CLINICAL CASE

Corneal Intraepithelial Neoplasia as a Cause of Visual Acuity Decrease: a Low-Cost Approach

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Abstract Introduction: Corneal intraepithelial neoplasia is a dysplastic condition within the ocular surface squamous cell neoplasia spectrum. It is a rare condition that is seldom suspected, especially at its diffuse presentation. Once suspected, diagnosis and treatment are easy for a condition that if left untreated could be devastating. Clinical case: We present the case of a 63-year-old male patient presenting with a history of two weeks of right eye visual acuity decrease as only symptom. Right eye visual acuity was 20/40 and physical examination revealed a right cornea upper half geographic lesion with frosted appearance. After diagnostic rule out, epithelial scraping was decided, with low-grade corneal intraepithelial neoplasia reported by the pathology department. Management with mitomycin C 0.02% in two 2-week cycles with 3 topical applications per day, accompanied by fluorometholone 0.1% at the same dosage was then decided. Conclusions: The authors recommend the use of mitomycin C in developing countries. (creativecommons.org/licenses/by-nc-nd/4.0/).

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INTRODUCTION

Conjunctival-corneal intraepithelial neoplasia (CCIN) is a non-invasive dysplastic condition that occurs in the conjunctival-corneal epithelium and that is also considered to be a carcinoma in situ. CCIN is part of the dysplastic spectrum of ocular surface squamous cell dysplasias. The squamous cell carcinoma lesion begins with dysplastic changes (carcinoma in situ that can be mild, moderate or severe), to finally cross the lamina propria and become an invasive squamous cell carcinoma (Table 1)^{1,2}.

Of all tumors occurring in the ocular globe and its appendages, those of the ocular surface are the most common and, among these, neoplasias involving the epithelium account for one third to half the cases. When an epithelial tumor is diagnosed, 65% have not yet crossed the lamina propria. An incidence of corneal-conjunctival tumors of 0.13 to 1.9/100,000 has been reported, which is dependent on the geographic origin^{3,4}. As in all tumors, changes in ocular surface squamous cell neoplasm are due to a loss of affected cells life and division cycles control. Most important known risk factors are chronic exposure to ultraviolet rays, human papillomavirus (HPV) infection, p53 gene defective expression, male gender, age older than 60 years and human immunodeficiency virus (HIV) seropositivity².

CCIN clinical presentation can occur in two forms: nodular or diffuse, with nodular cases being more common and showing lesions or masses that may have changes in normal coloration, erosions, bleeding, reddening and foreign body sensation; in diffuse cases, the patient can be asymptomatic, or if there is corneal diffuse invasion, with visual acuity (VA) decrease³.

Establishing a diagnosis in a suspected case of CCIN has to be done by means of histopathology, either first by epithelial scraping, or after tumor en bloc resection⁵. Traditionally, CCIN had been treated with tumor resection, but up to 56% have been shown to relapse, and treatment has therefore had radiation, cryotherapy or topical chemotherapeutics added. Recently, the use of topical chemotherapeutic agents (5-fluorouracil, mitomycin C or interferon) alone has been shown to have the same effectiveness than excision plus cryotherapy⁴.

In this work, we describe a case of corneal intraepithelial neoplasia presenting for the first time with a chief complaint of VA decrease, which was topically treated with mitomycin C (MMC).

CLINICAL CASE

A 63-year-old male patient presented to our private practice with a chief complaint of visual acuity decrease over the two previous weeks. The patient had no relevant personal or medical history other than the use of bifocal glasses for hypermetropia and presbyopia. He also had no important hereditary or family history. At that time, he worked as an electrician installing telecommunication equipment for a private company. The patient referred right eye visual acuity decrease even with the use of glasses since two weeks prior, and that it had been progressive, without any other symptoms. On physical examination, right eye best-corrected visual acuity was found to be 20/40 (0.3 logMar) with

Table 1. Ocular surface squamous cell neoplasia evolution

Conjunctival-corneal intraepithelial neoplasia (carcinoma <i>in situ</i>)
a) Mild
b) Moderate
c) Severe
Corneal-conjunctival squamous cell carcinoma

Source: Developed by the authors.

+4.50 -2.25 x 97°, and 20/20 (0 logMar) with +3.25 .0.50 x 93° for the left eye, with best-corrected VA of 20/20 (0 logMar) in both eyes. Ocular movements and pupillary reflexes showed no abnormalities. Intraocular pressure was 14 mmHg for both eyes. On slit lamp examination, a right eye geographic lesion was observed at the corneal upper half, which included pupillary area with frosted appearance and dotting within. Slit lamp examination of the left eye was free of anomalies. Uncertain whether it was a corneal lesion caused by chemicals or a thermoelectric lesion the patient was unaware of, treatment was started with ciprofloxacin/dexamethasone 3 mg/1 mg/mL eye drops topically applied to the right eye thrice daily for 2 weeks, with indication for reassessment at the office two weeks after treatment was started.

When the patient attended two weeks later for reassessment, the lesion was observed to have spread to the right cornea lower pole and VA had not improved. Performing an epithelial scraping was then decided for histopathological assessment. Two weeks after the scraping, the pathology report indicated a low-grade corneal intraepithelial neoplasia (Fig. 1). Management was first started with mitomycin C 0.02% (0.02 mg/mL) eye drops thrice daily for 2 weeks and, finally, other 2 weeks with 3 applications per day (two complete courses), accompanied by fluorometholone 0.1% at the same dosage. Eight weeks after mitomycin C treatment had started, no corneal lesion was found and visual acuity had improved to 20/20 (0 logMar) in both eyes. One year after treatment completion, the patient had not experienced any new discomfort. He is currently on follow-up in order for any relapse to be early diagnosed (Fig. 2).

DISCUSSION

Conjunctival-corneal intraepithelial neoplasia is a rare condition, and the diffuse presentation is even more infrequent. Data of VA decrease with an unclear explanation would probably drive the clinician to study other causes prior to directly considering a neoplasm. It is important underscoring that, although the study of the most common conditions is imperative and unavoidable, this type of pathologies should always be taken into account when making differential diagnoses.

Recently, topical treatment of CCIN has been shown to be as effective as surgery, and to have even better long-term outcomes if surgery is not combined with neoadjuvant treatment. In 2014, Nanji et al. did not find statistically

Figure 1. Corneal epithelial scraping histology. The arrow points at corneal epithelium lower third, which shows cell dysplasia, normal architecture disorganization, pleomorphism and nucleus-cytoplasm ratio alteration. Neoplastic cells do not invade the stroma. It was reported as a low-grade conjunctival-corneal intraepithelial neoplasia. Source: Developed by the authors.

significant differences in terms of recurrence and complications between therapy with surgery or with interferon alpha 2B (IFN α -2B) for the management of corneal squamous cell carcinoma in a case-control study. In this study, recurrence in patients with surgery was 5%, whereas in the medically-treated group it was 3%⁶. Since there are no important differences, non-invasive intervention might be preferable.

It is a huge step being able to avoid invasive treatments in patients and expose them to less risk, while preventing the advancement of a disease that without control might get to cause blindness or even death, in a simple and tolerable way for the patient. It could be considered that the next step is to find the most effective topical medication with the best cost/benefit. Currently, mitomycin C and interferon alpha 2B (IFN α -2B) have been suggested to probably be the most effective drugs to treat CCIN, although some claim that the advantage IFN α -2B has, is that it produces less adverse effects in comparison with MMC. The risks we expose our patients to when using MMC

Figure 2. Corneal intraepithelial neoplasia evolution in a patient with right eye visual acuity decrease. A: Right corneal lesion at first consultation, with a dotted lesion with frosted appearance being observed. B: Right corneal lesion at first consultation, stained with fluorescein. C: Fluorescein-stained lesion 2 weeks after first consultation; there is advancement of the lesion to the corneal lower pole. D: Right corneal lesion after mitomycin C first course. E: Right cornea after second course completion. The lesion is not visible anymore. F: Right eye cornea one year after treatment with mitomycin C; no lesion is shown at all. Source: Developed by the authors.

include pain, irritation, erosion, symblepharon and limbal stem cell deficiency, with these effects depending on the employed dose⁶.

In a prospective study by Ballalai et al. with 23 patients observed for 24 months after the use of MMC for the treatment of CCIN, all cases were resolved, only one patient had recurrence, and 17.4% had corneal abrasion that was easily resolved with treatment¹⁷. In developing countries, IFN α -2B is an expensive option that is not accessible for most population in general; however, our case bears witness that with appropriate assessment and the necessary care, MMC remains an efficacious, safe and convenient treatment for the patient.

CONCLUSIONS

Conjunctival-corneal intraepithelial neoplasia is a form of carcinoma in situ that belongs to the spectrum of squamous cell neoplasia of the eye surface. Although it is a rare condition, and its diffuse presentation is even more infrequent, it must be always taken into account in the differential diagnosis of our patients with visual acuity acute decrease. Currently, diagnosis and treatment can be minimally invasive. For diagnosis, epithelial scraping and histopathological assessment is sufficient, and treatment consists in topical

chemotherapeutic agents, with resection being only necessary in large tumors. The authors recommend the use of mitomycin C 0.02% in developing countries.

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CONFLICT OF INTERESTS

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