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Regression of Presumed Primary Conjunctival and Corneal Intraepithelial Neoplasia With Topical Interferon Alpha-2b

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Purpose. To evaluate topical interferon alpha-2b (IFNα2b) as a lone therapy in the treatment of primary conjunctival and corneal intraepithelial neoplasia (CIN). **Methods.** Noncomparative, prospective, interventional case series. Seven patients from three institutions, treated between February and October 1999, with presumed primary CIN lesions (clinically diagnosed by corneal specialists) were given topical IFNα2b drops (1 million units/mL) four to six times daily. Follow-up was performed biweekly until there was complete clinical resolution of the presumed CIN lesions. Patients were to continue topical IFNα2b drops for 1 month after clinical resolution. Patient charts and clinical photographs were reviewed, and data were analyzed. **Results.** All seven eyes had complete resolution of the presumed CIN lesions after an average of 77.0 ± 59.2 days (range, 28–188 days). Average post-treatment follow up was 12.4 ± 2.5 months (range, 9–16 months). No patients were lost to follow-up. No recurrences have yet been seen. Side effects of treatment were limited to mild conjunctival hyperemia and follicular conjunctivitis in four (57.1%) eyes. In all cases, there was total resolution of conjunctival hyperemia and follicular changes within 1 month after cessation of the medication, without additional treatment. **Conclusions.** Topical IFNα2b alone may be an effective treatment of primary CIN. It appears to be a safe alternative to radiation, intralesional IFNα2b injection, and surgical excision with cryotherapy. Larger population studies with longer follow-up are recommended to better assess the risk of recurrence and other possible adverse effects.

Key Words: Conjunctival and corneal intraepithelial neoplasia—Interferon—Leukoplakia.

Conjunctival and corneal intraepithelial neoplasia (CIN) is a precancerous lesion of the ocular surface,[1] which is slowly progressive with a low malignant potential. It may be a precursor to squamous cell carcinoma.[2] Clinical differentiation between CIN and benign limbal lesions is based on characteristic clinical features and is not difficult.[3] CIN is usually elevated, involves the limbus, is described as gelatinous, papilliform, or leukoplakic, and may have characteristic tufts of blood vessels.[4] Many patients have corneal involvement, consisting of a gray intraepithelial plaque. This condition is more commonly diagnosed in older patients.[2] Known risk factors for CIN include human papillomavirus (HPV), HIV,[5] and ultraviolet exposure.[6] Men are more frequently affected than women.[2] Patients older than 70 years of age,[2] those with lightly pigmented irides,[6] and smokers are at increased risk.[7]

Previously designated terms for CIN include epithelioma (Von Graefe, 1860), limbal papilloma (Contino, 1911), epithelial plaque (Nicholls, 1939), intraepithelial epithelioma, Bowen's disease, Bowenoid epithelioma (McGavic, 1942), epidermalization and dyskeratosis (Ash, 1942), epithelial hyperplasia with or without dyskeratosis, precancerous condition of the bulbar conjunctiva (Janert, 1956), precancerous epithelioma of the limbus (Winter and Kleh, 1960), dyskeratotic epibulbar tumors (Irvine, 1963), limbal epithelioma (Pizzarello and Jakobiec, 1978), corneal intraepithelial neoplasia (Waring et al., 1984), conjunctival and corneal invasive neoplasia (Erie et al., 1986), ocular surface dysplasia (Lee and Hirst, 1992), tyloma, keratosis, and conjunctival callosities. The current nomenclature favors conjunctival and corneal intraepithelial neoplasia.

Differential diagnosis of CIN includes pannus,[8] actinic disease, pinguecula, pterygium, benign intraepithelial dyskeratosis,[8] keratinization of the corneal epithelium,[8] anterior basement membrane dystrophy,[3,8] malignant melanoma,[2] conjunctival papilloma,[2] nevus,[3] and pseudoepitheliomatous hyperplasia.[2]

The treatment of CIN has traditionally involved wide excision of the tumor[2,9] with application of cryotherapy to the surgical bed along with pathologic examination of excised margins.[3,10] Other treatments have included the use of external beam radiation,[2] strontium-90 radiation,[11] or Thiotepa drops.[12] Topical mitomycin-C,[13,14] topical vitamin A,[15] immunotherapy with dinitrochlorobenzene,[12] and phototherapeutic keratectomy with an excimer laser[16] have also been used to treat CIN.

Erie et al.[3] described 120 patients with CIN who had surgical excision of their tumor. A recurrence rate of 53% was noted when pathology studies showed involved margins (compromised by the tumor) and a 5% recurrence rate when pathology studies confirmed clear margins.

Interferons are a family of naturally occurring glycoproteins, discovered in 1957,[17] which bind to cell surface receptors and trigger a cascade of intracellular activity promoting antiviral and

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antitumor properties through direct and indirect mechanisms.[18] Interferon alpha-2b has been used successfully to treat condylomata acuminata, chronic hepatitis, Kaposi sarcoma, and hairy cell leukemia.[18] Intralesional use of IFNα2b has been effective for the treatment of small, primary, skin squamous and basal cell carcinomas[19,20] and CIN.[21]

We decided to investigate the efficacy of topical IFNα2b as a lone therapy for primary CIN based on the reported success of combination topical and intralesional lFNα2b for CIN,[21] one published case report of topical IFNα2b used on a recurrent CIN lesion,[22] and a similar case of ours (unpublished). We also considered its lack of toxicity in animal models.[23] Thirty-three percent of patients who had received intralesional IFNα2b for CIN had reported myalgias and flulike symptoms.[21] We avoided this mode of treatment in our series.

We postulated that the increased cost, stress, pain, and trauma associated with a surgical procedure could be avoided with topical IFNα2b treatment if the results obtained were comparable or better than those obtained with surgical excision. In a study of the effects of mitomycin-C on CIN, Frucht-Pery and Rozenman[13] reported three cases of CIN, one of which was included on clinical examination alone, without a pathology specimen, to confirm the diagnosis. Therefore, surgical biopsy can be avoided because of the pathognomonic clinical appearance of CIN lesions.[3]

METHODS

Seven patients with unilateral, presumed primary CIN (clinically diagnosed with slit-lamp biomicroscopic criteria) were included in this study. The diagnosis was made clinically by ophthalmologists who completed a corneal or external disease fellowship. We obtained informed consent from all patients for an experimental treatment protocol. Patients were consecutively included after diagnosis, and follow-up was performed at the Rand Eye Institute, the Harkness Eye Institute at Columbia University, or the SUNY Health Center at Brooklyn, between February and October 1999. Four ophthalmologists participated in the follow-up of the patients. Patients were prescribed topical IFNα2b drops (Schering Plough, Kenilworth, NJ, U.S.A.) 1 million units/mL four to six times daily. The entire content of a vial of 3×10^6 units of IFNα2b (Intron-A, Schering-Plough) consisting of 0.68 mL of predilutent was dissolved in 3.4 mL of balanced salt solution. The solution was viable for 30 days in a refrigerated state.

Patients were followed up biweekly after the initial diagnosis. Therapy was continued until there was complete clinical resolution (slit-lamp biomicroscopy) of the CIN lesions. Patients were to continue topical IFNα2b drops for 1 month after clinical resolution of the tumor. Patient charts were reviewed, and data were systematized using Microsoft Excel (Microsoft Corporation, Redmond, WA, U.S.A.).

RESULTS

We studied seven patients with presumed primary CIN (clinically diagnosed), who were treated with topical IFNα2b drops. The demographics of the population, days of treatment when total resolution was clinically confirmed, and total treatment time are shown in Table 1. There were six men (85.7%) and one woman (14.3%). All seven eyes had complete clinical resolution of the CIN lesions.

After resolution was clinically confirmed (mean follow-up, 14.4 ± 2.9 months) (Table 1), there were no recurrences. Five (71.4%) patients continued the topical IFNα2b for at least 1 month after clinical resolution. Two (28.6%) patients discontinued medication immediately after clinical resolution of CIN because of intolerance of their follicular conjunctivitis. Six patients have been followed up biweekly after the initial diagnosis, and one patient left the country 1 month after clinical resolution but has since been followed up in his country of origin. His ophthalmologist reported no recurrence up to the date this article was written. Side effects of treatment were limited to mild conjunctival hyperemia and follicular conjunctivitis in four (57.1%) of seven eyes. There was total resolution of conjunctival hyperemia and follicular changes within 1 month after cessation of the medication.

Patient 1

A 59-year-old French-Canadian man had a 2-month history of a red right eye with an accompanying white lesion. His medical history was unremarkable. He smoked a pack of cigarettes daily, and his skin was lightly pigmented. Uncorrected visual acuity was 20/25 in each eye. Biomicroscopy of the right eye showed a vascular, elevated gray, leukoplakic lesion, with an associated gray intraepithelial lesion with fimbriated margins. The corneal lesion measured 5.4 × 3.6 mm and extended from the 3-o'clock position to the 5:30 position. The remainder of the patient's examination was unremarkable (Fig. 1).

He began treatment with topical IFNα2b (10^6 units/mL) four times a day. After 29 days of treatment, the lesion had completely resolved and left an underlying pterygium. He completed a total of 96 days of treatment and has been followed up for 16 months without recurrence.

Patient 2

A 79-year-old man with a history of hypertension, increased cholesterol, and gout, controlled by medication, had no visual complaints. Examination showed a best-corrected visual acuity of

TABLE 1. *Statistical analysis of age, treatment time, resolution, and follow-up for patients with presumed CIN treated with topical IFNα2b*

	Age (yrs)	Resolution noted (after no. of days)	Total treatment (no. of days)	Follow-up (no. of mos)
Mean	74.1	77	106.3	14.4
Minimum	59	28	57	9
Maximum	80	188	188	18
Range	21	160	131	9
Median	75	54	101	15
Standard deviation	7.24	59.2	41	2.9

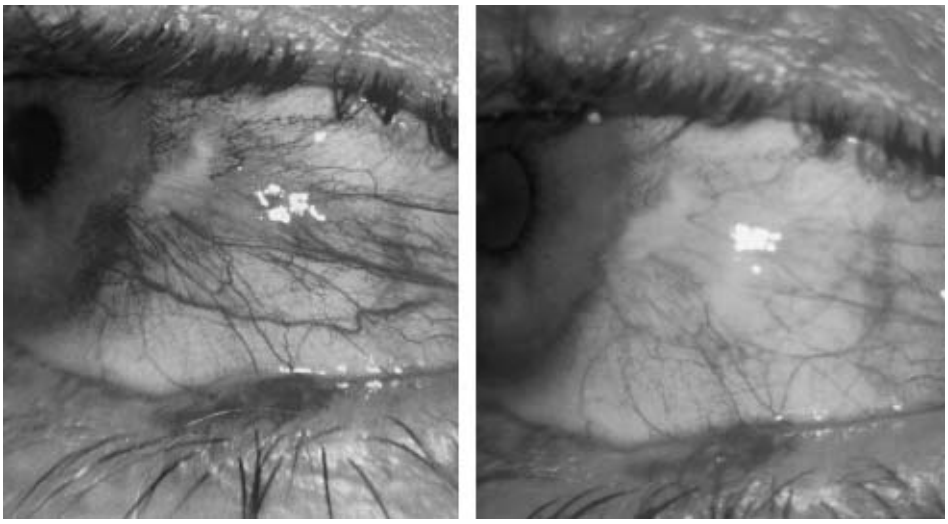

FIG. 1. Left, Pretreatment photograph of patient 1. Vascular, elevated gray, leukoplakic lesion with an associated gray intraepithelial lesion with fimbriated margins. The corneal lesion of the right eye measures 5.4 × 3.6 mm and extends from the 3-o'clock position to the 5:30 position. **Right,** After treatment.

20/30 in the right eye. Biomicroscopy showed a leukoplakic lesion whose conjunctival portion measured 7.4 × 4.0 mm; the corneal portion had two areas: 1.6 × 6.0 mm and 1.6 × 1.4 mm (Fig. 2).

The patient began topical interferon four times a day. There was no evidence of resolution of the lesion in the first 8 weeks, so the topical interferon was increased to six times a day. The lesion resolved during the next 4 months. The drops were stopped as soon as complete resolution of the lesion was noted (180 days of therapy) because of symptomatic inferior palpebral follicular conjunctivitis. One month after discontinuation of therapy, there was complete resolution of follicles. The patient has been followed up for an additional 12 months without recurrence.

Patient 3

An 80-year-old white woman had a 1-month history of a foreign body sensation in her right eye. Her medical history was significant for pulmonary sarcoidosis and hypercholesterolemia. Examination showed best-corrected visual acuity of 20/20 in the right eye and counting fingers at 4 feet in her left eye. Slit-lamp examination showed a 6.2 × 3.1 mm, vascularized, gray, gelatinous lesion with extension onto the corneal epithelium in her right eye (Fig. 3). There were nuclear sclerotic cataracts and macular pigmentary changes, worse in the left eye.

The patient began taking IFNα2b (10^6 units/mL) four times a day with improvement noted at the 2-week follow-up visit. The lesion had completely regressed by day 54 of treatment. Treatment was continued for a total of 101 days despite follicular conjunctivitis. After 13 months of follow-up, there has not been a recurrence.

Patient 4

A 74-year-old white man had redness and irritation of his eyes for several weeks. His medical history was significant for hypertension. On examination, uncorrected visual acuity was 20/25 in each eye. Lower lid laxity was noted bilaterally. In the left eye, a 3.6 × 2.5 mm gelatinous, gray, vascular lesion was found at the inferonasal limbus, extending onto the cornea.

Treatment with IFNα2b (10^6 units/mL) was started on his left eye four times a day. The lesion had regressed completely by day 28 of treatment. The patient then had follicular conjunctivitis. The interferon drops were discontinued after 57 days of treatment. No recurrences have been seen after 9 months of follow-up.

Patient 5

A 73-year-old lightly pigmented white man had a suspicious limbal lesion on his right eye. He had a history of squamous cell carcinoma on his back. Best-corrected visual acuity measured 20/40 in each eye. A small area of actinic change with a feeder vessel was noted at the 8-o'clock position of the limbus of his right

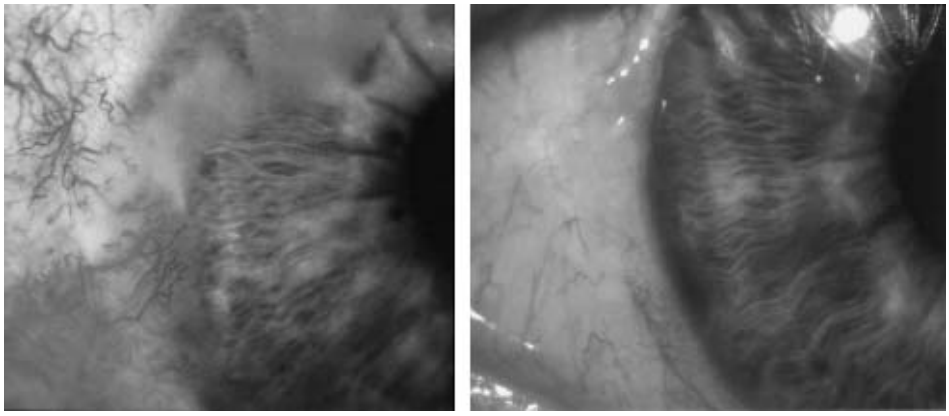

FIG. 2. Left, Pretreatment photograph of patient 2. Leukoplakic lesion with conjunctival involvement measuring 7.4 × 4.0 mm; the corneal portion has two areas: 1.6 × 6.0 mm and 1.6 × 1.4 mm. **Right,** After treatment.

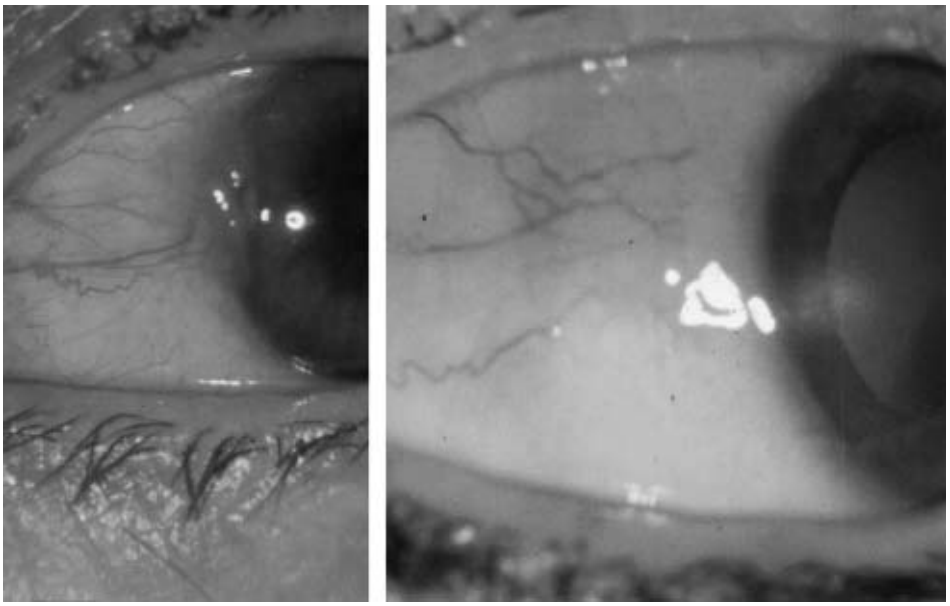

FIG. 3. Left, Pretreatment photograph of patient 3. Vascularized, gray, gelatinous lesion with extension onto the corneal epithelium in the right eye, measuring 6.2 × 3.1 mm. **Right,** After treatment.

eye. We elected to observe the lesion. Two months later, a larger (3.5 × 2.7 mm), elevated, white, placoid lesion with an accompanying feeder vessel and minimal gray extension onto the corneal surface was found (Fig. 4). The remainder of the patient's examination was remarkable for mild nuclear sclerosis.

Treatment began with topical IFNα2b (10^6 units/mL) four times a day. After 1 month, the lesion was no longer elevated, and the feeder vessel began to shrink in girth. Total resolution was noted by day 83 of treatment. Medication was stopped after 101 days of treatment. There have been no recurrences after 15 months of follow-up. The patient then reported that he was recently diagnosed with an osteosarcoma of his right femur. Radiation and surgery to place a steel rod was performed with the return of his ability to walk.

Patient 6

A 75-year-old white man with well-controlled hypertension had no visual complaints. Examination showed a visual acuity of 20/70 in the left eye. Biomicroscopy showed a leukoplakic lesion located at the left nasal limbus. The conjunctival portion measured 6.0 × 2.0 mm with a 1-mm extension onto the cornea (Fig. 5).

The patient began using topical IFNα2b (10^6 units/mL) drops four times a day. He had complete resolution of the lesion after 120 days of therapy. He developed symptomatic inferior palpebral follicular conjunctivitis; at that time, therapy was stopped. There was complete resolution of the follicular reaction 1 month after the cessation of topical interferon. The patient went on to undergo cataract extraction in that eye and had postoperative vision of

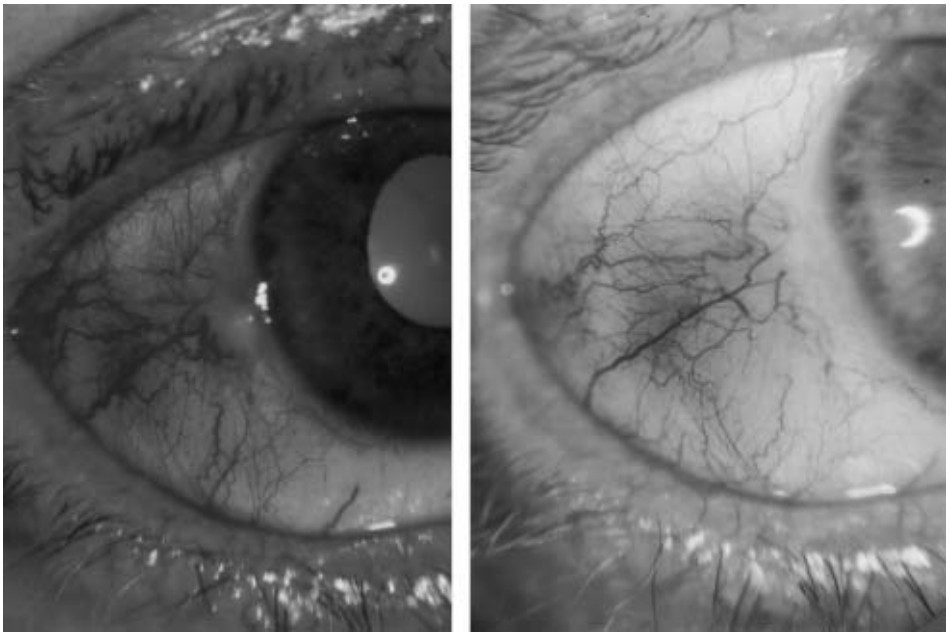

FIG. 4. Left, Pretreatment photograph of patient 5. An elevated, white, placoid lesion measuring 3.5 × 2.7 mm, with an accompanying feeder vessel and minimal gray extension onto the corneal surface. **Right,** After treatment.

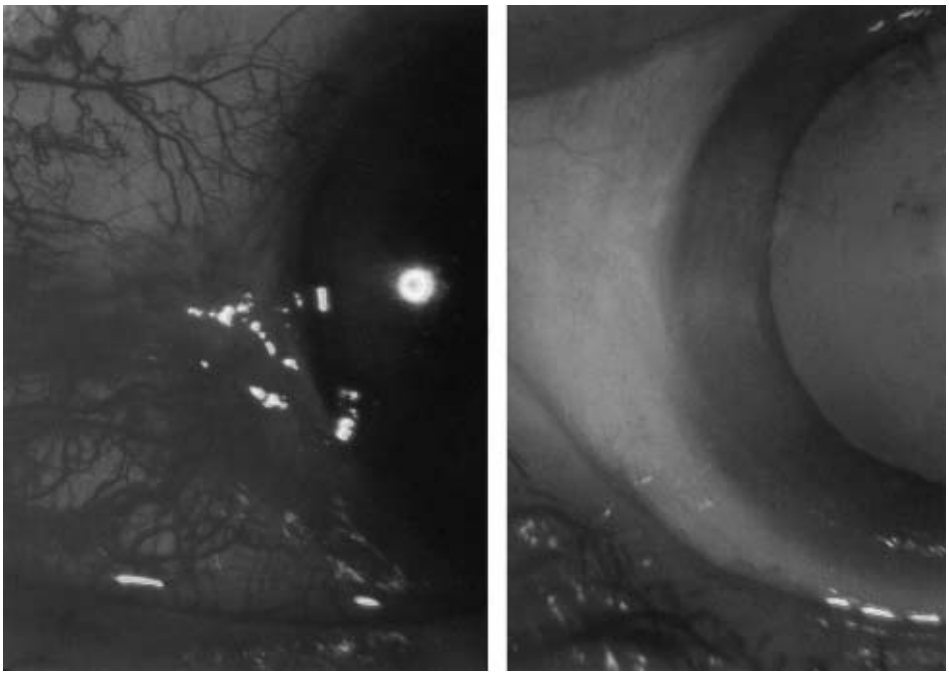

FIG. 5. Left, Pretreatment photograph of patient 6. Leukoplakic lesion located at the left nasal limbus. The conjunctival portion measures 6.0 × 2.0 mm, with a 1-mm extension onto the cornea. **Right,** After treatment.

20/20. The patient has been followed up for 12 months after cessation of therapy without recurrence.

Patient 7

An 80-year-old man had a lower lid lesion identified as squamous cell carcinoma. The lesion was excised with a subsequent skin graft involving the left lower lid and nose. The patient complained of redness and irritation of the left eye with worse vision than the right eye. Additional history included medically treated hypertension. Examination showed a visual acuity of 20/70 in the left eye. Biomicroscopy showed an elevated leukoplakic lesion with an anterior gray extension onto the cornea with fingerlike extensions over the visual axis, extending 5.0 mm from the limbus. Approximately 50% of the corneal surface was involved.

The patient began using topical interferon six times daily. Within 1 week there was significant regression of the corneal lesion. Its largest dimension now extended only 2.5 mm onto the cornea. Within 2 weeks, vision improved to 20/30 in the left eye with only wispy remnants of the original lesion. Within 5 weeks, there was no evidence of the lesion, and visual acuity was 20/20. The patient continued using topical interferon for 1 month after resolution. The patient has been followed up in his native country, Pakistan, and his ophthalmologist reported no recurrence during the next 12 months.

DISCUSSION

In this study, diagnosis of primary CIN was made clinically by fellowship-trained corneal specialists. All CIN lesions were elevated, involved the limbus, were gray and gelatinous, and had characteristic tufts of blood vessels as described by Sanders and Bedotto.[4] All our patients had corneal involvement consisting of a gray intraepithelial plaque. Considering the pathognomonic clinical appearance of CIN, surgical excision without previous confirmation of diagnosis has been considered appropriate for suspicious lesions.[3,13] Therefore, a biopsy is not absolutely necessary for diagnosis. Biopsy of these lesions would defeat one of our main objectives because we attempted to avoid any surgical procedure. Biopsy may be indicated when clinical features are not pathognomonic or a corneal specialist is not involved in the patient's care. Impression cytology may also be helpful as a diagnostic tool.

The increased cost, stress, pain, and trauma associated with a surgical procedure were avoided by using topical IFNα2b alone. We used topical IFNα2b drops (Intron, Schering Plough), 3×10^6 IU per container, diluted to 3 mL (1×10^6 IU/mL). The medication is stable for 30 days after reconstitution. The cost is approximately $65 for this 30-day supply, but may vary according to region.

Punctal plugs were not necessary in this case series. Topical IFNα2b has shown no discernible conjunctival or corneal abnormalities on histopathologic or ultrastructural evaluation in rabbits.[23] None of our patients had corneal or conjunctival changes requiring punctal occlusion.

Excellent results were achieved with topical IFNα2b without any adjunct treatment, leading to a clinical resolution in 100% of cases. The traditional treatment of CIN has consisted of excision of the tumor with application of cryotherapy to the surgical bed. Pathologic examination of the excised margins has been important because many lesions are incompletely excised because of diffuse lateral growth. CIN can spread along the basal conjunctival layers far beyond the clinical lesion.[3] In a study of 120 patients undergoing excision with or without possible adjunct radiation, there was a 53% recurrence rate when margins were involved (containing tumor) and 5% when pathology studies confirmed clear margins.[3] Other recurrence rates have varied between 7% and 69% depending on involvement of excised margins, primary treatment, and follow-up time.[2,10,11,24]

Mitomycin-C has been used effectively to treat CIN.[13,14] One hundred percent[13] and 85%[14] success rates were reported in treating recurrent lesions, but serious complications, such as corneal-

scleral melting and depletion of limbal stem cells, is possible. Treatment with mitomycin is contraindicated in patients with Sjögren syndrome, rosacea, and atopy[14] possibly limiting its availability of use.

Topical treatment is advantageous because the entire ocular surface comes into contact with the therapeutic agent. In a study of recurrent CIN, intralesional IFNα2b was used with topical IFNα2b[21] to ensure tumor contact with the agent and to speed the rate of resolution. Results were excellent, but 33% of patients had side effects of myalgia and overnight fevers, typically associated with systemic absorption of interferon.

In this study, none of the patients experienced any systemic side effects. The only side effects in our study were localized conjunctival injection and follicular conjunctivitis in four (57.1%) of seven eyes. These episodes resolved with discontinuation of the drops. Because topical IFNα2b was shown to have no corneal or conjunctival epithelial toxicity,[23] we surmise that the folliculosis was induced by the vehicle, which contains 0.9% benzyl alcohol, glycine, and human albumin. In the future, different delivery formulations may be found to elicit less of an allergic response. The results obtained thus far are comparable to or better than those obtained with surgical excision or cryotherapy. However, the characteristic slow growth of recurrent lesions with the potential for malignant change (5% of CIN) suggests that long-term follow-up is necessary.[2,6] In one series, two recurrences occurred 10 years after surgical excision.[24] We consider that our mean follow-up of 14.4 ± 2.9 months (range, 9–18 months) cannot be considered sufficient to evaluate the rate of recurrence.

In addition to CIN, we have successfully used IFNα2b intralesionally to treat two patients with conjunctival lymphoma.[25]

CONCLUSION

Topical IFNα2b alone may be an effective treatment of primary CIN. It appears to be a safe alternative to radiation, intralesional IFNα2b injection, and surgical excision with cryotherapy. Further studies on larger population groups are recommended, with longer follow-up, to better assess the risk of recurrence and other possible adverse effects.

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