as type 1 diabetes and neurotoxicity may also arise (11-15). Dry eye syndrome, uveitis, ocular myasthenia gravis, and conjunctivitis are widely recognized as ICI-related adverse reactions in the eyes (16-18). Furthermore, there have been documented cases of thyroid associated ophthalmopathy (19), dry eye syndrome (20,21), optic neuropathy (22), orbital myopathy (23), keratitis (24,25), vortex keratopathy (26), corneal ulceration and even perforation (27) and epiphora (28).

However, it remains uncertain whether combination therapy will elevate the risk of toxicity for NSCLC patients due to the variable characteristics of the drug utilized and individual patient factors. Although ocular adverse events (AEs) associated with PD-1/PD-L1 inhibitors are infrequent, limited research is available in this area. The majority of ocular immune-related AEs stem from case reports, safety analyses, and some observational studies. In this study, we present a case of progressive vision loss as an ocular complication in a patient with NSCLC following treatment with the PD-1 inhibitor sintilimab in combination with the anti-angiogenic drug anlotinib. This finding contributes to the growing body of evidence regarding adverse ocular reactions associated with various PD-1 inhibitors and combination therapies, thereby enhancing our understanding of these potential complications. We present this article in accordance with the CARE reporting checklist (available at

Highlight box

Key findings

- This is the first case report of a corneal ulcer caused by programmed cell death-1 (PD-1) inhibitor sintilimab combined with multi-targeted receptor tyrosine kinase inhibitor anlotinib.

What is known and what is new?

- Both targeted drugs and immunotherapy drugs can cause ocular side effects.
- Anlotinib may destabilize the internal environment of the ocular surface, resulting in lack/imbalance of tear film growth factors, delayed healing of corneal cells, dry eye, and ultimately lead to corneal ulcer. As they increase the immune response, PD-1 inhibitors can act on other normal cells on the ocular surface, causing dry eye syndrome, indirectly or directly damaging corneal epithelial cells, and resulting in corneal ulcers.

What is the implication, and what should change now?

- Some adverse reactions may cause irreversible eye injury, which should be closely monitored clinically. Therefore, it is particularly important for oncologists to understand and predict the possible side effects and to refer ophthalmologists in time.

Figure 1 Anterior segment OCT images of the left eye (a 1 mm × 1 mm circular shape below the pupil of the left eye and an irregular deep corneal ulcer about 2 mm × 3 mm in the temporal side, with obvious thinning of corneal layers). OCT, optical coherence tomography.

https://tcr.amegroups.com/article/view/10.21037/tcr-23-1952/rc).

Case presentation

A 65-year-old Chinese woman was diagnosed with lung adenocarcinoma (cT1aNmM1, bone metastases), negative for endothelial growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Her medical history included hyperlipidemia and fatty liver. From 2014 to 2019, she was receiving treatments for chemotherapy intermittently. During treatment, liver and kidney function impairment and first-degree myelosuppression were observed, which could be improved after symptomatic treatment without ocular adverse reactions. The final curative effect was evaluated as stable condition. In July 2020, examination revealed brain metastases, and four courses of sintilimab + anlotinib were performed. The patient began to experience vision loss in November, and she visited the ophthalmology clinic of The Second Affiliated Hospital of Guangzhou University of Chinese Medicine due to the unsatisfactory treatment outcome.

The patient complained about redness, pain and vision loss in the left eye since a month prior. Visual acuity in the right eye was 0.5, and visual acuity in the left eye was 0.3. Slit lamp examination revealed red and edematous left eyelid, conjunctival hyperemia, old leukoplakia in the center of the cornea, thinning of the leukoplakia, focal thinning of the cornea at 1 o'clock, focal anterior adhesion of the iris, and lens opacity. The anterior segment photo and optical coherence tomography (OCT) image of the left eye showed corneal thinning of the defect area (*Figure 1*), which led to it being defined as a corneal ulcer. Bandage contact lenses and recombinant bovine basic fibroblast growth factor (FGF) eye drops were given to promote repair and regeneration. When asking her pathogenetic process, she reported that her eyes felt mildly dry after the second course of chemotherapy on August 2020, and the eye dryness became obvious and difficult to relieve in September. The visual acuity in both eyes was 0.5 at that time. The Keratograph 5M (Ocular, Germany) revealed an imbalance of tear film stability and meibomian gland dysfunction, which was classified as dry eye, and she received corneal bandage lens, sodium hyaluronate eye drops, and prednisolone.

On 16 November 2020, the patient's visual acuity in the right eye decreased to 0.05, and the visual acuity in the left eye was 0.3. Slit lamp examination revealed epithelial dissolution, ulceration, no pus coating, white secretion, and thinning of the corneal stroma in the central cornea of the right eye. The scope of the central corneal lesion of the left eye was reduced to 2 mm × 2 mm, and the remaining structures were basically the same as before. The OCT image of the right anterior segment showed focal corneal thinning (*Figure 2*). At that time, levofloxacin eye drops were added to the treatment.

Subsequently, the oncology department discontinued sintilimab and anlotinib, and changed the anti-tumor regimen to vincristine + methylprednisolone to suppress immunity; however, her vision did not fully recover.

Visual acuity in the right eye on 26 February 2021 was recorded as hand motion, and that of the left eye was 0.05. Slit lamp examination showed that local thinning of the cornea and the epithelium had been repaired, with perilesional corneal edema and corneal endothelial folds. Tobramycin and dexamethasone eye drops, diclofenac sodium eye drops, and levofloxacin eye drops were administered. Three days later, the visual acuity in the right eye was the same as before, and the visual acuity of the left eye was 0.3. OCT of the anterior segment of both eyes showed that the corneal epithelium had been repaired and there was a subepithelial defect (*Figure 3*). On 8 March, the photograph of the anterior segment was reviewed (*Figure 4*).

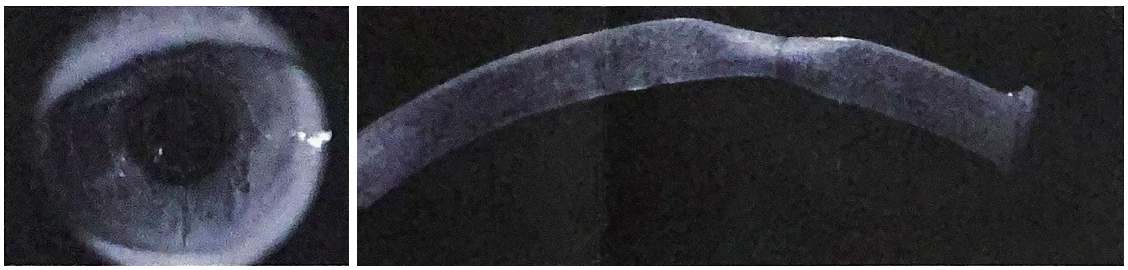

Figure 2 OCT image of the anterior segment of the right eye (a transverse fusiform ulcer about 5 mm × 2 mm in size can be seen on the temporal cornea, reaching deep into the stroma layer and thinning the cornea). OCT, optical coherence tomography.

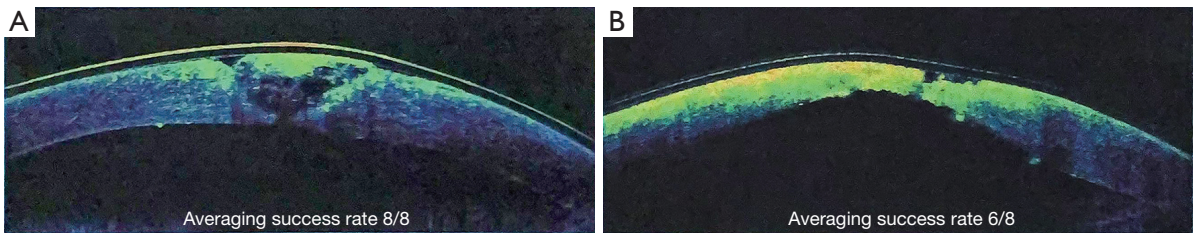

Figure 3 OCT images of the anterior segment of both eyes. (A) Left eye: corneal epithelial repair, subepithelial defect; (B) right eye: corneal stroma thinning, corneal subepithelial defect. OCT, optical coherence tomography.

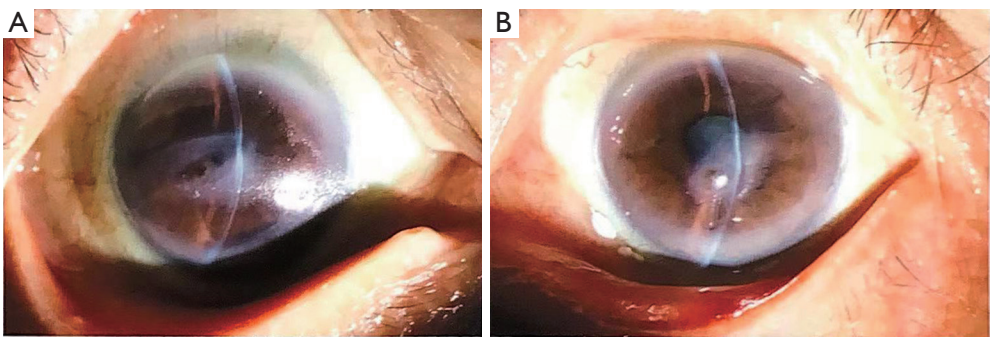

Figure 4 Photograph of the anterior segment of both eyes, corneal edema less severe than before, and a corneal scar is obvious (A: left eye; B: right eye).

The visual acuity of both eyes was the same as before, and the corneal edema diminished. The treatment mainly aimed to protect the cornea and reduce inflammation. On 23 March, her vision remained the same, and she received fluorometholone + anti-inflammatory treatment. Considering that the corneal scar could not be removed, the patient was advised to undergo keratoplasty. Due to the lack of transplant donors, corneal transplantation was not performed. Eventually, the patient's lung cancer advanced and ultimately resulted in her passing due to a lung infection, with a projected life expectancy of seven years. The study was in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

There are various mechanisms for tumor cells to escape the body's immunity, one of which is PD-L1 expression. PD-L1 expressed by tumor cells can recognize and bind to the PD-1 on T lymphocytes, thereby weakening the ability of immune cells to recognize and eliminate tumor cells, achieving the role of immune escape (29). Sintilimab is an immunoglobulin G4 (IgG4) monoclonal antibody that blocks the immunosuppressive response mediated by the PD-1 pathway by binding to the PD-1 receptor on the surface of T cells and increase the cytotoxicity against tumor cells of tumor infiltrating lymphocytes (TILs) (30). A study has shown that angiogenesis is closely related to tumor immune microenvironment and vascular endothelial growth factor (VEGF) can block T cell infiltration, transport, and inhibit the induction, proliferation, and maturation of immune cells, so that the body can decrease tumor activity (31). Appropriate inhibition of VEGF can improve the tumor immune microenvironment, turn it into an immune activation state, and improve the effect of tumor immunotherapy (32). Anlotinib is a multi-targeted receptor tyrosine kinase inhibitor (TKI) independently developed in China, which mainly inhibits production of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), FGF receptor (FGFR), stem cell growth factor receptor, and other kinase activities (33).

A real-world study showed that anlotinib combined with PD-1 inhibitors had higher ORR and longer PFS than PD-1 inhibitor monotherapy (34). In a phase 1b trial of sintilimab combined with anlotinib for advanced NSCLC, the results showed that 22 enrolled patients had an ORR of 72.7%, a disease control rate (DCR) of 100%, and a median PFS of 15 months (6). The chemotherapy-free regimen of ICIs combined with anti-angiogenic drugs has achieved considerable clinical effects, and provides an option for patients who cannot tolerate chemotherapy or have progressed after multiple lines of therapy.

However, immunosuppressive therapy and targeted therapy can also cause drug-related adverse reactions, mainly involving the skin, cardiovascular, endocrine glands, digestive, lung, kidney, and liver systems (35,36), and ocular adverse reactions are rare. This is the first case report of a corneal ulcer caused by sintilimab and anlotinib; therefore, there are an insufficient number of cases to provide better evidence for the views presented here.

Ocular irAEs have an annual incidence of 1.1% (11). They can occur at any time during treatment, even after discontinuation of ICIs, and common ocular AEs occur at a median of 6 weeks [interquartile range (IQR), 0–16 weeks] (18,37). Anlotinib-induced adverse reactions were mainly within 2 months after administration (73.68%) (38). This is consistent with the timing of our case.

Various factors contribute to the occurrence of corneal ulcers induced by ICIs and targeted drugs. Growth factors such as VEGF, FGF, and platelet-derived growth factor (PDGF) are expressed in normal tissues such as conjunctival endothelium, corneal stroma, endothelium, and corneal epithelium. Binding to its receptor stimulates corneal cell proliferation, biochemistry, increases vascular permeability, and helps corneal cell recovery and homeostasis (39). Anlotinib may destabilize the internal environment of the ocular surface, resulting in an imbalance or lack of growth factors in the tear film, and lead to ocular surface damage and the development of dry eye. It also delays corneal surface healing, reduces the proliferation of corneal epithelial cells, and further aggravates dry eye development. In addition, VEGF is an important neurotrophic growth factor for corneal nerves. After local anti-VEGF treatment, corneal nerve density and fiber numbers are reduced, nerve regeneration is delayed, and dry eye is caused, which in turn leads to corneal ulcers (40). However, a study has shown that anlotinib exerts anti-neovascular effects by blocking VEGFR and PDGFR as well as downstream signaling pathways, has a positive effect on regulating ischemia and hypoxia in ocular tissues, and has no obvious *in vitro* cytotoxicity or *in vivo* tissue toxicity (41).

Other targeted drugs can also cause corneal and ocular surface diseases. ASP-5878, which targets EGFR, VEGFR, RET and SRC kinases, can cause swirling deposits in the cornea, resulting in blurred vision (42). The multi-target TKI inhibitor regorafenib (43) is mainly anti-VEGF and can cause severe corneal perforation. In addition, the FGFR-TKI infigratinib (44) can cause dry eye, severe punctate keratitis, and recurrent corneal ulcers. EGFR inhibitors such as cetuximab and erlotinib have been reported to cause ocular adverse reactions, such as rash, eyelash overgrowth (longer, curly, stiffer), eyelid inversion, trichiasis, blepharitis, abnormal tear film function (45,46), and even persistent corneal epithelial defects (47), corneal lysis, and perforation (48-51). Anlotinib has many targets, and its mechanism of causing keratopathy may be similar to that of other TKI drugs. In addition, anlotinib can inhibit vascular repair by inhibiting VEGFR, PDGFR, etc., leading to hand-foot syndrome (52).

The most common clinical manifestations of ICI-related

ocular toxicity were dry eye (3–24%), uveitis (1%), and ocular muscle weakness. Other less common ophthalmic AEs include central retinal vein occlusion, retinal detachment, conjunctivitis, ocular myositis, vasculitis, keratitis, episcleritis, choroidopathy, and optic neuropathy (11,18,53-58). Under physiological conditions, PD-L1 is highly expressed in the corneal epithelium and negatively regulates the expression of chemokines in the cornea to prevent the occurrence of autoimmunity. A study has shown that the downregulation of PD-L1 expression leads to an imbalance of the immune system that regulates the corneal and conjunctival inflammatory microenvironment, triggering dry eye, and further aggravates corneal inflammation in patients with dry eye (59). It can even cause corneal perforation (60).

Autoimmune disorders such as Sjogren syndrome (SS) may act on the lacrimal glands, causing eye discomfort or inflammation in the early stage of the disease and visual impairment or even blindness in the late stages (61). However, the patient did not complain of obvious eye discomfort before the use of immune drugs. After ICI treatment, the patient's dry eye symptoms aggravated with the increase of the course of treatment. Therefore, corneal ulcer due to autoimmune diseases was not considered. Unfortunately, there were no immunological tests to justify.

Therefore, we speculate that sintilimab causes dry eye, and anlotinib further exacerbates dry eye symptoms, inhibits corneal vascular repair and neuronutrition, exacerbates dry eye, and may cause corneal inflammation and eventually corneal ulcer. In addition, systemic nutritional deficiency in cancer patients can also delay ulcer healing.

After 5-month continuous treatment, the patient felt that the pain in the eyes was better than before. During the period of corneal scarring, the patient said that her vision sometimes improved and sometimes deteriorated, but the eyes still could not fully recover, which made her very anxious and depressed.

At present, there are no accurate predictors for the occurrence of ocular AEs related to immunosuppressants and targeted drugs, but patients with blurred vision and dry eye symptoms should monitored carefully in order to facilitate early identification, diagnosis, and treatment. In terms of treatment, antibiotic eye drops to prevent secondary infection and use of drugs that promote corneal repair are routine treatments, and discontinuation of targeted or immunotherapy should be considered in patients with persistent non-healing corneal ulcers.

Conclusions

In conclusion, both targeted drugs and immunotherapy drugs can cause ocular side effects. Although ocular side effects are relatively mild compared with the systemic reactions, they can seriously threaten the vision and life quality of patients. Some adverse reactions can cause irreversible eye damage, for which vigilant observation is advised. In the early stages of cancer treatment, it is crucial to closely monitor ocular health and visual function in patients undergoing immune and targeted therapy. Particular attention should be given to preventing and managing mild symptoms such as dry eye and conjunctivitis. Oncologists must possess a comprehensive understanding of potential side effects and proactively consult with ophthalmologists when necessary.

However, current knowledge regarding ophthalmic side effects primarily relies on case reports, necessitating further comparative trials to investigate the impact of each anticancer drug on ocular health along with its underlying mechanisms. Given the escalating number of cancer patients, it is imperative to develop more reliable methods for assessing the correlation between patients' ocular symptoms and drug usage, such as scoring scales. This study presents novel findings by identifying corneal ulcers induced by sintilimab and anlotinib for the first time while providing new data into ocular adverse reactions caused by oncology drugs alongside outlining potential mechanistic pathways leading to these AEs.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1952/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1952/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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