Topical Interferon alfa-2b for the treatment of Conjunctival and Corneal Intraepithelial Neoplasia (CIN)

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Abstract:
Conjunctival and corneal intraepithelial neoplasias (CIN) are the most common conjunctival malignancies. Surgical excision with cryotherapy is the gold standard in treatment of CIN. Recent studies show success using topical and injectable Interferon alfa2b.

I. Case History
- Patient demographics:
  - 56 year old white male

- Chief complaint:
  - lesion of right lower lid c associated irritation and tearing for 2 weeks. Told by last optometrist a week ago that he had “cancer in his eye”

- Ocular, medical history: Pt previously seen/followed with other VA for regular exams, history available to us:
  Ocular:
  - history of anterior uveitis OU 5/19/2011
  - history of foreign body removal OS 3/21/11
  - seen at VA on 6/5/11 where diagnosed with chalazion OD
  - possible CIN OS
  Medical:
  - Colonic polyps
  - Vitamin B12 deficiency
  - Hypercholesterolemia
  - Nicotine dependence
  - Tinea Unguium
  - Seizures
  - Alcohol dependence

- Medications
  Ocular:
  - Interferon Alfa-2b 1Mu/mL in refresh
  - Oral antibiotics 1 pill PO bid
  Systemic:
  - no known meds
II. Pertinent findings

- Clinical:
  - large elevated lesion inferior nasal palpebral conjunctiva OD
  - meibomian gland stasis, telangiactatic vessels and thickened lid margins OU
  - nasal pinguecula OD
  - nasal gelatinous lesion with fern like appearance of feeder vessels extending towards caruncle, minimal corneal involvement ~0.5mm, no anterior chamber findings

- Physical:
  - visible exposure to the sun; tanned skin

- Laboratory studies
  - Vitamin A tested, sample not viable because exposed to light

- Radiology studies
  - none

- Others
  - Confocal OCT: confocal imaging suspicious for CIN
  - photos taken for documentation

III. Differential diagnosis

- Primary/leading
  - conjunctival papilloma
  - pinguecula/ pingueculitis
  - keratinized pinguecula
  - conjunctival intraepithelial neoplasia (CIN)

- Others
  - conjunctival papilloma
  - conjunctival dermoid
  - conjunctival retention cyst
  - phlyctenulosis
  - pannus
  - malignant melanoma
  - pseudoepitheliomatous hyperplasia

IV. Diagnosis and discussion

Using confocal OCT analysis this patient was diagnosed with conjunctival intraepithelial neoplasia nasally in the left eye and a keratinized nasal pinguecula of the right eye. Conjunctival and corneal intraepithelial neoplasias (CIN) are the most common conjunctival malignancies in the United States, seen primarily in older individuals. Risk factors include, but are not limited to; UV light exposure, human immunodeficiency virus, human papilloma virus, and on rare occasions asthma in younger individuals. Men are at a higher risk as well as those with lightly pigmented irides. Smokers are also at a greater risk. These lesions are slow progressing with low malignancy potential.

Differentiation between CIN and benign conjunctival/limbal lesions such as pterygium and pinguecula may be based on characteristic clinical features. These include tufts of vessels feeding a gelatinous papillary lesion, vascularized conjunctival
leukoplakic lesions, or a vascularized opaque membranous tissue extending on to the corneal surface. They are typically unilateral and can evolve, though rarely, into invasive squamous cell carcinomas if not treated sufficiently. It can become metastatic or invade the eye, but this is rare.

Prior to the possibility of topical treatment, surgical excision would often be performed for suspicious lesions in the absence of a biopsy confirmed diagnosis. Therefore, biopsy is not required, though beneficial, for absolute diagnosis. With the less invasive option of topical treatment, initiation of treatment prior to or even without biopsy may become more frequent and accepted.

CIN has the ability to spread along the basal conjunctival layers beyond the lesion site. Previous treatment with excision and cryotherapy would call for pathological examination of the margins to guarantee complete removal of the lesion. CIN’s ability to spread beyond the lesion site makes this treatment a higher risk for recurrence due to satellite lesions remaining outside the excised area. Recurrence rates with excision and cryotherapy have varied from 7% and 69%. The use of a topical treatment like Interferon alfa2b would allow for full coverage of all affected areas, potentially leading to minimal recurrences.

V. Treatment, management

Previously, surgical excision combined with cryotherapy was seen as the gold standard in treatment of this conjunctival neoplasia. Unless cryotherapy is adjunctively done with excision and clean margins, residual tumor potentially remain leading to a 50% or more recurrence rate of neoplasia. However, extensive and repeated surgical excision puts the patient at risk for limbal stem cell deficiency and other ocular surface complications. For patients that have previously had a filtering bleb for glaucoma treatment or those who may need filtering surgery in the future, having surgical excision with adjunct cryotherapy may ruin bleb functionality or the ability for future bleb placement. For these reasons other adjunctive therapies have been explored in addition to surgical removal. These therapies include vitamin A therapy, radiation, mitomycin-C, phototherapeutic keratectomy with excimer laser and f-fluorouracil. Recent studies and clinical cases have begun to show success in the minimally invasive treatment with Interferon alfa2b in both ophthalmic solution and injections. We have explored the use of ophthalmic solution for treatment.

Interferons are glycoproteins that have antiviral and antiproliferative effects, and because CIN may have some viral etiology, interferon alfa-2b (INF alfa2b) intralesion injections or topical treatments are considered to be potentially effective in the elimination and remission of this neoplasia. Injection of this glycoprotein causes a systemic susceptibility and possible adverse reactions like fever, myalgias, or “flu-like” symptoms in 33% of patients. There have also been some reported cases of retinopathy or neuropathy from injection. Therefore, the non-invasive topical use of INF alfa2b has become a potential safe and effective treatment of CIN. INF alfa2b used topically has shown no corneal toxicity and very rare follicular reaction with hyperemia, both of which ended with cessation of treatment. However, the benefits of treatment, currently, far outweigh the risks/adverse events reported.
Previous case reports have shown that with INF alfa2b topical treatment visible changes occurred within a month of starting drop regimen. However, the larger the lesion the more prolonged treatment regimen is needed for resolution. Corneal lesions are the first to respond to treatment with conjunctival lesions taking longer, sometimes with pinguecula-like sequelae. Initial treatment is one drop four times a day with a one-month follow-up. If improvement is noted there has been documentation of tapering to three times a day for a month, twice a day for a month, and once a day for remaining month. Other case reports have shown that treating four times a day until complete resolution with no taper results in a completely receded lesion.

Our patient was started on INF alfa2b drops (1 million units/mL) four times a day in the left eye only. He was seen for a three-week follow-up. The lesion was slightly less gelatinous than previously noted allowing slight visibility to underlying scleral vasculature. Previous studies have shown that mean-time to resolution is 4 to 22 weeks with a mean-time of 12 weeks.

VI. Conclusion
Topical IFN alfa2b, alone, is a potentially effective alternative therapy for the treatment of CIN. The use of a topical agent versus excision with combined cryotherapy will reduce cost, pain, risk for complications and recurrence for the patient. There is further research to be done on the dosage and prolonged maintenance and follow-up with this treatment.

VII. Bibliography


