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Topical mitomycin C treatment in corneal and conjunctival intraepithelial neoplasia: A case report

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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Abstract

Corneal and conjunctival intraepithelial neoplasia is a slowly progressive ocular surface lesion with low malignant potential. Owing to the high recurrence rates, cryotherapy or topical chemotherapy is used with surgical treatment. In this paper, we report the histopathologic findings and treatment of a case of intraepithelial neoplasia that began in the conjunctiva and progressed to the cornea. A 75-year-old woman presented with complaints of redness, irritation and lacrimation in her left eye for around 1 month. Slit-lamp examination revealed a papilliform mass on the nasal conjunctiva along with involvement of the adjacent corneal epithelium. Conjunctival excisional biopsy showed a moderate epithelial dysplasia. Topical 0.04% mitomycin C was administered 4 times daily for 3 weeks. No recurrence was observed in the following 18 months.

Keywords: Conjunctival intraepithelial neoplasia, Dysplasia, Mitomycin C

Introduction

Ocular surface squamous neoplasia (OSSN) encompasses the ocular surface epithelial tumor spectrum from intraepithelial dysplasia to invasive squamous cell carcinoma. Corneal and conjunctival intraepithelial neoplasia may spread in the cornea with conjunctival and limbal origin and are slowly progressing lesions with low malignancy potential. These lesions, which do not pass the basal membrane, are histopathologically mild, moderate, or severe dysplasia [1]. Factors such as smoking, exposure to ultraviolet light, ocular surface injury, vitamin A deficiency, human papilloma virus infection and acquired immunodeficiency syndrome play roles in disease development [2, 3]. Promoter mutations in the telomerase reverse transcriptase gene were identified as contributing factors by Scholz et al. [4] in patients with conjunctival OSSN.

The distinction between invasive and non-invasive conjunctival epithelial lesions is crucial for their treatment. Therefore, incisional and excisional biopsies, which may indicate the invasiveness of the lesion, are useful for obtaining a definitive diagnosis. Although surgical excision remains the first choice of treatment modality, the introduction of topical chemotherapy in recent years has rapidly changed the therapeutic approach [5]. Owing to the high recurrence rates, complementary treatments such as cryotherapy and topical chemotherapy are applied after surgical excision. Mitomycin C (MMC), 5-fluorouracil and interferon a2b are among the chemotherapeutic agents used for medical treatment [6, 7].

In this study, we aimed to assess the treatment and outcome of a patient with intraepithelial neoplasia beginning in the conjunctiva and progressing to the cornea.

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Case presentation

On ocular examination, her best-corrected visual acuity was 0.00 logMAR in the right eye and 0.5 in the left eye. Biomicroscopic examination revealed a grade 4 cataract in the left eye and papilliform mass in the nasal conjunctiva of nearly 3×4 mm (Figure 1). Neovascularization was not observed in the cornea. A grey opaque lesion and an epithelial defect were found in the area adjacent to the limbus in the nasal cornea. Split-lamp examination of the cornea revealed that the lesion did not reach the stroma. The anterior chamber and fundus examinations, as well as the anterior and posterior segment examinations of the right eye were normal. The patient was considered to have an intraepithelial neoplasia beginning from the conjunctiva, extending to the cornea. She was informed of the possible complications and asked to sign a consent form. The excisional biopsy from the lesion was performed with 2-mm clear margins. A 0.02% MMC solution (Mitomycin C Kyowa, Kyowa Hakko Kogyo Co Ltd., Tokyo, Japan) was administered for 30 seconds to the open tissue, which was then irrigated with physiologic serum. The conjunctival wound site was not sutured, and the sclera was left open. Corneal epithelial debridement was performed with a blunt spatula. Tissue excised from the conjunctiva was sent to the pathology department for histopathological assessment. After the patient's epithelium had fully healed, MMC (0.04%, 4×1) treatment was begun on the fifth postoperative day and continued for 3 weeks. Ocular irritation and conjunctival hyperemia were observed during the treatment but ceased after MMC drop treatment was stopped. The histopathological sections of the tissue showed moderate epithelial dysplasia (Figure 2, 3). Immunohistochemistry was human papilloma virus negative. Examination of the patient at 1 month did not reveal staining of the conjunctiva and cornea. No cloudiness was observed in the cornea. The patient had a cataract surgery on the same eye 2 months after the initiation of the topical MMC treatment. After the surgery, the visual acuity in the left eye increased to 0.00 logMAR. The patient was followed up with slit-lamp biomicroscopy for recurrence, with check-ups every month for 6 months and then every 3 months thereafter. Recurrence was not observed during the 18 month-follow-up (Figure 4). Written informed consent was obtained from the patient for the publication of this report and the accompanying images.

Figure 1: Papilliform mass in the nasal conjunctiva of the left eye

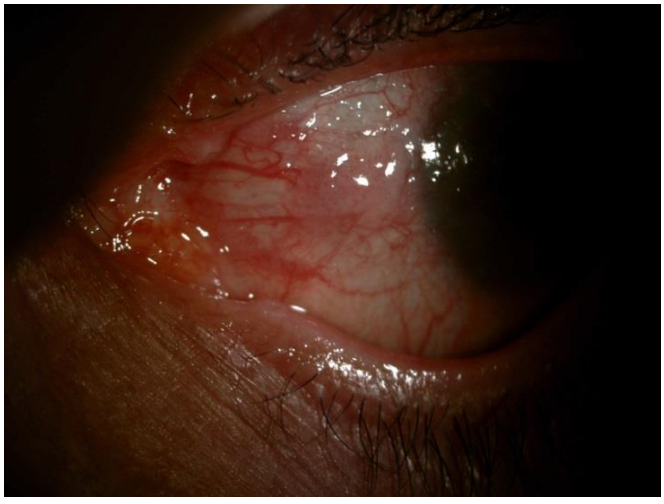


Figure 2: Histopathological picture showing acanthosis in the epithelium, increased cellularity and moderate dysplasia (Hematoxylin & Eosin x10)

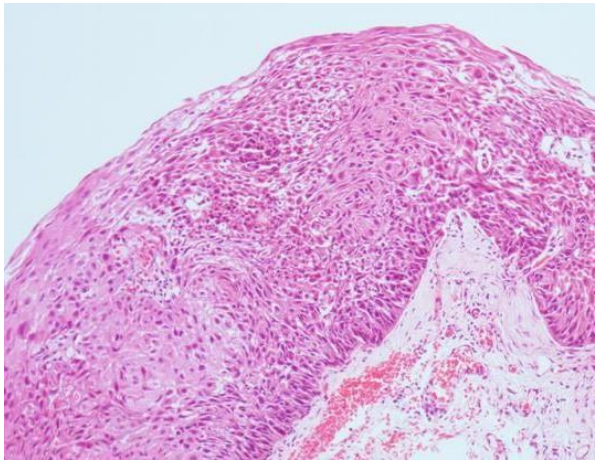


Figure 3: Increased ki-67 proliferation index in dysplastic epithelium (Ki-67x20)

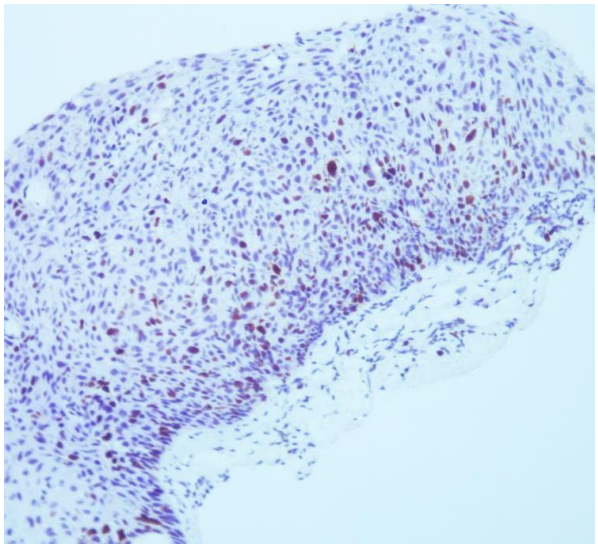
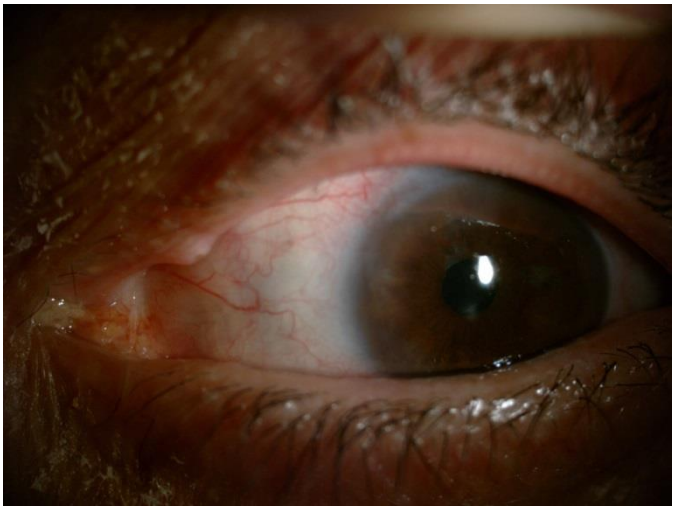


Figure 4: Postoperative image after excision of neoplasm and cataract surgery



Discussion

The aim of treatment for corneal and conjunctival intraepithelial neoplasia is to remove the neoplastic epithelium and prevent recurrence. The most important criterion for determining the recurrence rate is excision with positive surgical margins [8]. The recurrence rate after primary excision with pathologically clear margins is 33% [9]. Owing to the high recurrence rates, ocular surface damage such as limbal stem cell damage and corneal and conjunctival scarring may develop because of repeated surgery. Cryotherapy or topical

chemotherapy was used with surgical treatment to prevent recurrences and avoid risks. Adjuvant topical chemotherapy has several advantages, including targeting of the tumor cells, treatment of the entire ocular surface, simplicity of the treatment and reduced patient morbidity. As a topical chemotherapeutic agent, MMC was used for the treatment of microscopic disease and prevention of recurrence after surgical excision. MMC is used for both pigmented and non-pigmented epithelial tumors [5, 10].

MMC is an antibiotic isolated from *Streptomyces caespitosus* that affects the cell cycle as an alkylating agent. In topical application under aerobic conditions, MMC generates free radicals and has a cytotoxic effect. MMC-related changes in the ocular surface epithelium may persist for at least 8 months after topical treatment [11]. Before MMC was used for ocular surface neoplasia treatment, it was commonly used in glaucoma and pterygium surgery owing to its antiproliferative effect on subconjunctival fibroblasts. MMC was first shown to be effective against corneal intraepithelial neoplasia by Frucht-Pery and Rozenman [12] in 1994, and later studies supported its efficacy for ocular surface tumors [10, 13]. Currently, MMC is used as a complementary treatment for corneal and conjunctival intraepithelial neoplasia. Treatment uses 0.02% or 0.04% MMC doses after surgical excision [6, 13]. In topical use, MMC has a higher rate of adverse effect than 5-fluorouracil and interferon a2b. On the other hand, MMC as a monotherapy has high efficiency, and the conjunctival intraepithelial neoplasia resolution time is shorter [5]. We thought that our patient, who had a conjunctival mass removed from the same localization 1 year previously, had a recurrent conjunctival intraepithelial neoplasia. Owing to the corneal and conjunctival involvements in our case, we applied 0.02% MMC during surgery and topical 0.04% MMC treatment after surgery to prevent recurrence. During the follow-up examinations, no recurrence was found in the cornea or conjunctiva.

Although MMC is accepted as a safe chemotherapeutic agent for topical treatment of ocular surface neoplasia, temporary ocular side effects such as hyperemia, chemosis, corneal epitheliopathy and scleral thinning may be observed. These side effects usually regress with the addition of topical steroids or nonsteroidal anti-inflammatory drugs or interruption of MMC chemotherapy. Rarely observed but significant complications are limbal stem cell deficiency, scleromalacia, cataracts and corneal ulcers [14, 15]. Cornea and scleral melting can be prevented by waiting for epithelial healing before topical MMC application after surgical excision. Severe complications were not observed in our patient, and mild side effects such as conjunctival hyperemia and lacrimation resolved after MMC drop application was stopped. No sequelae developed.

Conclusion

Topical MMC administration after surgical excision and corneal debridement may be a highly effective and reliable adjuvant treatment choice for conjunctival and corneal intraepithelial neoplasia to reduce recurrence rates. The effectiveness of MMC for ocular surface neoplasia treatment can be better determined in further prospective studies.

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