BMC Ophthalmology

CASE REPORT

Open Access

Presumed reactivation of herpes simplex virus-associated endothelial keratitis after treatment with topical interferon-α 2b for ocular surface squamous neoplasia

Sepehr Feizi[1*], Mohsen Zare[1] and Hamed Esfandiari[1]

Abstract

Background To report a case of herpes simplex virus (HSV)-associated endothelial keratitis in a patient receiving topical interferon (IFN)-α 2b for the management of ocular surface squamous neoplasia (OSSN).

Case presentation A 65-year-old female was diagnosed with OSSN characterized by gelatinous growth on the left cornea, without conjunctival involvement. She had no history of herpetic keratitis. The patient was treated with topical IFN-α 2b 1 million IU/ml four times daily, leading to complete clinical resolution of the OSSN within three months. However, four months after initiating treatment, while still on the medication, she presented with decreased visual acuity, ocular injection, and pain in the left eye. Slit-lamp examination revealed central corneal stromal edema, infiltration, and keratic precipitates. A diagnosis of HSV endotheliitis was made, and IFN-α 2b was discontinued. The patient was treated with topical betamethasone 0.1% six times daily and oral acyclovir 400 mg five times daily, resulting in complete resolution of the disciform keratitis within three weeks. There has been no recurrence of herpetic infection or OSSN during 10 months of follow-up after discontinuing all medications.

Conclusion Ophthalmologists should be alert to the possibility of recurrent herpetic keratitis in patients treated with IFN-α 2b for OSSN who present with sudden visual decline.

Keywords Ocular surface squamous neoplasia, Topical interferon-α 2b, Herpes simplex virus-associated endothelial keratitis

*Correspondence:
Sepehr Feizi
sepehrfeizi@yahoo.com
[1]Ocular Tissue Engineering Research Center, Research Institute for Ophthalmology and Vision Science, Shahid Beheshti University of Medical Sciences, No. 23, Paidarfard St., Boostan 9 St., Pasdaran Ave, Tehran, Iran

Background

Ocular surface squamous neoplasia (OSSN) is the most common non-melanocytic tumor affecting the epithelium of the conjunctiva, limbus, and cornea [1]. Its spectrum of invasiveness ranges from squamous epithelial dysplasia to invasive squamous cell carcinoma [1–3]. Although typically a low-grade, slow-growing tumor, delayed diagnosis and treatment can lead to local invasion and, in rare cases, metastasis [3, 4]. Historically, surgical excision with wide margins using the "no-touch" technique has been the standard treatment for OSSN due to its ability to rapidly resolve the tumor, provide histopathologic samples, and attain low recurrence rates when clear margins are achieved [3]. However, surgical excision of the tumor carries the risk of significant complications, including conjunctival scarring, symblepharon formation, and limbal stem cell deficiency, emphasizing the need for alternative treatments [3].

Interferon (IFN)-α 2b is a naturally occurring glycoprotein with antiviral, antitumor, and immunomodulatory properties [5]. Multiple studies have demonstrated its efficacy as a primary treatment for OSSN [2, 6]. Topical IFN-α 2b is generally well-tolerated with minimal adverse effects [7–9]. However, ophthalmologists who prescribe this medication must be aware of its potential ocular adverse reactions which may emerge with its wider application. Herein, we report a case of herpes simplex virus (HSV)-associated endothelial keratitis in a patient receiving topical IFN-α 2b for the treatment of OSSN.

Case report

In March 2023, a 62-year-old female presented with a gradual, painless reduction in visual acuity in her left eye that began four months prior. Her past medical history was unremarkable, with no prior history of herpetic keratitis or herpes simplex or herpes zoster infection in other parts of the body. Examination revealed a best-corrected visual acuity of 20/20 in the right eye and 20/320 in the left eye. Slit-lamp examination of the right eye was unremarkable. In contrast, the left cornea showed a gelatinous growth originating from the nasal limbus and extending onto the corneal surface, without conjunctival involvement. The lesion covered four-fifths of the epithelial area, displaying well-defined, fimbriated, and elevated margins with an opalescent, ground-glass-like appearance (Fig. 1A). Notably, there was no corneal neovascularization. The anterior chamber, crystalline lens, intraocular pressure, and retina were normal in both eyes. Based on the clinical findings, a diagnosis of OSSN of the left cornea was made, and the patient was started on topical IFN-α 2b, 1 million IU/ml four times daily. By June 2023, her left eye's visual acuity improved to 20/32 with + 1.50 D correction, and slit-lamp examination revealed a clear cornea with no signs of OSSN. The patient was advised to continue IFN-α 2b eye drops for additional two months.

In July 2023, the patient returned with complaints of decreased visual acuity, ocular injection, and pain in her left eye, which had begun two weeks earlier. Visual acuity had deteriorated to 20/400 with correction. Examination revealed conjunctival and ciliary injection, central corneal stromal edema, infiltration, Descemet's membrane folds, and keratic precipitates (Fig. 1B and C). There was no anterior chamber reaction or hypopyon. Corneal sensation was normal and intraocular pressure was 19 mm Hg in the left eye. The patient was diagnosed with HSV-associated endothelial (disciform) keratitis. Topical IFN-α 2b was discontinued, and treatment was initiated with topical betamethasone 0.1% six times daily and oral acyclovir 400 mg five times daily. This regimen led to complete resolution of the herpetic keratitis within three weeks, after which the medications were gradually tapered and discontinued over two months.

At her most recent follow-up in August 2024, the corrected visual acuity in her left eye was 20/40, with a mostly clear cornea except for a mild central stromal scar (Fig. 1D). There has been no recurrence of either herpetic infection or OSSN in the 10 months following cessation of all medications.

Discussion and conclusion

Our case report demonstrates that topically administered IFN-α 2b is an effective first-line monotherapy for primary OSSN, consistent with previous studies [2, 6]. This treatment is generally well tolerated, with minimal adverse effects. Reported side effects of topical IFN-α 2b include moderate follicular conjunctival reactions, reactive lymphoid hyperplasia, superficial punctate keratopathy, and corneal epithelial microcystic formation [7–9]. These complications typically resolve upon discontinuation of treatment [7–9].

To our knowledge, this is the first case report to describe HSV-associated keratitis in a patient treated with topical interferon for OSSN. This case challenges the prevailing view that topical interferon is effective in treating herpetic keratitis [10, 11]. Interferons are biological cytokines with broad nonspecific antiviral activity. They initiate a cascade of intracellular antiviral mechanisms in infected cells and function as immunomodulators, recruiting macrophages, natural killer cells, and cytotoxic T cells to eliminate affected cells [5]. Previous studies have explored the role of topical interferon in managing herpetic epithelial keratitis [10, 11]. These studies found that interferon monotherapy alone has no significant effect in treating herpetic dendritic ulcers [10, 11]. However, when combined with synthetic antiviral agents such as trifluorothymidine or acyclovir, interferon dramatically enhances the efficacy of these antiviral drugs,

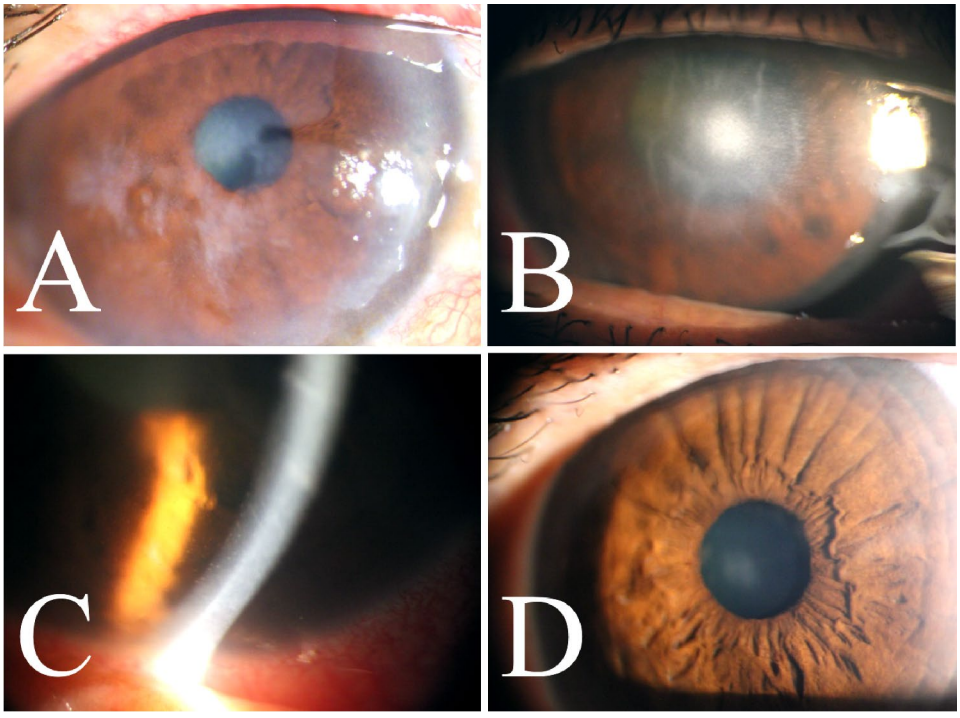

Fig. 1 **A**) Slit-lamp photograph of the left cornea shows a gelatinous lesion with well-defined margins advancing from the nasal limbus onto the corneal surface, consistent with ocular surface squamous neoplasia (OSSN). **B** and **C**) Four months after topical interferon-α 2b treatment, slit-lamp images demonstrate central corneal stromal edema, infiltration, Descemet's membrane folds (**B**), and keratic precipitates (**C**), indicative of herpes simplex-associated endothelial keratitis, with no evidence of OSSN. **D**) Ten months after discontinuing all medications, the slit-lamp photograph shows a small stromal scar with no recurrence of herpetic infection or OSSN

promoting faster healing of HSV epithelial keratitis [10, 11].

Topical interferon, as an adjunctive therapy to antivirals, appears to have limited or no effect on stromal and endothelial keratitis. The limited efficacy of interferon in stromal and endothelial keratitis may be attributed to its poor penetration into the deeper layers of the cornea, due to its large molecular size. Additionally, while dendritic keratitis results from active viral replication and cytopathic effects on corneal epithelial cells, which can be countered by topical interferon in combination with antivirals, stromal and endothelial keratitis are primarily driven by immunological reactions rather than viral replication. This distinction likely explains the lack of efficacy of interferon in these deeper forms of HSV keratitis.

Some medications, including corticosteroids, prostaglandin analogues, and epinephrine-like compounds, have been reported to increase the risk of recurrent herpetic disease and exacerbate the severity of HSV-associated keratitis [12, 13]. Our case suggests a potential activation of herpetic keratitis with the use of topical IFN-α 2b. The role of interferon in inducing HSV keratitis has been demonstrated in animal models [14]. Administered interferons recruit neutrophils and other inflammatory cells, stimulating the release of cytokines, such as prostaglandins, which are crucial for epithelial repair [14]. However, prostaglandins also serve as a common pathway for stimulating viral replication and recurrence of HSV keratitis, as seen with certain medications like latanoprost used in glaucoma management [12, 13]. Although establishing a direct causal relationship based on a single case is challenging, topical IFN-α 2b may increase the risk of herpetic keratitis recurrence by elevating prostaglandin concentrations in the cornea.

In conclusion, the role of IFN-α 2b in reactivating HSV-associated endothelial keratitis in our patient remains speculative. Nonetheless, clinicians should be mindful of the possibility of herpetic keratitis when patients treated with IFN-α 2b for OSSN present with sudden visual deterioration. Additionally, patients should be carefully screened for a history of herpetic keratitis before initiating IFN-α 2b treatment, and those with a positive history may require closer monitoring during therapy. Further studies involving more cases are necessary to draw definitive conclusions regarding the relationship between IFN-α 2b and HSV reactivation.

Acknowledgements
Not applicable.

Author contributions
Research idea, study design, data interpretation: SF; concept, data acquisition: SF and MZ; SF wrote the first draft of the manuscript; HS supervised and discussed the work; SF reviewed and approved the final version of the

manuscript; all authors had full access to all the data and take responsibility for the integrity of the final manuscript.

Funding
Not applicable.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participants
Not applicable.

Consent for publication
Written informed consent for the use of personal details and associated images was obtained from the patient.

Competing interests
The authors declare no competing interests.

Received: 9 November 2024 / Accepted: 3 April 2025
Published online: 09 April 2025

References

1. - Kim BH, Kim MK, Wee WR, Oh JY. Clinical and pathological characteristics of ocular surface squamous neoplasia in an Asian population. Graefes Arch Clin Exp Ophthalmol. 2013;251(11):2569–73.
2. - Monroy D, Serrano A, Galor A, Karp CL. Medical treatment for ocular surface squamous neoplasia. Eye (Lond). 2023;37(5):885–93.
3. - Nanji AA, Moon CS, Galor A, Sein J, Oellers P, Karp CL. Surgical versus medical treatment of ocular surface squamous neoplasia: a comparison of recurrences and complications. Ophthalmology. 2014;121(5):994–1000.
4. - Galor A, Karp CL, Oellers P, Kao AA, Abdelaziz A, Feuer W, Dubovy SR. Predictors of ocular surface squamous neoplasia recurrence after excisional surgery. Ophthalmology. 2012;119(10):1974–81.
5. - Lewczuk N, Zdebik A, Bogusławska J. Interferon alpha 2a and 2b in ophthalmology: a review. J Interferon Cytokine Res. 2019;39(5):259–72.
6. - Al Bayyat G, Arreaza-Kaufman D, Venkateswaran N, Galor A, Karp CL. Update on pharmacotherapy for ocular surface squamous neoplasia. Eye Vis (Lond). 2019;6:24.
7. - Parulekar MV, Khooshabeh R, Graham C. Topical and intralesional interferon therapy for recurrent lacrimal papilloma. Eye (Lond). 2002;16(5):649–51.
8. - Aldave AJ, Nguyen A. Ocular surface toxicity associated with topical interferon alpha-2b. Br J Ophthalmol. 2007;91(8):1087–8.
9. - Lee GA, Hess L, Glasson WJ, Whitehead K. Topical interferon alpha-2b induced reactive lymphoid hyperplasia masquerading as orbital extension of ocular surface squamous neoplasia. Cornea. 2018;37(6):796–8.
10. - Guess S, Stone DU, Chodosh J. Evidence-based treatment of herpes simplex virus keratitis: a systematic review. Ocul Surf. 2007;5(3):240–50.
11. - Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane Database Syst Rev. 2015;1(1):CD002898.
12. - Ekatomatis P. Herpes simplex dendritic keratitis after treatment with Latanoprost for primary open angle glaucoma. Br J Ophthalmol. 2001;85(8):1008–9.
13. - Deai T, Fukuda M, Hibino T, Higaki S, Hayashi K, Shimomura Y. Herpes simplex virus genome quantification in two patients who developed herpetic epithelial keratitis during treatment with antiglaucoma medications. Cornea. 2004;23(2):125–8.
14. - Hendricks RL, Tumpey TM, Finnegan A. IFN-gamma and IL-2 are protective in the skin but pathologic in the Corneas of HSV-1-infected mice. J Immunol. 1992;149(9):3023–8.

Publisher's note