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Case report

Corneal melt in conjunctival intraepithelial neoplasia

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ABSTRACT

Purpose: Report a case of corneal melt in a patient with conjunctival intraepithelial neoplasia (CIN) treated with topical interferon (IFN) alpha-2B.

Observations: An 89-year-old man presented with gelatinous paralimbal lesions of the left eye extending onto the cornea with corneal neovascularization extending 5–6 clock hours. Nasally there was mild absence of the terminal vascular loops of the limbal palisades of Vogt and conjunctivalization. Diffuse punctate epithelial erosions were noted. The corneal graft displayed subepithelial and stromal edema. Anterior segment optical coherence tomography detected hyperreflectivity, sectional thickened epithelium, and abrupt transitions from normal to abnormal tissue. The patient was treated with excision of the corneal and conjunctival lesions with cryotherapy to the conjunctival borders. Excisional biopsy revealed CIN Grade 3 and carcinoma in situ of the cornea. Topical IFN alpha-2B four times daily was initiated postoperatively. Two months later, a central epithelial defect developed. The cornea progressively thinned and corneal melt ensued. The patient had several risk factors for corneal melt including neurotrophic cornea, early limbal stem cell deficiency, history of cryotherapy, keratoconjunctivitis sicca, and chronic use of glaucoma medications and steroid medications.

Conclusions: Interferon alpha-2B is an effective first line treatment for CIN with few side effects. It's side effects include punctate epithelial erosions, conjunctival hyperemia, and follicular conjunctivitis. We report a case of pre-existing keratoconjunctivitis sicca, early limbal stem cell deficiency, neurotrophic cornea, and newly diagnosed CIN Grade 3; it was treated with surgical excision, cryotherapy, and topical IFN alpha-2b with development of corneal melt 2 months later. Caution should be taken when using interferon alpha -2b in patients with pre-existing keratoconjunctivitis sicca, neurotrophic cornea, or limbal stem cell deficiency as it could exacerbate these conditions resulting in corneal melt.

1. Introduction

Ocular surface squamous neoplasia (OSSN) is a spectrum of dysplasia that involves the squamous cells of the conjunctiva, cornea and limbus. It consists of benign papillomas, corneal-conjunctival intraepithelial neoplasia (CIN), carcinoma in situ (CIS) and squamous cell carcinoma (SCC). It most frequently occurs at the junction of the corneal epithelium and exposed areas of bulbar conjunctiva.[1] Risk factors include ultraviolet-β radiation exposure, human papilloma virus, human immunodeficiency virus, corneal transplant, immunosuppression, old age, fair skin, and smoking.[1,2] Traditionally, surgical excision with subsequent cryotherapy has been used as a treatment for CIN.[2–7] However, there are pitfalls to this treatment approach such as loss of limbal stem cells, corneal melt, epitheliopathy, and higher risk of tumor recurrence when compared to topical therapy.[2–4] Interferon alpha-2b (IFN) has found favor due to its minimal side effect profile. IFN alpha-2b is the recombinant form of IFN-alpha that works at cell surface receptors to produce antiviral and antitumor activities and is an effective treatment for a wide range of OSSN.[5–10] Here, we report a case of corneal melt in CIN that was treated with excision, cryotherapy, and topical IFN alpha-2b.

2. Case report

An 89-year-old Caucasian male presented with left eye pain and gelatinous paralimbal lesions of four months duration. The referring physician was initially treating the patient for a recurrent corneal erosion with sodium chloride ointment six times per day to the left eye. He was referred due to concern for squamous cell carcinoma on the cornea and conjunctiva. His ocular history consists of a penetrating keratoplasty in 1995 due to corneal scarring from trauma with a nail gun, pseudophakia bilaterally, moderate-severe glaucoma in the left

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eye, and glaucoma suspect in the right eye. He was on loteprednol etabonate ointment three times per day in the left eye, dorzolamide once in the morning in the left eye, and latanoprost once at night in the left eye. His medical history included Type 2 diabetes, hypertension, hyperlipidemia, peripheral vascular disease, basal cell carcinoma of scalp status post Mohs excision in 2014, and squamous cell carcinoma of scalp status post excision in 2009. He denied a history of smoking. There was no past medical history of rheumatoid arthritis or Sjogren's syndrome, no labs were performed to confirm the negative history.

On examination, his visual acuity was 20/20 in the right and hand motion in the left. Intraocular pressures were 16 and 15, right and left respectively. On the left there was increased lower lid laxity with delayed snapback, and increased upper lid distractibility. Severe keratoconjunctivitis sicca with densely diffuse punctate epithelial erosions were present. Nasally there was mild absence of the terminal vascular loops of the limbal palisades of Vogt, loss of the interpalisadal intraepithelial rete ridges, and nasal corneal conjunctivalization. Superiorly, nasally, and inferiorly there was injection and engorgement of bulbar conjunctival vessels. Superonasally there was corneal neovascularization extending onto the graft from 7 to 1 o'clock. Nasal gelatinous paralimbal lesions extended onto the cornea for 4 clock hours. Diffuse bullae were noted along with stromal and subepithelial edema of the graft. A posterior chamber intraocular lens was noted. There was no view of the fundus in the left eye (Fig. 1). The right eye had moderately diffuse punctate epithelial erosions, a posterior chamber intraocular lens, and a normal funduscopic exam. An anterior segment spectral-domain optical coherence tomography (SD-OCT) was obtained showing hyperreflective nodules creating transmission defects, sections of thickened epithelium, intraepithelial cysts, and abrupt transitions from normal to abnormal tissue (Fig. 2).

An excisional biopsy with cryotherapy to the conjunctival borders was performed. Histopathologic analysis of the tissue revealed severe corneal squamous dysplasia with CIS and CIN Grade 3. An amniotic membrane was placed on post-operative day 1. Topical IFN alpha-2b (1 million units/1mL) four times per day was begun. The use of topical IFN alpha-2b for conjunctival and corneal squamous cell cancer is considered off label use in the United States. The muro ointment and loteprednol etabonate werediscontinued; he was placed on vigamox four times per day for four weeks and a weekly 4,3,2,1 prednisolone acetate 1% taper. The amniotic membrane was replaced every 3–4 weeks.

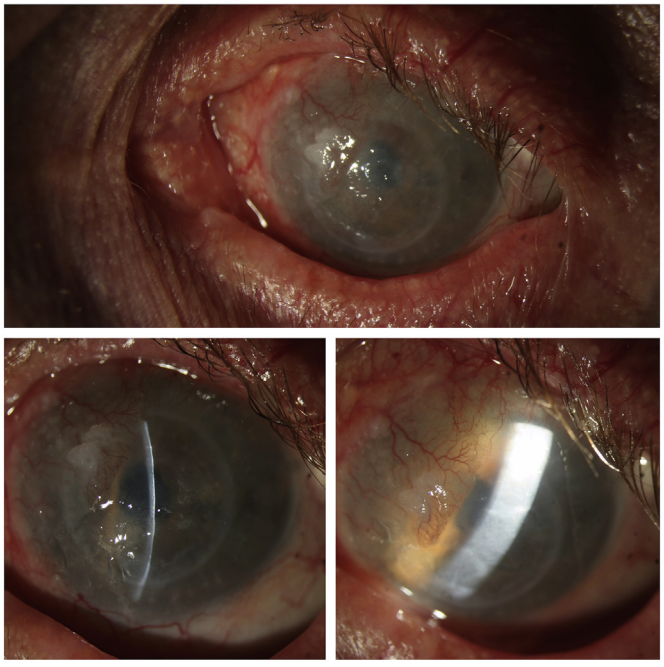

Fig. 1. Slit lamp photo of the left eye. Nasally there was absence of the terminal vascular loops of the limbal palisades of Vogt, loss of the interpalisadal intraepithelial rete ridges, and nasal corneal conjunctivalization. Superiorly, nasally, and inferiorly there was injection and engorgement of bulbar conjunctival vessels with corneal neovascularization superonasally from 7 to 1 o'clock. Gelatinous paralimbal lesions extending onto cornea for 4 clock hours including the graft-host-junction. Visible bullae centrally.

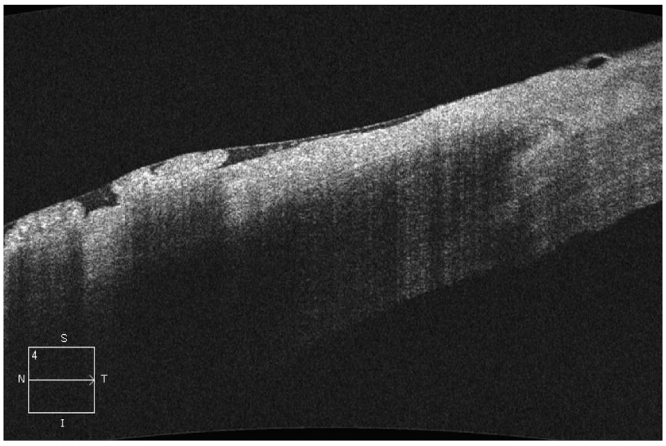

Fig. 2. An anterior segment spectral domain optical coherence tomography of the left eye. Distinctive features include hyperreflective nodules, thickened epithelium, and abrupt transition from normal to abnormal tissue.

Three weeks postoperatively the patient was started on oral doxycycline. A new epithelial defect was noted 8 weeks following initiation of topical IFN alpha-2b. The cornea progressively continued to thin. A SD-OCT was obtained showing stromal thinning and epithelial remodeling (Fig. 3). The interferon alpha-2b and prednisolone acetate therapy were discontinued. Eleven weeks postoperatively severe central thinning of the cornea was noted. Cyanoacrylate glue was applied to the thin area with a bandage contact lens. Fourteen weeks postoperatively the cornea perforated and the patient was taken to the operating room for corneal glue removal and a tectonic corneal graft. In the operating room, the central cornea was noted to have a 3 mm(V) x 3 mm(H) absence of epithelium and stroma with an intact Descemet's membrane. Approximately 300° of corneal neovascularization, obliteration of the terminal vascular loops and interpalisadal intraepithelial rete ridges, superior, temporal and inferior conjunctivalization (Fig. 4). Cultures did not yield any organisms (Video). Verbal consent was obtained from the patient to publish this study, patient identifiers were excluded.

3. Discussion

To date, there has been one published case of corneal melt in a patient with invasive SCC on IFN alpha-2b. A 47 year old female with keratoconus had a presumed ptyergium that was biopsied. Resultant pathology was consistent with CIN grade 1. She was treated with topical IFN alpha-2b and retinoic acid. Two weeks later she reported irritation and was concurrently started on fluoromethalone. Seven months later despite observable tumor regression she developed corneal melt. The IFN alpha-2b, retinoic acid were discontinued. She was started on doxycycline and resumed on FML with stabilization of her corneal melt. Her previously biopsied limbal lesion was biopsied again revealing SCC with eventual enucleation.[11]

In this case report, we present a case of penetrating keratoplasty on chronic steroid medication, neurotrophic cornea, keratoconjunctivitis sicca, early signs of limbal stem cell deficiency, and CIN treated with cryotherapy to the conjunctival borders and IFN for two months. Subsequently the complication of corneal melt occurred. Corneal melt is most frequently associated with pre-existing tear-film abnormalities stemming from keratoconjunctivitis sicca, Sjogren's syndrome and rheumatoid arthritis.[12] Limbal stem cell deficiency in severe cases may

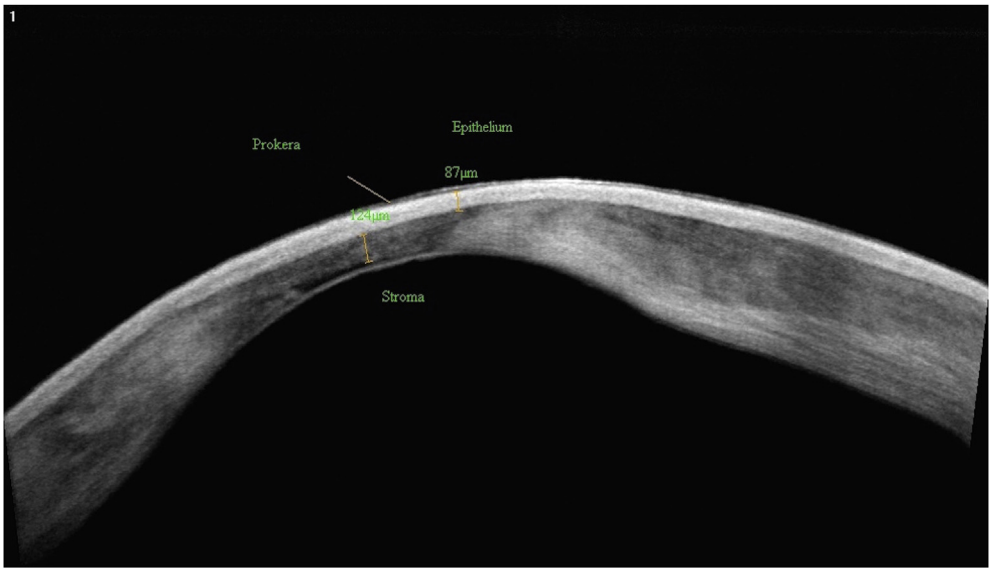

Fig. 3. An anterior segment spectral domain optical coherence tomography of the left eye demonstrating an amniotic membrane, epithelial remodeling, and stromal thinning.

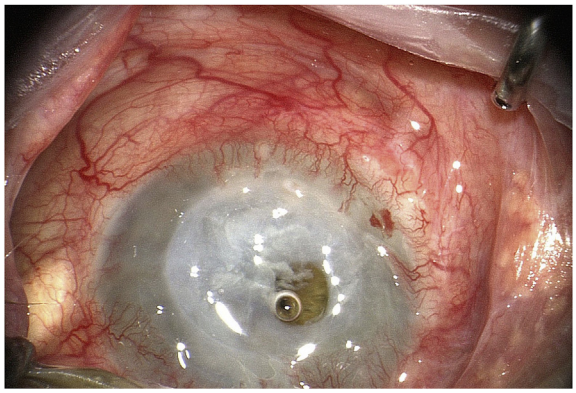

Fig. 4. Intraoperative photo of the left eye demonstrating conjunctival injection, corneal neovascularization superotemporally, temporally, inferotemporally with corneal melt and visible Descemet's membrane.

also lead to corneal thinning and perforation.[13] Cryotherapy, if used to create too deep of a freeze, may cause corneal or scleral melting.[14] It has also been associated with nonsteroidal anti-inflammatory drugs (NSAIDS) and steroids.[15] Neurotrophic corneas are more susceptible to epithelial defects, delayed corneal healing, and can also be precursors to stromal melt.[16] Corneal squamous cell carcinoma can also cause progressive invasion of the stroma precipitating a corneal melt. Corneal epithelial defects usually initiate the melting process. Immune mediators and collagenase enzymes attack the exposed stroma and the inflammatory cells further compound the ulcerative melting.[12] One of the dreaded complications is corneal perforation due to extensive progression of corneal melt.

IFN alpha-2b eye drops have several side effects such as ocular discomfort, photophobia, punctate epithelial keratitis, conjunctival hyperemia, and follicular conjunctivitis.[3,6–8]

Most of these side effects are self-limited and abate by one month after cessation of treatment.

A case report by Yin-Tsu et al. reports a 71-year-old male with multiple myeloma treated with IFN alpha-2b intramuscularly (3 million units) for 10 years. He developed biopsy proven Sjogren's syndrome, and severe superficial punctate keratopathy treated with topical steroids. His cornea progressed to develop multiple melting sterile ulcers in the left central cornea. It was suggested that the patient's severe dry eye and corneal melting ulcers could be due to unknown autoimmune mechanism related to long-term IFN alpha-2b administration.[17]

IFN alpha-2b has been shown to cause punctate epithelial keratitis when used topically. It has been linked to a case of corneal melt in combination with topical retinoic acid. Corneal melt was also noted when IFN alpha-2b was used intramuscularly with concurrent topical steroid use.[6–8,11,17] Our patient had several risk factors for developing corneal melt. Prior to treatment he had severe keratoconjunctivitis sicca of the left eye and early evidence of limbal stem deficiency. An environment for a neurotrophic cornea was created given his history of penetrating keratoplasty, chronic steroid suppression, and concurrent use of glaucoma medications. Following excision, cryotherapy of conjunctival borders, on postoperative day one IFN alpha-2b and prednisolone acetate 1% were initiated. There is concern that the IFN alpha-2b exacerbated his risk factors. Cryotherapy may cause limbal stem cell deficiency which is associated with corneal melt. Intraoperatively if used for too long it may also cause corneoscleral melt. However that was not indicated in the operative report.

4. Conclusion and importance

Studies have highlighted the need for control studies that have longer follow-up times in order to elicit possible rarer side effects of IFN alpha-2b.[9,10] Specifically trials evaluating IFN alpha-2b with and without topical steroid use to more definitely establish a causal relationship between IFN alpha-2b and corneal melt. However, since CIN has a relatively low disease prevalence, case reports such as the report we present here, will be instrumental in unveiling some of the potential side effects of IFN alpha-2b eye drops. Caution should be given when initiating treatment with IFN alpha-2b in patients with pre-existing evidence of keratoconjunctivitis sicca, neurotrophic cornea, or limbal stem cell deficiency.

Patient consent

Verbal consent was obtained for the publication of this paper. Patient identifiers were excluded.

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Authorship

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

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2020.100689.

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