Topical Mitomycin Chemotherapy for Conjunctival Malignant Melanoma and Primary Acquired Melanosis With Atypia

Clinical Experience With Histopathologic Observations

Hakan Demirci, MD; Steven A. McCormick, MD; Paul T. Finger, MD

Objectives: To clinically evaluate topical mitomycin chemotherapy in patients with diffuse, multifocal, or recurrent primary acquired melanosis with atypia and/or conjunctival malignant melanoma and to histopathologically study ocular tissue samples obtained before and after treatment.

Methods: Chemotherapy with topical mitomycin, 0.04% 4 times daily, was administered for 28 days as the primary and only treatment in 7 patients (after biopsy) and for 7 days as adjuvant therapy to excision and cryotherapy in 5 patients. Mean follow-up was 38 months. Five patients developed subconjunctival recurrences, for which 2 underwent orbital exenteration and 3 were treated conservatively. Histopathologic specimens of conjunctival, adnexal, and ocular tissues obtained before and after chemotherapy were evaluated.

Results: Regression of tumor was observed in 11 patients with primary or adjuvant topical mitomycin chemotherapy. One patient with nodular melanoma was resistant to mitomycin chemotherapy. Histopathologic findings included regionally variable conjunctival epithelial atrophy and thinning. Dyskeratosis and focal keratinization in conjunctival epithelium were noted. Epithelial nuclei were occasionally pyknotic in areas of atrophic epithelium. Subepithelial inflammation was present and was most intense in areas with severe atrophy and/or keratosis. Two patients with primary treatment and 2 with adjuvant treatment developed subconjunctival recurrence. In patients with recurrent malignant melanoma, the deeper layers of the lamina propria were involved, with sparing of the epithelium and superficial lamina propria. Transient keratoconjunctivitis was observed in all patients during treatment. In evaluation of the exenteration specimens, corneal, scleral, episcleral, retinal, and anterior structures were within normal limits.

Conclusions: Topical mitomycin chemotherapy was found to induce regression of conjunctival melanoma and primary acquired melanosis with atypia. When mitomycin chemotherapy was used as an adjuvant to excision and cryotherapy, 2 (40%) of 5 patients experienced tumor recurrence at a mean of 4.3 years’ follow-up. Our histopathologic findings demonstrated a long-term mitomycin chemotherapy–related effect on the conjunctiva. The degree of chronic atrophy and inflammation was not clinically significant. The pattern of effect and location of recurrent disease suggest that this regimen of topical mitomycin chemotherapy was most effective for superficial tumors. No complications that would preclude use of our dose regimen were noted. Although subconjunctival or orbital recurrences were noted, topical mitomycin chemotherapy warrants further investigation as an alternative treatment for primary acquired melanosis with atypia and conjunctival malignant melanoma.


PRIMARY ACQUIRED melanosis (PAM) with atypia and conjunctival malignant melanoma (MM) affect mostly middle-aged white people.1-3 Treatment modalities in the management of PAM with atypia and conjunctival MM have included local surgical removal (with or without cryotherapy), radiotherapy, and exenteration.4-6 As a vision-sparing alternative, local excision with cryotherapy has become the most commonly used treatment.10 However, long-term follow-up of such “conservative” treatments has shown that local recurrences are common.8 Local recurrences may be (in part) due to the fact that these tumors can be variably pigmented or nonpigmented and the tumor can be multifocal. Because the pigmented margin is commonly used as a guide for most conservative treatments, the true tumor’s edge may be missed. Pathological evaluations of excised specimens have clearly demonstrated patches of amelanotic melanoma extending beyond hyperpigmented areas.11 These findings are particularly disturbing in that failure of local control is most likely to lead to the development of multifocal disease, systemic...
PATIENTS AND METHODS

Twelve patients, 8 women and 4 men, with biopsy-proven PAM with atypia or conjunctival MM were treated with topical mitomycin, 0.04% (Bristol Laboratories, Princeton, NJ). Before treatment, we obtained approval from the internal review board and the pharmacy committee of The New York Eye and Ear Infirmary, New York, for the purpose of investigating topical chemotherapy for the treatment of conjunctival neoplasia.

In this study, the average age of patients was 56 years (range, 31-72 years), and mean follow-up was 38 months (range, 6-67 months). Our methods of topical mitomycin chemotherapy have been described previously.13,14 Briefly, each patient was dispensed one bottle of mitomycin, 0.04% solution, each week. With the patient in a supine position, a drop of mitomycin was placed into the superior conjunctival fornix 4 times a day. Patients and their families were requested to wear latex gloves when handling the medication. The bottles were returned for disposal.

Topical mitomycin chemotherapy was used in 7 patients as the primary and sole treatment, and drops were given for 28 days. Because of the moderately severe keratoconjunctivitis, patients first use topical mitomycin solution for 14 days, after which it was discontinued for 14 days, followed by a second course of treatment for 14 days. These 7 patients were treated for recurrence after conservative treatment (eg, excision and cryotherapy) or for diffuse, multifocal disease and were considered to be at high risk for failure and complications of conservative treatment (excision or cryotherapy). Topical mitomycin chemotherapy was also used as an adjuvant treatment in 5 patients. The drops were given for 7 days, starting within 2 weeks of primary excision and cryotherapy. These 5 patients had experienced recurrence after previous conservative treatment (eg, excision and cryotherapy) or had risk factors for recurrence (but could be treated with excision and cryotherapy).

Excision and cryotherapy were applied by the same surgeon (P.T.F.). Our technique indicates that all pigmented tissues (tumors) were excised, with 2- to 3-mm clinically “tumor-free” margins. If there was tumor extension onto the cornea, affected epithelium plus 2 mm of normal-appearing corneal epithelium were removed. The subjacent epidermal tissues were scrubbed with absolute alcohol, then quickly and copiously irrigated.13,23-26 Superficial cryotherapy was applied to all the exposed episcleral and epicorneal tissues within the bed of excision by large, flat, oval cryotherapy tips (Cabot Medical, Langhorne, Pa) in a double freeze-thaw fashion.

After treatment, all patients were evaluated at 3-month intervals. Each examination consisted of a visual acuity determination and a complete ophthalmic examination. All conjunctival surfaces, including palpebral and tarsal conjunctiva, were examined. Palpation included the eyelids and periorbital tissues and examination for preauricular or cervical adenopathy. The nasal antra were also inspected.27 Additional medical evaluations for metastases and anemia were performed or requested every 6 months, including a physical examination, complete blood cell count, serum multianalyzer profile-12, γ-glutamyltransferase measurement, and a yearly chest radiograph.

All patients underwent biopsy examination before therapy. Over the years after treatment, subsequent biopsies were performed as necessary. During follow-up, 5 recurrences were observed for which 2 exenterations were performed. Histopathologic observations of the conjunctival, adnexal, and orbital specimens were noted.

RESULTS

TUMOR RESPONSE

Tumor characteristics and responses to therapy are summarized in Table 1 and Table 2, respectively. The histopathologic diagnoses of the 7 patients in whom topical mitomycin chemotherapy was the primary and sole
treatment after excisional biopsy were as follows: 5 patients had PAM with atypia (stage IB), 1 had invasive melanoma with subepithelial infiltration (stage IIB), and 1 had clinically diagnosed conjunctival MM recurrence based on corneal epithelium extension. Of 5 patients who underwent adjuvant topical mitomycin chemotherapy, 2 had PAM with atypia (stage IB), 2 had PAM with focal invasion (stage IIA), and 1 had invasive melanoma (stage IIB).

We found that patient 1 had nodular and subepithelial rests of melanoma, which did not disappear after a 28-day course of primary mitomycin chemotherapy. We decided to perform excision and cryotherapy for residual disease, but, despite additional treatment, this patient experienced orbital recurrence after 17 months and underwent exenteration. Fifty-two months after topical mitomycin chemotherapy and 32 months after exenteration, the tumor had spread to a cervical node, and a metastatic survey was positive for melanoma.

The other 6 patients who had mitomycin as their primary and sole treatment after excisional biopsy exhibited clinical regression of their pigmented lesions (Figure 1). Biopsies were repeated to rule out residual malignancy or recurrent disease after chemotherapy (Table 2 and Table 3).

Table 1. Patient, Tumor, and Treatment Parameters*

<table>
<thead>
<tr>
<th>Patient No./Age, y/Sex</th>
<th>Disease Type</th>
<th>Treatment Date, mo/y</th>
<th>Mitomycin Concentration, %†</th>
<th>Treatment Duration, d</th>
<th>Histopathologic Type</th>
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*PAM indicates primary acquired melanosis; MM, malignant melanoma.
†Mitomycin was administered 4 times daily to all patients.

Table 2. Responses to Mitomycin Chemotherapy†

<table>
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<tr>
<th>Patient No.</th>
<th>Response</th>
<th>Partial</th>
<th>Complete</th>
<th>Local Control</th>
<th>Metastasis</th>
<th>Melanoma</th>
<th>Death</th>
<th>Cryotherapy</th>
<th>Vision</th>
<th>Adverse Effects</th>
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<td>8 Adjuvant Adjuvant No† No No Yes 30 Prosthesis KC None 67</td>
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*KC indicates keratoconjunctivitis; CLL, chronic lymphocytic leukemia.
†Exenterated patients.
‡Subconjunctival or orbital recurrence.
§Cataract was not caused by mitomycin chemotherapy.
tinization (Figure 2, A and B). In severely atrophic and thinned areas, epithelial nuclei were occasionally pyknotic (Figure 3, A). Subepithelial inflammation, largely consisting of mononuclear cells, and stromal fibrosis were seen in areas with atrophic epithelium. This finding was most intense in areas with severe atrophy and/or keratosis (Figure 3, A). Histopathologic findings in conjunctival specimens derived from patients treated for 28 and 7 days were similar (Figure 4). Overall, post–mitomycin chemotherapy conjunctival epithelial changes were similar to the changes in patients without recurrences.

Results of all conjunctival biopsies performed after topical mitomycin chemotherapy were negative (Table 3). Two patients in the primary treatment group later de-

Figure 1. The upper bulbar conjunctiva of a patient with biopsy-proven multifocal and nodular primary acquired melanosis with atypia before topical mitomycin chemotherapy (A) and 12 months after excisional biopsy, cryotherapy, and adjuvant topical mitomycin chemotherapy (B).

Figure 2. Posttreatment biopsy specimen from patient 1 shows areas with prominent atrophy, as evidenced by a thinned conjunctiva, mild keratosis, nuclear pleomorphism, and apparent pyknosis focally (A); other areas where the conjunctiva is relatively unremarkable, showing only mild chronic inflammation and minimal, nonspecific reactive epithelial changes (B); and areas with recurrent tumor occurring prominently in the epithelium of pseudoglands of Henle (C).

Table 3. Demographic Data for Patients Who Underwent Biopsy After Mitomycin Treatment

<table>
<thead>
<tr>
<th>Patient No./Age, y/Sex</th>
<th>Disease Type</th>
<th>Treatment Type*</th>
<th>Local Control</th>
<th>Biopsy Date, mo/y</th>
<th>Follow-up, mo</th>
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<td>Multifocal</td>
<td>Nodular</td>
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<td>Posttreatment</td>
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<td>No</td>
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<td>11/1996</td>
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<tr>
<td>5/70/F</td>
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<td>No</td>
<td>12/1996</td>
<td>2/1998</td>
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<tr>
<td>8/69/F</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>1/1993</td>
<td>1/1994</td>
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<tr>
<td>9/36/F</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>6/1994</td>
<td>4/1997</td>
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<tr>
<td>10/31/M</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>5/1994</td>
<td>1/1998</td>
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</table>

* Primary indicates patients used only topical mitomycin treatment for 28 days; adjuvant, topical mitomycin treatment was used as an adjuvant to excision and cryotherapy for 7 days.
† Exenterated patients.
‡ Subconjunctival or orbital recurrences.

veloped subconjunctival recurrences. Both of these patients, treated for PAM with atypia, developed subconjunctival recurrences 4 months after treatment. One of these patients had a history of cutaneous melanoma of the eyelid margin. Both recurrent lesions were treated with excision and cryotherapy.

Of 5 patients treated with adjuvant topical mitomycin chemotherapy after excision and cryotherapy, 2 developed subconjunctival recurrences. One patient was treated for conjunctival MM, and subconjunctival recurrence developed 44 months after topical mitomycin chemotherapy. Excision and cryotherapy were applied to recurrent disease, and the patient's condition has been stable (with respect to local control) for 7 months. The other patient initially had a nodular melanoma and developed 2 recurrences (1 and 3 years later). Excision and cryotherapy were used, but 5 years later orbital recurrence developed and exenteration was performed. Results of the patient's most recent metastatic survey were negative 7 months after exenteration. Postoperative topical mitomycin chemotherapy did not prevent wound closure or cause wound dehiscence.

In the patients who had recurrences, we found that the deeper layers of lamina propria were involved, with sparing of the epithelium and superficial lamina propria. The conjunctival epithelium was free of disease (Figure 3, B). In the specimen from the patient with resistant disease, scattered neoplastic cells were present along the tracts of pseudoglands of Henle (Figure 2, C).

TOXIC EFFECTS

Topical mitomycin chemotherapy induced a relatively severe but transient keratoconjunctivitis in all patients (Table 2). This complication took 4 to 6 weeks to resolve in patients treated for 28 days. The severity and duration of keratoconjunctivitis were less in patients treated for 7 days.

Of patients treated for 28 days, 1 developed a round corneal epithelial defect thought to be caused by a mechanical injury from the dropper tip. Another patient developed a focal area of corneal haze that did not affect her vision. Cataracts developed in 2 patients but could not be directly attributed to treatment. No patient developed scleral or corneal thinning. At the last examination, visual acuities were within 1 line of pretreatment values in 6 of 7 patients. One was exenterated for recurrence (Table 2).

In patients treated with adjuvant topical mitomycin chemotherapy, there were no clinically apparent scleral or corneal toxic effects. No cataracts were observed. Four of these 5 patients have maintained the most recent vision within 1 line of their pretreatment visual acuity. One was exenterated for recurrence (Table 2).

In exenteration specimens, episcleral, corneal, iris, ciliary body, lens, scleral, and retinal tissues were normal (Figure 5). No toxic effects were observed in these structures. In the lacrimal gland, we observed no histological changes.
Excision and cryotherapy is the most commonly used treatment for conjunctival MM and PAM with atypia, but it has been associated with recurrence rates ranging from 23.5% to 79.0% (Table 4). Folberg et al suggested that recurrence was associated with incomplete excision or corneal involvement. Moreover, patients with multifocal conjunctival disease are more likely to have recurrences than patients with unifocal disease.

Topical mitomycin chemotherapy is being used in the treatment of conjunctival neoplasia. Thus far, it has been used for conjunctival squamous intraepithelial neoplasia, PAM with atypia, and conjunctival MM. It has also been used in glaucoma and pterygium surgery. Topical chemotherapy is attractive because it offers a method of treating the entire conjunctiva with less dependence on the tumor margins. It addresses the need to treat the entire "conjunctiva at risk" for containing occult malignant foci. In these studies, topical mitomycin has been found to induce tumor regression without serious clinical complications.

In our series, all patients had a history of excision and cryotherapy or underwent excisional biopsy before mitomycin chemotherapy, which might make a bias in the interpretation of histopathologic results. However, if we consider that the patients experienced recurrence after conventional treatment (excision and cryotherapy) and we performed the biopsy after all inflammation or healing completely ended (at least 3 months), the results were most likely related to topical mitomycin chemotherapy. Although excisional biopsies performed before topical mitomycin chemotherapy might have affected our results, because our patients have high-risk factors for failure (such as diffuse, multifocal disease), local control should be related to topical mitomycin chemotherapy rather than excisional biopsy. Also, we did not observe differences between the early and late biopsy specimens after topical mitomycin chemotherapy.

This study evaluates the clinical and histopathologic effects of topical mitomycin chemotherapy on normal and diseased ocular tissues. It seemed that topical mitomycin chemotherapy affected the structure of conjunctival epithelium. This finding is similar to that reported after adjuvant subconjunctival mitomycin treatment for glaucoma surgery. In one study, the conjunctival epithelium was irregular in thickness and showed dyskeratosis and focal keratinization. Although it seems that mitomycin chemotherapy may be toxic to the conjunctival epithelium, it is difficult to explain why its effects are regionally variable. This finding may be related to naturally variable access of a topical drop to the exposed conjunctiva (eg, bulbar) vs the relatively hidden and folded fornical conjunctiva. It may also be related to the differential responses of normal vs tumor-bearing conjunctiva.

Other researchers have used topical applications of mitomycin for urinary bladder carcinoma. Murphy et al showed that intravesicular MMC therapy cytologically caused multinucleation, vacuolization, degeneration, and necrosis of superficial urothelial cells in the urinary bladder epithelium, apparently related to toxic drug effects. To complicate matters, alkylating agents can induce regressive and degenerative cellular alterations that mimic atypia and malignancy. The resulting atypical cellular features cannot always be distinguished with certainty from those seen in malignant cells. Therefore, evaluation of the conjunctival epithelial changes in patients using topical mitomycin should take into consideration that these changes might also mimic recurrent or incompletely treated disease.

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**Table 4. Summary of Recurrence Rates in Different Studies**

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<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>Recurrence Rate, %</th>
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</thead>
<tbody>
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<td>Crawford, 1980</td>
<td>Case series (conjunctival MM)</td>
<td>19</td>
<td>79.0</td>
</tr>
<tr>
<td>Folberg et al, 1985</td>
<td>Case series (PAM with atypia)</td>
<td>28</td>
<td>60.7</td>
</tr>
<tr>
<td>Jakobiec et al, 1989</td>
<td>Case series (conjunctival MM)</td>
<td>62</td>
<td>40.0 for PAM with atypia 90.0 for multifocal MM 11.0 for unifocal MM</td>
</tr>
<tr>
<td>Lommatzsch et al, 1990</td>
<td>Case series (conjunctival MM)</td>
<td>81</td>
<td>23.5</td>
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<tr>
<td>De Potter et al, 1993</td>
<td>Case series (conjunctival MM)</td>
<td>68</td>
<td>56.0</td>
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<tr>
<td>Paridaens et al, 1994</td>
<td>Case series (conjunctival MM)</td>
<td>256</td>
<td>55.1</td>
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MM Indicates malignant melanoma; PAM, primary acquired melanosis.
Our histopathologic evaluations suggest that the recurrences were more likely to have originated within the deeper layer of lamina propria or orbital tissues. All post-treatment conjunctiva and superficial layers of the lamina propria were free of melanoma. This finding suggests that our regimen of topical mitomycin chemotherapy was most effective for intraepithelial or superficial disease. If the lesion invades the substantia propria or is nodular, our concentrations and route of delivery may not be effective. Our findings could be explained by poor drug penetration into the substantia propria of the conjunctiva, the tumor-volume, or both. It is also possible that some cancer cells may be resistant to mitomycin chemotherapy.

In evaluation of exenteration specimens, we did not observe any superficial ocular, intraocular, or orbital toxic effects related to topical mitomycin chemotherapy. This may be related to the length of our follow-up or to the dose of mitomycin used in our study. In contrast, severe complications such as uveitis and scleral involvement have been reported after mitomycin treatment of pterygium. An analysis of these studies shows that the use of low concentrations or shorter periods of therapy was relatively safe. Results of our study also show that the atrophy and inflammation noted on histopathologic examination were not clinically significant.

We noted that the conjunctival epithelial changes persisted for an extended period even after the treatment was discontinued. This finding supports the known pharmacological properties of mitomycin. This effect of treatment may continue for many years, mimicking the action of ionizing radiation. Therefore, similar to an irradiated melanoma, one must not presume that residual conjunctival pigmented tissue is capable of growth or metastases.

We investigated only 1 concentration and 2 durations of topical mitomycin chemotherapy. Future studies of topical mitomycin chemotherapy will clarify its effect on the conjunctival epithelium. New chemotherapeutic agents (eg, cisplatin) should be evaluated for the treatment of conjunctival-corneal lesions. Well-designed, prospective, randomized, comparative studies are needed in this field.

Results of this study show long-term biological effects of topical mitomycin chemotherapy. We found conjunctival atrophy and thinning, nuclear changes, and subconjunctival inflammation. These changes are persistent but not clinically significant. Although mitomycin chemotherapy was particularly effective in the treatment of epithelial disease, subconjunctival or orbital recurrences can be seen. No complications that would preclude further investigation of this approach were noted.

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Reprints: Paul T. Finger, MD, The New York Eye Cancer Center, 115 E 61st St, New York, NY 10021 (e-mail: http://www.eyecancer.com).

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