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A case of sight threatening complications from topical 1% 5-fluorouracil in the treatment of ocular surface squamous neoplasia

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ABSTRACT

Purpose: 1% topical 5-fluorouracil (5-FU) is a treatment for ocular surface squamous neoplasia (OSSN) due to its effectiveness, low cost, and tolerable side effect profile. To our knowledge there is no reported sight-threatening corneal complication of 1% 5-FU for the treatment of OSSN.

Observations: We report a 78 year-old man with bilateral conjunctival intraepithelial neoplasia (CIN) who developed bilateral corneoscleral ulceration and corneal perforation of the left eye after 1% 5-FU topical treatment.

Conclusions and Importance: Our case report describes serious potential complications of 1% 5-FU, reviews possible risk factors associated with poor outcomes, and discusses our treatment approach.

1. Introduction

5-fluorouracil (5-FU), a structural analog of thymine, blocks the enzyme thymidylate synthetase and inhibits DNA and RNA production. Topical 5-FU ophthalmic drops are frequently used for the primary treatment of ocular surface squamous neoplasia (OSSN). At a concentration of 1%, the drops are dosed 4 times a day for 1 week to 1 month followed by a variable medication holiday. The cycle is continued until the patient achieves clinical resolution. Although there have been a few reports of serious corneal complications including ulceration and perforation with a higher single dose (5%, or 5mg in 0.1ml) injectable 5-FU used as anti-fibrotics for glaucoma filtration surgery,[1,2] no report exists with the lower concentration 1% topical 5-FU used in OSSN. We report a case of a patient with corneal perforation associated with the use of 5-FU for conjunctival OSSN, specifically conjunctival intraepithelial neoplasia (CIN).

2. Case report

A 78 year-old Korean American male with no significant medical history and a past ocular history of primary open angle glaucoma, presented with bilateral, progressive conjunctival lesions. The patient reported no pain or vision loss. No other new skin lesions were noted, including no oropharyngeal lesions on in-office examination. The patient was noted to have a chronic flat hypopigmented lesion on the nose which was thought to be from previous skin trauma. On presentation, his visual acuity with correction was 20/25–2 in each eye. Slit lamp examination revealed bilateral conjunctival lesions consistent with OSSN involving the inferior bulbar, tarsal and forniceal conjunctiva, but was otherwise unremarkable, including no lagophthalmos, although lid laxity was noted (Figs. 1 and 2). CIN was diagnosed following incisional biopsy (Fig. 3). The patient was started on a 1% 5-FU biweekly cycle of 4 times a day for one week followed by a one week holiday. The patient missed his 1 month follow up appointment due to the 2020 coronavirus crisis in New York City at that time. He returned 2 months after the initial visit and reported completion of the 1-month 5-FU supply. He was found to have significant clinical regression of the bilateral OSSN but had new bilateral conjunctival injection (Figs. 1 and 2). He was started on an additional biweekly cycle of 5-FU. He was also started on artificial tears dosed 4 times a day and neomycin-polymyxin-dexamethasone 0.1% drops dosed 3 times a day for presumed 5-FU induced conjunctivitis. Three weeks later the bilateral OSSN lesions had completely clinically regressed but he developed small bilateral corneal epithelial defects. The 5-FU and neomycin-polymyxin-dexamethasone 0.1% drops were discontinued. Bandage contact lenses were placed, and the patient was started on ciprofloxacin drops 4 times a day in both eyes. One week later he appeared slightly improved but the following week the epithelial defects progressed to 100% in the right eye and 80% in the left eye.

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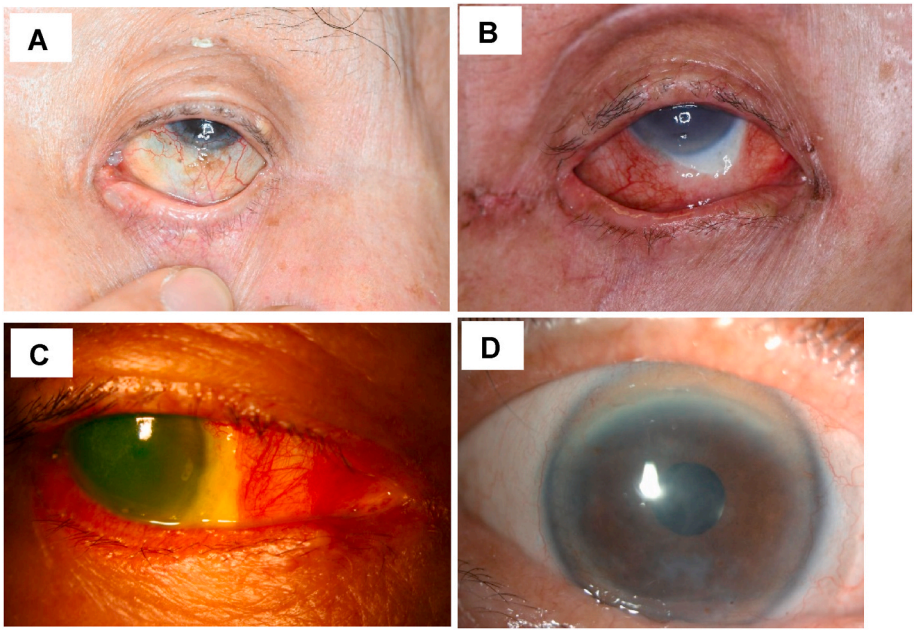

Fig. 1. Progression of patient's right eye. Conjunctival ocular surface squamous neoplasia (A); 5-fluorouracil related conjunctivitis (B); Sterile corneoscleral ulceration (C); Moderate corneal scarring (D).

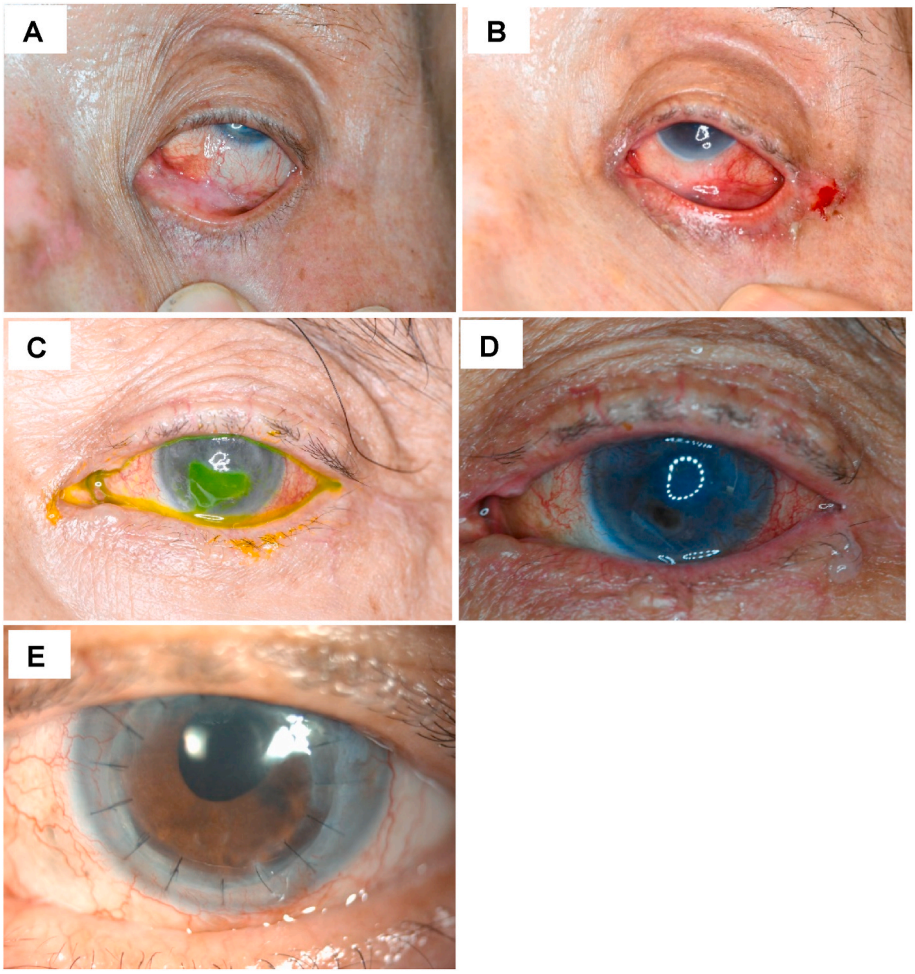

Fig. 2. Progression of patient's left eye. Conjunctival ocular surface squamous neoplasia (A); 5-fluorouracil related conjunctivitis (B); Sterile corneoscleral ulceration (C); Descemetocele (D); Penetrating keratoplasty at postoperative month 4 visit (E).

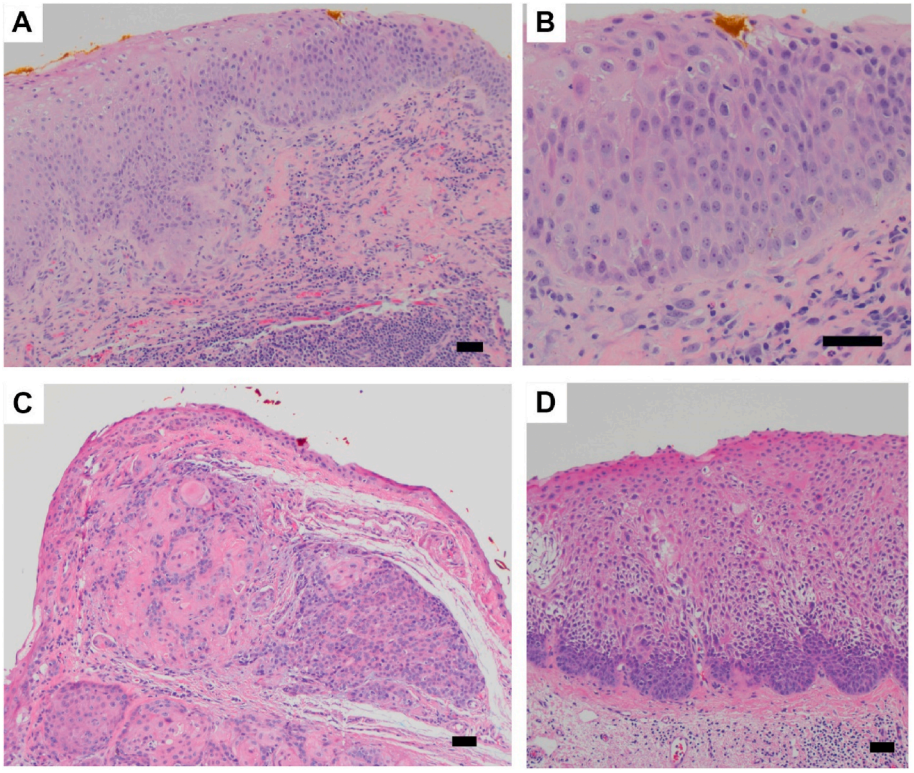

Fig. 3. (A and B) Histopathologic exam of left eye conjunctival lesion. Inflamed conjunctival mucosa with extensive squamous metaplasia and focal dysplasia, however no invasive component was seen (A). In the areas of high grade dysplasia, the neoplastic cells displayed relatively amphiphilic cytoplasm with increased nuclear atypism – including prominent nucleoli – and brisk mitotic activity (B). (C and D) Histopathologic exam of right eye conjunctival lesion. (C) Squamous cell carcinoma, characterized by keratin pearls, invades into the conjunctival submucosa (C). In the adjacent regions, extensive carcinoma in situ was identified which was characterized by marked nuclear atypism – including anisonucleosis and hyperchromasia – and loss of polarity (D). (For all panels: hematoxylin and eosin, scale bar = 50 μm.).

The bandage contact lenses were discontinued, and amniotic membrane rings (Prokera, Biotissue, Miami FL) were placed in each eye. Five days later a sterile corneoscleral ulceration was noted in both eyes (Figs. 1 and 2). Additionally, a small conjunctival lesion suspicious for residual or recurrent OSSN was noted in the left eye. The amniotic membrane rings were replaced, and he was started on doxycycline 100mg by mouth 2 times a day and prednisone 40mg by mouth daily. The patient was taken to the operating room 3 days later for excision of the conjunctival lesion with cryotherapy in the left eye and bilateral amniotic membrane placement. The pathology of the conjunctival lesion was determined to be squamous cell carcinoma (SCC) in-situ with negative margins (Fig. 3). Over the next 2 months, he was treated with serial replacements of amniotic membrane rings; the ulcerations slowly began to regress in both eyes. Oral prednisone was tapered to 30mg daily and then to 20mg daily. However, at a subsequent 2 week follow up visit, a new descemetocele was noted in the left eye (Fig. 2). The right eye was fully epithelialized with anterior stromal scarring. Prior to this visit he started prednisolone acetate 1% drops 4 times a day in each eye on his own without our knowledge. The prednisolone acetate drops were immediately discontinued. Oral prednisone was increased to 50mg daily, valacyclovir 1g 2 times a day was started empirically for possible herpes simplex virus, and an autoimmune workup was completed to help rule out a systemic collagen vascular disease. The evaluation included a complete blood count, erythrocyte sedimentation rate, C-reactive protein, rapid plasma reagin, Sjogren's Syndrome A and B antibodies, anti Jo 1 antibody, anti scleroderma 70 antibody, anti smith antibody, anti U1rnp antibody, pANCA and cANCA, rheumatoid factor, antinuclear antibody, hepatitis C antibodies. The results were unremarkable. In addition, a nasopharyngeal PCR test for SARS-CoV-2 infection was negative. A shield was placed, and the plan was made for a penetrating keratoplasty. The descemetocele perforated 4 days later and a 7.5mm penetrating keratoplasty was done that same day. Histologic examination of the cornea showed acute focal inflammation, no dysplasia, and no bacteria or fungi. At present, the patient is more than 6 months out from the transplant surgery and there has been no recurrence of the ulcerations (Figs. 1 and 2). There was however a recurrence of the OSSN which showed microinvasive SCC in the right eye (Fig. 3). It was treated with complete excision and cryotherapy to the margins.

3. Discussion

We present a case of a patient with CIN treated with topical 1% 5-FU who developed sight-threatening corneal complications. Corneal ulceration and perforation have been shown to occur only with the higher injectable doses (2.5–5mg) used as anti-fibrotics in glaucoma filtering surgery.[1,2] Furthermore, these severe cases were associated with patient comorbidities that impair wound healing such as exposure keratopathy and diabetes mellitus. Multiple studies have shown that topical 1% 5-FU for the treatment of OSSN is effective and largely safe, without any cases of sight-threatening adverse reactions.[3–7]

Our workup did not identify any preexisting systemic or ocular comorbidities that explain the outcome of our patient. Underlying herpes keratitis is a possibility and unfortunately we did not formally test corneal sensation or obtain herpes specific laboratory tests. However it is a less likely etiology in our patient due to the bilateral ulceration, and his lack of atopy.[8]

Although our patient claimed to be adherent with the medication dosing, there was an unsupervised one month interval during treatment due to the 2020 coronavirus crisis which could have resulted in medication misuse and increased corneal toxicity. Additionally, we observed that the corneal complications began and subsequently dramatically worsened with the use of topical steroid drops. Neomycin-polymyxin-dexamethasone 0.1% was initially prescribed for the 5-FU induced-conjunctivitis and was discontinued at the onset of the bilateral epithelial defects. The prednisolone acetate 1% was not prescribed by us, but the patient had been using it when he progressed to a descemetocele. Interestingly we found systemic steroids to be helpful in treating the ulcerations and histology of the corneal button confirmed that there was acute focal inflammation. The effects of steroids on corneal epithelial cells and keratocytes are complex, sometimes inducing apoptosis and other times inducing proliferation.[9] These differences may in part be explained by the route of administration, topical

versus systemic.

Before beginning 5-FU treatment for OSSN we recommend that patients be carefully assessed for potential comorbidities that could contribute to corneal complications, especially in light of the diminishing use of topical interferon alfa-2b in the United States.[10] We also recommend strict compliance and patient education when using topical chemotherapy, for misuse may result in increased toxicity. Lastly we recommend that topical steroids be used with caution in patients being treated with topical 1% 5-FU. Future studies are suggested comparing 5-FU protocols to identify the safest and most effective treatment strategy.

3.1. Patient consent

The patient verbally consented to publication of the case.

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

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References

1. Knapp A, Huer DK, Stern GA, et al. Serous corneal complications of glaucoma filtering surgery with postoperative 5-fluorouracil. *Am J Ophthalmol.* 1987;103:183–187.
2. Hickey-Dwyer M, Wishart PK. Serious corneal complication of 5-fluorouracil. *Br J Ophthalmol.* 1993;77:250–251.
3. Yeats RP, Ford JF, Stanton CA, et al. Topical 5-fluorouracil in treating epithelial neoplasia of the conjunctiva and cornea. *Ophthalmology.* 1995;102:1338–1344.
4. Yeats RP, Engelbrecht NE, Curry CD, et al. 5-fluorouracil for the treatment of intraepithelial neoplasia of the conjunctiva and cornea. *Ophthalmology.* 2000;107:2190–2195.
5. Parrozzani R, Lazzarini D, Alemany-Rubio E, et al. Topical 1% 5-fluorouracil in ocular surface squamous neoplasia: a long-term safety study. *Br J Ophthalmol.* 2011;95:355–359.
6. Joag MG, Sise A, Murillo J, et al. Topical 5-fluorouracil 1% as primary treatment for ocular surface squamous neoplasia. *Ophthalmology.* 2016;123:1442–1448.
7. Venkateswara N, Mercado C, Galor A, et al. Comparison of topical 5-fluorouracil and interferon alfa-2b as primary treatment modalities for ocular surface squamous neoplasia. *Am J Ophthalmol.* 2018;199:216–222.
8. Wilhelmus KR, Falcon MG, Jones BR. Bilateral herpetic keratitis. *Br J Ophthalmol.* 1981;65:385–387.
9. Ryu JS, Ko JH, Kim MK, et al. Prednisolone induces apoptosis in corneal epithelial cells through the intrinsic pathway. *Sci Rep.* 2017;7:4135.
10. Shah SU, Kaliki S, Kim HJ, Lally SE, Shields JA, Shields CL. Topical interferon alfa-2b for management of ocular surface squamous neoplasia in 23 cases: outcomes based on American joint committee on cancer classification. *Arch Ophthalmol.* 2012;130(2):159–164.