Case Report

CONJUNCTIVAL AND CORNEAL INTRAEPITHELIAL NEOPLASIA: THE OUTCOME OF WIDE EXCISION OF TUMOUR WITH CYCLICAL ADJUVANT TOPICAL MITOMYCIN-C- A CASE SERIES

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ABSTRACT

A study was conducted to report the outcome of Mitomycin-C (MMC) treatment following wide excision, cryotherapy, conjunctival reconstruction with or without Amniotic Membrane Transplantation(AMT) in patients with conjunctival and corneal intraepithelial neoplasia. Unilateral suspicious gelatinous conjunctival growth in four patients with duration of presentation ranged from 1-3 month was examined. Three patients demonstrated conjunctival lesion extension into the cornea, and in the fourth patient, lesion was limited to limbus. All underwent wide excision and cryotherapy followed by AMT in 2 patients and direct closure in the other 2 patients. Post-surgery topical antibiotics and steroids was initiated. Histopathology confirmed mild to moderate conjunctival intraepithelial neoplasia (CIN) in all four cases thus topical chemotherapy was initiated with weekly on-off cycles of topical MMC 0.02 % 6 hourly. Number of cycles varied from 3-4 depending on patient tolerance and side effects. All patients responded well with no recurrence noted during follow up. Wide excision, cryotherapy by double freeze thaw technique followed by conjunctival reconstruction by AMT or direct closure remains a primary treatment option in CCIN. Adjuvant therapy with 0.02% MMC is found to be effective for prevention of CIN recurrence but requires close monitoring for side effects.

INTRODUCTION

Conjunctival and Corneal Intraepithelial Neoplasia (CCIN) comprises of a spectrum of neoplastic disorders collectively known as Ocular Surface Squamous Neoplasia (OSSN). It is a precancerous lesion with slow progression and low malignant potential traditionally affecting the elderly. The degree of dysplasia may vary from mild to severe. Although many options are available in treating CCIN, the current preferred management is wide excision of the tumour followed by adjuvant topical Mitomycin-C 0.02% in cycles [1].

CASE SERIES

We share 4 cases of CCIN which were diagnosed and treated in the Ophthalmology Department of Hospital Sungai Buloh.

Case 1

Sixty-eight-year-old Chinese lady, with underlying diabetes mellitus and hypertension presented with a progressively enlarging conjunctival-corneal growth, over a period of three months causing redness and foreign body sensation. At presentation, the best corrected visual acuity (BCVA) in the right eye was 6/12. There is an elevated pigmented lesion at the limbus measuring 4.0mm vertically x 6.0mm horizontally at 3 – 4 oclock position, with the presence of feeder vessels (Figure 1).The conjunctiva was mildly injected with absence of corneal epithelial defect on fluorescein staining. The lens was mildly cataractous. The posterior segment was normal. The BCVA in the left eye was also 6/12, attributed to an immature cataract, otherwise the rest of the anterior and posterior segment was found to be normal.

She underwent wide excision of the conjunctival corneal lesion. This was followed by cryotherapy to the margins of the remaining bulbar conjunctiva using double freeze thaw technique and the ocular surface was reconstructed with amniotic membrane (Figure 2). The surgery was uncomplicated and post operatively was managed with topical Prednisolone acetate 1% and Chloramphenicol 0.5% two hourly as well as ointment Chloramphenicol 1% at night.

The histopathological examination (HPE) demonstrated conjunctival intraepithelial neoplasia with moderate differentiation and a clear excised margin. Once the conjunctiva and cornea had healed, adjuvant chemotherapy was commenced with four cycles of topical Mitomycin-C 0.02% four times a day as weekly on-off cycles. The patient was able to tolerate the cyclical chemotherapy with no recurrence over fifteen months follow up with preservation of vision at 6/9 (Figure 3).

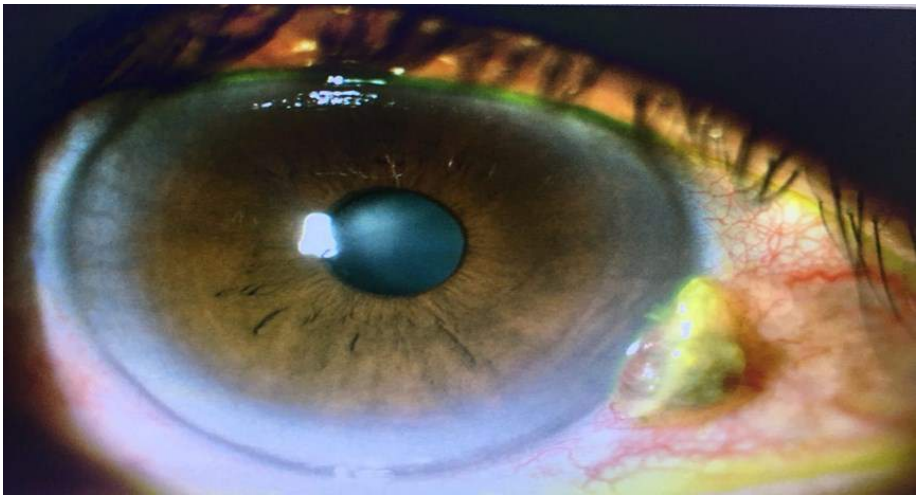

Figure 1: Elevated pigmented lesion with feeder vessel.

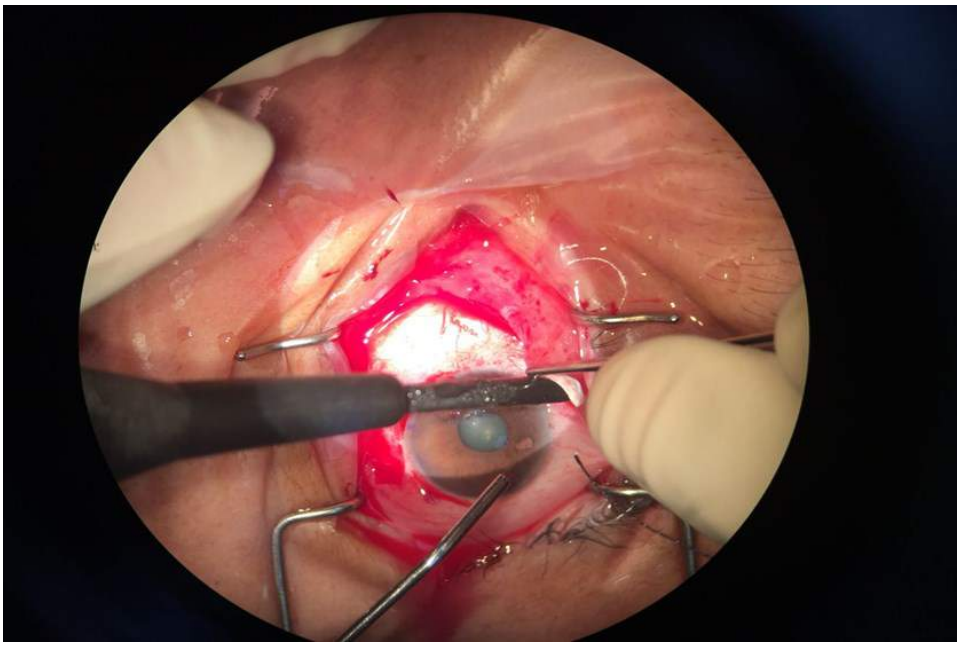

Figure 2: Intraoperative cryotherapy by double freeze thaw technique after a wide excision of the tumour.

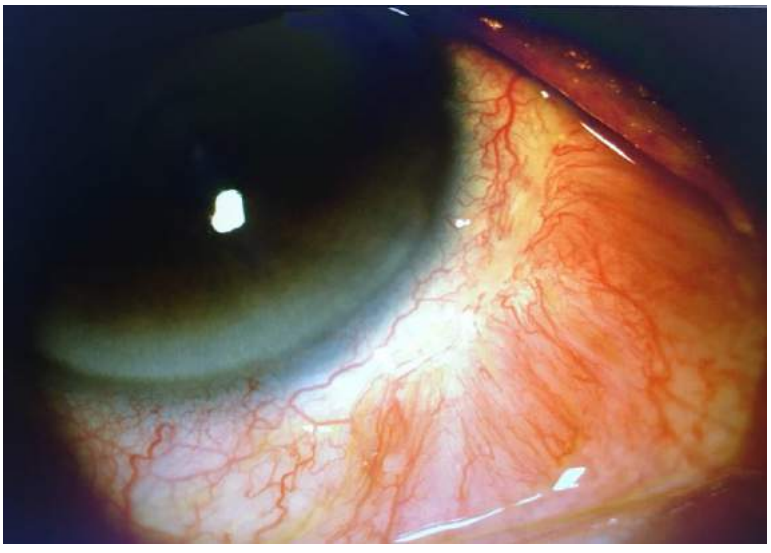

Figure 3: After completion of 4 cycles of topical Mitomycin C

Case 2
Fifty-seven year old Chinese male, a lorry driver with previous history of benign parotid gland tumour removal presented with an asymptomatic painless mass in the left eye which did not increase in size for a duration of 1 month. He had BCVA of 6/9 with normal posterior segment. However, the nasal conjunctiva of the left eye was mildly injected. An elevated gelatinous mass with leukoplakia measuring 3.1mm horizontally and 4.0mm vertically extending approximately 2.0mm into the cornea was noted (Figure 4). There was no epithelial defect with fluorescein staining and no feeder vessels were seen.

He underwent wide excision of the conjunctival tumour with superficial keratectomy. Keratectomy was performed 2mm from corneal edge while excision of conjunctiva was 4mm form the tumour edge. Double freeze-thaw technique cryotherapy was then applied, followed by ocular surface reconstruction with amniotic membrane transplant. The surgery was uncomplicated and post operatively he received similar treatment as Case 1. Histopathological Examination of the excised tissue confirmed conjunctival intraepithelial neoplasia with mild to moderate differentiation. The excised margin was clear. Weekly on-off topical Mitomycin-C was commenced and 3 cycles was completed uneventfully. At twenty two months of follow-up no recurrence was observed, and his BCVA remained at 6/9 .

Case 3
Fifty- three year old Chinese lady with underlying ocular surface disease secondary to chronic episcleritis presented with a suspicious growth on the left eye. She had dry eyes with suspected limbal stem cell deficiency. Her left BCVA was 6/6. Anterior segment examination revealed a conjunctival-corneal gelatinous mass nasally, measuring 10.0mm horizontally and 7.5mm vertically, associated with vascularization. The right eye was unremarkable with BCVA of 6/6. She underwent left wide excision of the conjunctival tumour with superficial keratectomy. The tumour excision was 2mm from corneal edge and 4mm from the conjunctival edge. Adjuvant cryotherapy with double freeze-thaw technique and direct closure of the excised conjunctival margins was done. Post operatively she also received topical steroid and prophylactic antibiotics. The excised tumour HPE demonstrated focal conjunctival intraepithelial neoplasia with mild differentiation and a clear histological margin. However, unlike the previous cases, she only managed to complete 2 cycles of weekly on-off topical Mitomycin–C. The third cycle was withheld as she developed conjunctival epithelial defect with severe filamentary keratitis. She continued treatment with topical Levofloxacin QID and intensive lubrication with preservative-free artificial tears. Fifteen months after the surgery, no recurrence was observed and the ocular surface condition was optimised resulting in vision of 6/9.

Case 4
Fifty-eight year old Chinese male with no previous comorbidity presented with complaint of left eye discomfort, associated with redness and tearing of one month duration. His left eye had a history of foreign body injury from a tree bark few years prior. Bilateral BCVA was 6/9. He had large gelatinous conjunctival-corneal mass measuring 9 mm horizontally and 6mm vertically nasally in the left eye. The growth extend approximately 2mm into the cornea. The posterior segment was normal. The right eye was unremarkable. Similar wide excision was performed with superficial keratectomy, where excision was 2mm form corneal edge and 4mm from conjunctival edge of tumour. This was followed by double freeze-thaw technique adjuvant cryotherapy

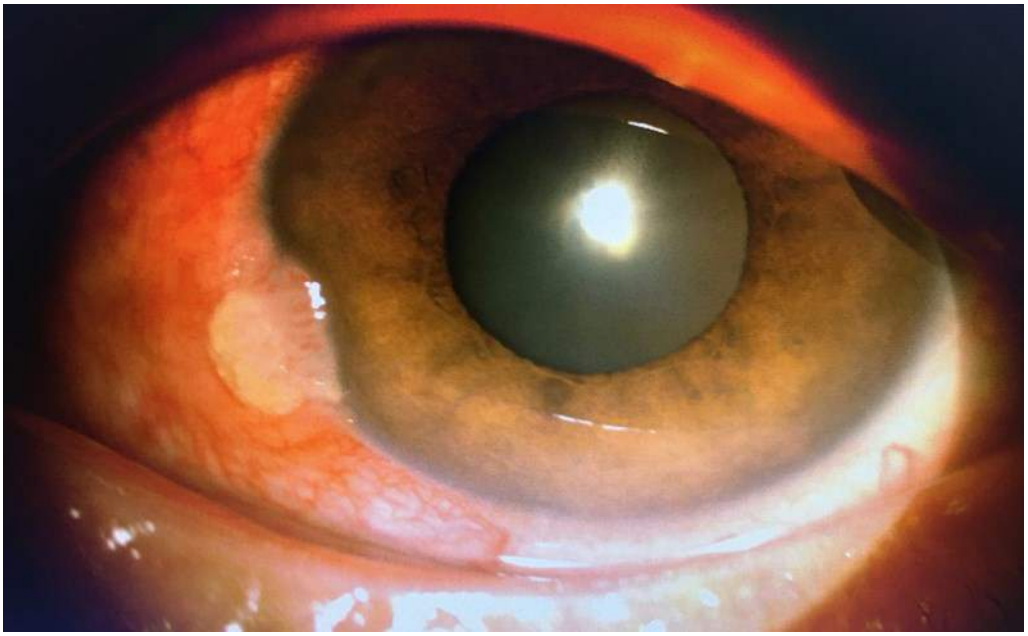

Figure 4: Elevated nasal conjunctival lesion with leukoplakia.

and direct closure of conjunctival excised margins. He was treated with similar postoperative medication as previous cases. Histopathology of the excised tumour revealed mild to moderate differentiation of conjunctival intraepithelial neoplasia. He received 4 cycles of weekly on-off topical Mitomycin with no recurrence noted at ten months. His left BCVA remained 6/9.

DISCUSSIONS

Conjunctival tumour is one of the most frequent tumours of the eye and adnexa, varying from benign to malignant lesions. They may arise from any type of the conjunctival cells but usually originate from epithelial and melanocytic cells. Approximately 40% of the tumours have an epithelial origin with 64.5 % of them being pre-cancerous lesions [2]. Clinical differentiation between pre-cancerous benign and malignant lesions is difficult, hence biopsy is required for a definitive diagnosis.

A precancerous lesion CCIN, varies in presentation from absent to variable signs and has symptoms like foreign body sensation, redness or irritation accompanied by the presence of an ocular surface tumour [3]. Commonly CIN appear at the limbus in the interpalpebral fissure and less commonly in the forniceal or tarsal conjunctiva. It appears as a fleshy, may be sessile or minimally elevated lesion. This limbal lesion may extend for a variable distance onto the adjacent corneal epithelium. At times it may have a white plaque (leukoplakia) over the surface due to secondary hyperkeratosis.

The definitive term of CIN is acquired from the histological study reserved for various degree of non-invasive conjunctival epithelial dysplasia [3]. The classification is made according to its location in relation to the epithelial basement membrane. Thus, these tumours are divided into conjunctival and/or corneal intraepithelial neoplasia when they are confined to the epithelium, and squamous cell carcinoma (SCC) when there is invasion of the epithelial basement membrane. CIN is classified as CIN I (mild dysplasia), CIN II (moderate dysplasia), and CIN III (severe dysplasia or carcinoma in situ) where atypical cells occupy the entire thickness of epithelium.

Treatment approach to CCIN is variable depending on the availability of surgical and chemotherapeutic agents in each centre [4]. In our centre, cases are managed by total wide excision of the tumour. This is followed by adjuvant cryotherapy and ocular surface reconstruction with or without amniotic membrane transplantation. Topical cyclical topical chemotherapy with mitomycin-C followed. Meticulous surgical wide excision is important to prevent recurrence as the edge of the tumour and depth of the lesion is difficult to delineate and the presence of micro-metastasis is a possibility. Furthermore, the tumour edges often appear clear and avascular, a misleading appearance of the true size of the tumour. It is advisable to maintain a dry field without irrigation to prevent tumour seeding and applying cryotherapy to the margins of the remaining bulbar conjunctiva using double freeze-thaw technique. Ocular surface can be reconstructed either by direct closure or with the use of amniotic membrane if there is extensive conjunctival excision exposing sclera. Amniotic membrane transplantation is advantageous as it possesses excellent anti-angiogenic, anti-microbial, anti-inflammatory action and most importantly it promotes healing in persistent epithelial defects by facilitating the adhesion and migration of basal epithelial cells [5].

Combination treatment with post-operative topical chemotherapeutic agents like Mitomycin–C (MMC), Fluorouracil or Interferon alpha-2b have been recommended as adjuvant therapy by many surgeons. In 2008, Huerva et al reported that topical INF alpha 2-b, combined with subconjunctival INF alpha 2-b, sometimes found to be effective as primary treatment for CIN in recurrent cases or retreatment after recurrence when INF has been used previously for a short period of time [6].

However, MMC is an affordable option and easily available in our centre hence this is our preference. It is a potent cytotoxic agent derived from Streptomyces Caespitous possessing antineoplastic and antifibroblastic properties which inhibits DNA synthesis phase thus rendering it effective with low rate of CCIN recurrence. The reported side effects include mild discomfort, ocular hyperaemia, photophobia, epithelial punctate keratitis and lacrimation which can interfere with continuation of the cycles [7]. The recommended concentration of topical MMC is 0.02% as it is less toxic when administered up to 14 days duration. However, up to 3-5 cycles can be administered on an on-off weekly basis. Many ophthalmologists have reported even though MMC is effective in eradicating CCIN, it could lead to a more sinister outcome of limbal stem cell deficiency. Therefore, in an attempt to decrease the incidence of side effects, a relatively low concentration of MMC (0.01%) was proposed [7,8].

The patients in our case series were followed up from 10 to 22 months duration and we are happy to report that no recurrence was observed in the treated eye. Previous literature review has reported relapses which can arise months to many years after resection of the tumour, therefore it is important to monitor these patients carefully even up to annually for life. Histopathology report which document the involvement of margins should be followed up more frequently as the recurrence rate is higher.

CONCLUSION

Adjunctive therapy post primary surgical wide excision of CCIN with 0.02% MMC is shown to be effective for prevention of CCIN recurrence but these patients still warrant close monitoring for side effects and complications. However, patients predisposed to ulceration or poor wound healing are

not candidates for topical chemotherapy. It is imperative to choose a mode of treatment which is safe but also effective.

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