Severe Anterior Segment Toxicity Associated to Long-Term Use of Topical Trifluridine

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INTRODUCTION

Antiviral topical medications appear to be one of the antimicrobial agents most commonly associated with local ophthalmic complications [1]. Their use is associated to medication-induced epithelial keratitis, punctal stenosis and canalicular stenosis in patients who have had chronic follicular conjunctivitis and conjunctival cicatrization related to the same drug [1]. Its long term use has also been postulated to cause conjunctival and anterior segment ischemia [2,3].

METHODS

A case report of a 71 year-old male who presented to our institute with bilateral keratitis and uveitis, after longstanding topical trifluridine (3FT) therapy for nine months for a presumed herpetic keratitis. He presented with bilateral epithelial defects, generalized corneal edema, pallor and chemosis of the bulbar conjunctiva, anterior uveitis, and uncontrolled ocular hypertension. He had no significant ophthalmic history other than narrow angle glaucoma controlled on medical therapy. Corneal cultures were found be negative. He subsequently developed spontaneous bilateral hyphemas, leading him to hand motions vision in both eyes (Figure 1). The hyphema of his right eye was removed through anterior chamber lavage, and a pars plana vitrectomy and lensectomy were performed to examine the posterior pole and assess a possible pan-ischemic event. Baerveldt glaucoma implantation and intravitreal bevacizumab injection were used at the end of the procedure.

RESULTS

One week after the surgical procedures in the right eye, his best-corrected visual acuity improved to 20/200 with a +9.00 aphakic correction. Laboratory investigations, cultures, PCR and stains were all negative or within normal limits. The same surgical plan was executed in the left eye thereafter.

Conclusions: To our knowledge this is the fourth reported case of toxic ocular changes not explainable other than by the chronic use of topical trifluridine. Emphasis is made on reducing the incidence of potentially disastrous adverse effects with the use of selective topical antiviral drugs.

Figure 1 Parts a and b. Severe anterior segment toxicity both eyes. a, Ciliary injection, epithelial defect, corneal edema, and hyphema in the right eye. b, Ciliary injection, epithelial defect, corneal edema and hyphema in the left eye.
was executed thereafter. Laboratory investigation included a complete blood count with differential, complete metabolic panel, HLA-B27 antigen, sedimentation rate, C-reactive protein, antinuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor, angiotensin-1 converting enzyme, human gammahemagglutinin virus antibody detection, rapid plasma reaginin and fluorescent treponemal antibody absorption test, which were all within normal limits or negative. Cultures, PCR and stains from vitreous and anterior chamber taps were negative.

DISCUSSION

We present a case of a 71 year old male treated with trifluridine for a long term (nine months) period due to a presumed bilateral herpetic keratitis. He presented to the clinic with ocular signs of conjunctival and corneal epithelial toxicity and some other signs of conjunctival ischemia (pallor and chemosis) and anterior segment inflammation (uveitis) related to the chronic use of trifluridine. Some days later, he developed more severe signs and symptoms that would be consistent with augmented anterior segment toxicity and possible ischemia.

Antiviral topical medications are antimicrobial agents commonly associated with local ophthalmic complications [1]. Their use is associated to medication-induced epithelial keratitis, punctal stenosis, canicular stenosis, chronic follicular conjunctivitis, and conjunctival cicatrization [1]. Other adverse effects include conjunctival injection, stromal edema and haze, mild iritis and its long term use has been postulated to cause conjunctival and anterior segment ischemia [2,3]. Some cases of severe Anterior Segment Toxicity (ASI) directly associated with the chronic use of trifluridine have been reported in the literature [2-4].

Idoxuridine, trifluridine, and vidarabine act as thymidine analogs and inhibit DNA polymerase, forming defective viral DNA [5]. Their use is associated with ocular surface toxicity explainable by their nonselective action on infected and noninfected host cell DNA molecules [6].

None of the previously known systemic or ocular factors to develop ASI were present in our case as demonstrated by the laboratory investigations [7]. Therefore we could attribute the severe anterior segment toxic signs to the chronic use of 3FT. Although the bilateral presentation argues against an infectious herpetic etiology, cases of anterior segment ischemia associated chronic vasculitis related to herpes simplex keratouveitis have been reported and this phenomenon could not be ruled out without a conjunctival biopsy [8]. We did not perform anterior segment fluorangiography as an objective test of ischemia due to the poor visualization of the iris and anterior segment. However, we do report clinical signs that are often unequivocal of anterior segment ischemia.

This is the fourth reported case of severe anterior segment toxic changes not explainable other than by the long-term use of trifluridine. The incidence of these potentially disastrous conditions could be further reduced with the use of selective topical antiviral drugs targeted against infected cells, as ganciclovir and acyclovir [6,9].
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REFERENCES