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Conjunctival Intraepithelial Neoplasia: A Case Report

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Conjunctival Intraepithelial Neoplasia: A Case Report

Abstract

Background: Gelatinous, vascularized lesions of the conjunctiva are a subset of ocular surface tumors that are derived from various cell types. The more worrisome origins include diagnoses of conjunctival intraepithelial neoplasia (CIN) and squamous cell carcinoma (SCC). Topical treatments such as mitomycin-C, 5-fluorouracil, and interferon alfa-2b are now used as single therapy or in conjunction with surgical excision.

Case Report: This case features a 78-year-old Caucasian male with CIN treated with surgical removal and topical interferon alfa-2b. In addition to discussing the details of this case, this report highlights important caveats of the treatment and management of the condition as well as a review of ocular surface squamous neoplasia.

Conclusion: Clinical observation of a conjunctival lesion can assist with determining severity and includes documentation of the size, shape, and consistency of the lesion, presence of a feeder vessel (indicating a more advanced ocular surface lesion), and anatomical location. The clinician can determine if the lesion is wholly within the conjunctiva or fixed to the globe by simple physical manipulation of it.Gonioscopy can provide the clinician with information regarding intraocular angle and posterior cornea involvement. Additional testing such as B-scan, anterior segment OCT, and MRI can provide additional information about the invasiveness of such lesions. Depending on the surgeon's preference, excision and cryotherapy, topical monotherapy, or a combination treatment may be used in these cases. Prognosis is favorable in most cases if treated early and there is limited recurrence.

Keywords

ocular surface squamous neoplasia, conjunctival intraepithelial neoplasia, squamous cell carcinoma, interferon, excision, anterior segment imaging

INTRODUCTION

Conjunctival lesions are classified as congenital or acquired groups.[1] All conjunctival lesions combined tend to affect men and women equally.[2] However, there is a preponderance of conjunctival squamous cell carcinoma (SCC), papilloma, conjunctival nevus, and pingueculae or pterygium types that affect males.[2,3] Conjunctival lesions predominantly present in Caucasian populations.[2] Ocular surface squamous neoplasia (OSSN) includes a spectrum of lesions originating from corneal and conjunctival epithelium, including epithelial dysplasia, intraepithelial neoplasia, and SCC.[1,3-5] Risk factors include: ultraviolet light exposure, older age, light skin pigmentation, tobacco smoker, occupational petroleum exposure, human papilloma virus (HPV) infection, human immunodeficiency virus (HIV) seropositivity, xeroderma pigmentosa, and vitamin A deficiency.[1,3,4,6,7] The gold standard treatment of OSSN lesions involves surgical excision using a no-touch method demonstrated by Shields.[8,9] While the traditional treatment plan for OSSN lesions involves excision, removal, and biopsy, topical treatments in conjunction with the no-touch excision or as single therapy have emerged.

CASE REPORT

INITIAL PRESENTATION

A 78-year-old Caucasian male presented for his first visit to the Department of Veterans Affairs (VA) eye clinic for an opinion regarding the possibility of a recurring tumor on his left eye. The patient noted a lesion that was gradually growing over the past three months on his left conjunctiva. He denied any changes in vision, headaches, dizziness, diplopia, or eye pain. The patient revealed an ocular history of excision and cryotherapy for a conjunctival lesion in the same area on July 2, 2013. No biopsy results were available. The patient had last followed up with his oculoplastic specialist on July 17, 2014 but was lost to follow-up for that condition following a cross-country move.

This patient had a complicated ocular history for which he was managed outside of the VA system. He brought hard-copy documentation of his previous examination and medical records. Ocular history revealed severe stage primary open-angle glaucoma OS>OD status-post trabeculectomy OS, cataract extraction OU, and non-exudative age-related macular degeneration OU. His ocular medications included Combigan® (brimonidine tartrate/timolol maleate 0.2%/0.5%) every morning OD, latanoprost 0.005% at bedtime OD, and dorzolamide twice daily OD (While the management of these ocular conditions is

pertinent to the individual, it has less relevance to this case report, and therefore, will not be discussed in-depth.). The patient's family history was positive for glaucoma; he stated his mother and brother were both diagnosed with the condition.

His medical history was positive for hyperlipidemia, impaired fasting glucose, gastroesophageal reflux disease, hypertension, neoplasm of prostate, and chronic kidney disease. His current systemic medication included hydrochlorothiazide 25 mg/triamterene 37.5 mg, terazosin HCL 2 mg, simvastatin 20 mg, lisinopril 40 mg, and potassium chloride 10 meq. He was oriented to person, place, and time.

The patient's best corrected visual acuities were 20/20 OD and 20/50+ OS with a spectacle prescription of -0.75 -2.00 x 093 OD and -0.75 -1.25 x 102 OS. There was no improvement with pinhole OS. This visual acuity was stable from his previous examinations. Motilities were full and smooth in all gazes OU. No pain or diplopia on eye movement was noted. Cover test demonstrated orthophoria at distance and four prism diopters of exophoria at near. Confrontation visual fields revealed inferior constriction OD and OS. Pupils were equal, round, and reactive to light with a 1+ relative afferent pupillary defect (RAPD) OS. Amsler grid testing revealed no metamorphopsia nor scotoma OD; however, metamorphopsia inferiorly OS was reported.

Anterior segment evaluation of the OD revealed normal lid appearance, clear and intact cornea, clear and quiet conjunctiva, deep and quiet anterior chamber, and mild iris atrophy superiorly. Anterior segment evaluation of the OS revealed normal lid appearance, corneal pannus inferiorly, a vascularized conjunctival lesion superior-nasally with overlap onto the cornea extending 3 mm (total lesion size measured at 6.7 x 7.5 mm, Figure 1), a shallow, avascular bleb superior-temporally, deep and quiet anterior chamber, and flat iris. Physical manipulation of the conjunctival lesion showed movement without fixation to the globe. No obvious feeder vessel was observed. Intraocular pressures were measured at 9:45AM using Goldmann applanation tonometry at 19 mm Hg OD and 19 mm Hg OS; with massage of OS, the pressure was decreased to 12 mmHg, which may suggest the bleb may be under-filtering. Gonioscopy showed visible ciliary body in all quadrants OU with 1+ pigmentation inferiorly OU; there was no observation of intraocular invasion by the conjunctival lesion OS. Posterior chamber intraocular lenses were clear and centered OU. Central corneal thickness was measured as 563 microns OD and 575 microns OS. The patient was dilated using one drop of 1% tropicamide OU.

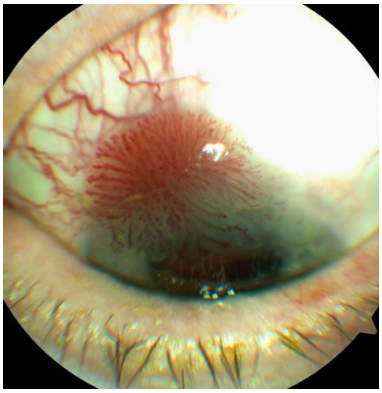

FIGURE 1: Anterior segment image OS. The image displays the vascularized conjunctival lesion superior-nasally with extension onto the superior cornea.

The differential diagnoses to consider for the conjunctival lesion in this case include:

- Conjunctival intraepithelial neoplasia (CIN) – This will generally manifest as a white, gelatinous, usually stalk-like lesion near the limbus with vascularization.
- Squamous papilloma – This will generally have a sessile, red, gelatinous appearance in adults, and is commonly associated with human papilloma virus 16 and 18.
- Squamous cell carcinoma (SCC) – This will generally manifest as a red, gelatinous mass, typically in the interpalpebral region with possible extension onto the cornea with a feeder vessel present.

A thorough evaluation was performed to establish a baseline as this was the patient's first visit. Posterior segment evaluation demonstrated vitreous syneresis with complete posterior vitreous detachment OU. The optic discs displayed generalized minimal rim tissue OU. A cup-to-disc ratio of 0.80 round was documented with minimal rim tissue inferiorly, and a Drance hemorrhage was observed inferior-temporally OD. The optic nerve OS displayed a cup-to-disc ratio of 0.90 without visible rim tissue inferiorly and minimal rim tissue superiorly; optic nerve head pallor was observed OS. A significant mix of hard and soft drusenoid changes without the presence of a choroid neovascular membrane (CNVM) was visible in the macula OU. Retinal blood vessels demonstrated a normal ratio of 2/3 OU, and the peripheral retina was intact with no holes, tears, or detachments 360° noted OU. Fundus photographs (Figures 2 & 3) and optical coherence tomography (OCT, Figures 4 & 5) were ordered and performed the same day.

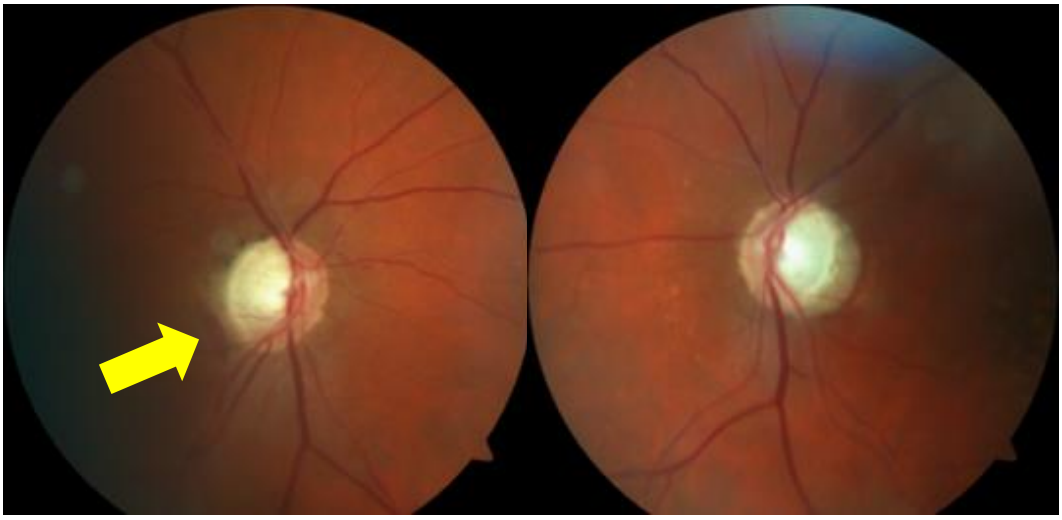

FIGURE 2: a side-by-side optic nerve head (ONH) image of OD and OS. The images display the minimal rim tissue of each optic nerve as well as the Drance hemorrhage inferior-temporally to the ONH OD (yellow arrow).

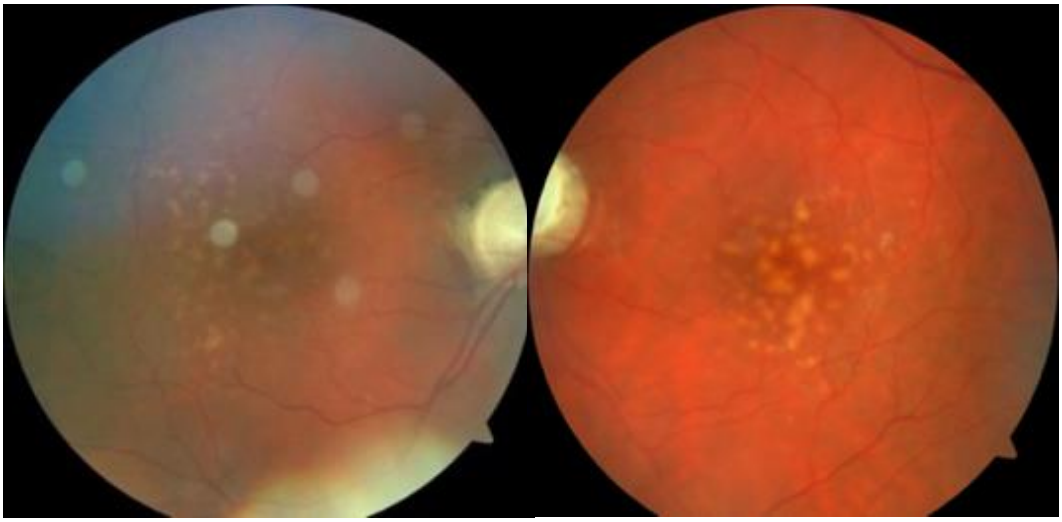

FIGURE 3: a side-by-side macula image of OD and OS. The images display Age Related Eye Disease Study (AREDS) category 3 non-exudative macular degeneration changes. No CNVM was observed in either eye.

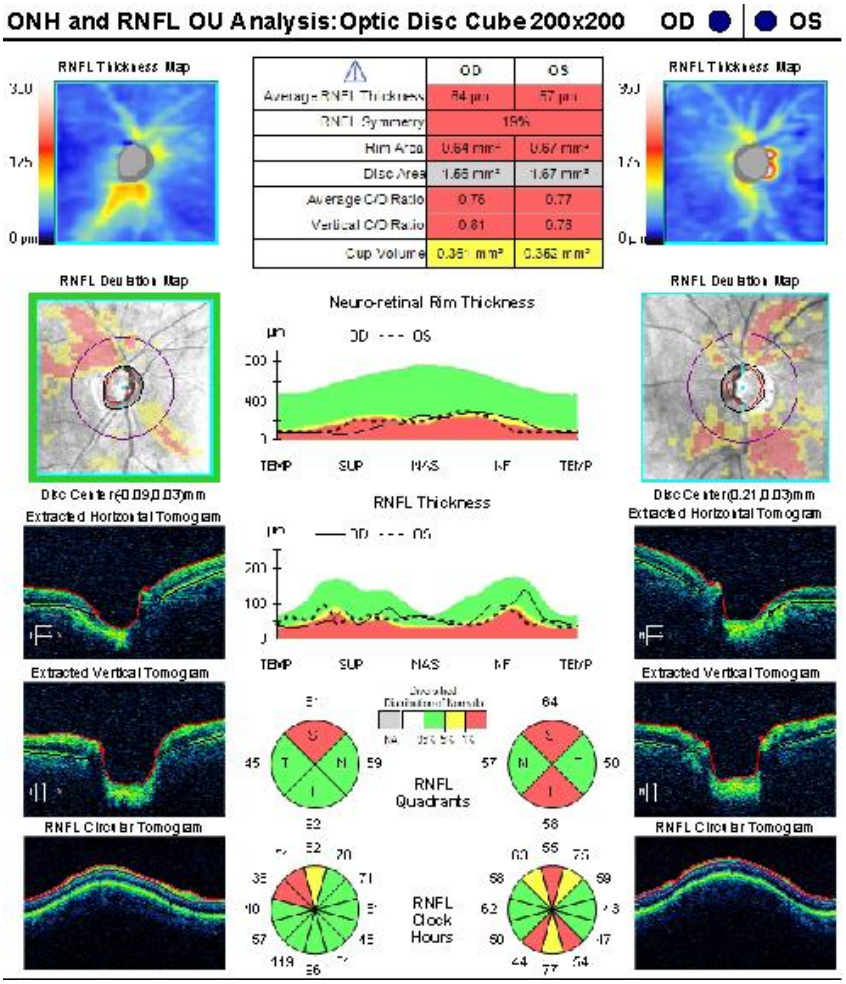

FIGURE 4: an ONH and retinal nerve fiber layer (RNFL) analysis of OD and OS. The average RNFL thickness is 64 microns OD and 57 microns OS. The vertical cup-to-disc ratio is measured at 0.81 OD and 0.78 OS. Superior thinning can be observed OD with superior and inferior thinning observed OS.

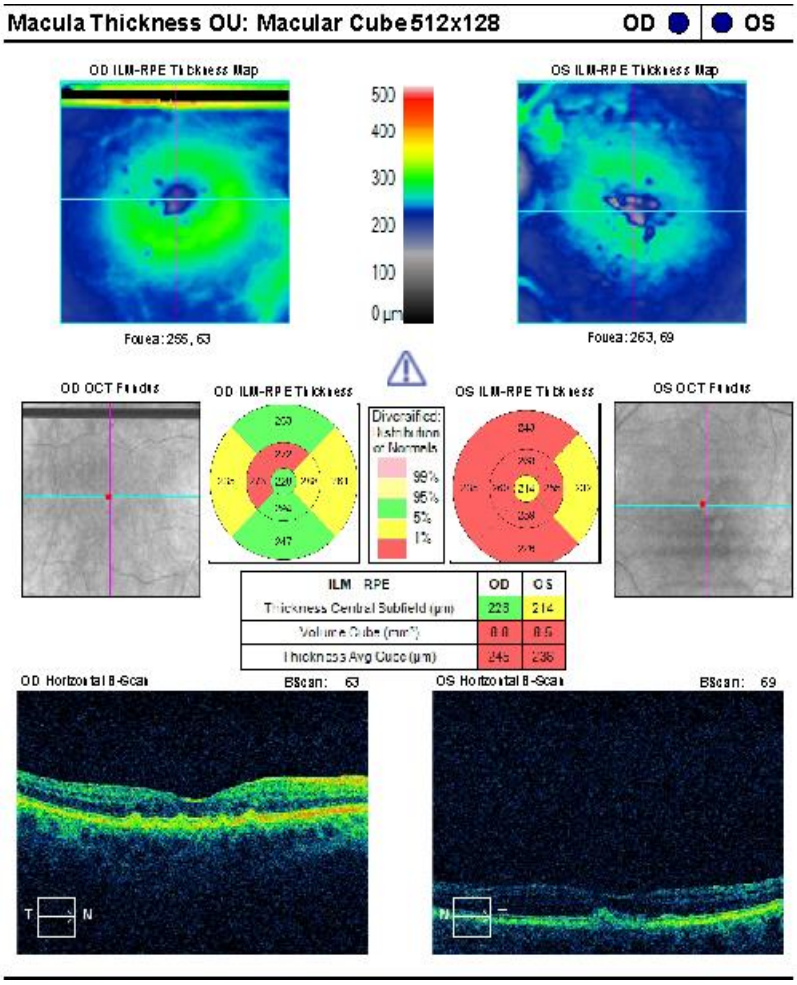

FIGURE 5: a macula thickness image OD and OS. The central thickness is measured at 228 microns OD and 214 microns OS. Drusenoid changes are apparent OU.

Given our patient's history and findings, he was diagnosed with a conjunctival neoplasm with high suspicion for conjunctival intraepithelial neoplasia OS. The patient was extensively counseled regarding the findings and the need for an ocular oncology referral. A consultation was placed with the nearby VA Medical Center. Additionally, the patient was diagnosed with severe stage primary open-angle glaucoma OU. This assessment was reached based on the hard-copy Humphrey visual field (HVF) records the patient brought with him the day of the examination. A goal IOP of 14 mm Hg OU was previously established by the outside provider. As this patient was not at goal, the patient was given a drop regimen sheet and his medications were updated to the VA formulary drops: latanoprost qhs OU, dorzolamide/timolol bid OD, and brimonidine tid OD. The patient was also

diagnosed with AREDS category 3 non-exudative age-related macular degeneration (ARMD) OU. AREDS recommendations were reviewed, and he was given an Amsler grid and started on AREDS 2 supplementation. The patient chose to continue his care with his outside eye care provider for glaucoma and ARMD management.

VA Medical Center Appointment

The patient's conjunctival lesion was evaluated at the VA Medical Center following his initial presentation. He was referred to the Kellogg Eye Center Department of Ocular Oncology for excision and biopsy of the conjunctival lesion with a presumed diagnosis of conjunctival intraepithelial neoplasia.

Kellogg Eye Center Appointment

The patient presented to the Kellogg Eye Center for treatment by the ocular oncologist. Absolute alcohol was applied to the corneal epithelium 2 mm anterior to the lesion with a weck-cell soaked in alcohol. Excision biopsy of the corneal lesion with lamellar keratoplasty of left eye was performed. The lesion was dissected from the cornea with a no-touch technique. Single freeze-thaw cryotherapy of the cornea of the left eye at the limbus was performed. Excision of the left inferior and superior limbal conjunctiva with underlying sclera was performed. Double thaw cryotherapy of the left inferior limbal conjunctiva was performed. Following the procedures, the patient was given a prescription for topical interferon alfa-2b 1 million units/Ml four times daily in the left eye with bottle replacement every 14 days.

A non-formulary request for the topical interferon alfa-2b 1 million units/Ml was required prior to the medication release. Upon the request's approval, the medication was compounded at a specialty pharmacy and given to the patient to be used four times daily OS. The patient was followed regularly after completion of the excision. Biopsy results confirmed the diagnosis of conjunctival squamous cell carcinoma in-situ (CIN Grade III/III).

Eye Clinic Visit #2

The patient presented to the VA eye clinic for a second visit for an anterior segment check following the recent appointment with the Kellogg Eye Center. The patient was status-post excision and cryotherapy. The patient, under the care of Kellogg Eye Center, also had received four sub-Tenon's interferon injections between October 2015 and January 2016. Post-operative reports showed a decrease

in vision OS to 20/70-2 without improvement on pinhole. He had two more appointments scheduled for May and June 2016.

Corrected visual acuities at this visit were 20/20- OD and 20/200-2 OS with habitual correction. There was no improvement with pinhole OS. External evaluation had not changed.

Anterior segment evaluation of the OD was the same as his last visit, while the OS showed dense superficial punctate staining from medicamentosa which covered the entire cornea. The vascularized, gelatinous lesion was entirely excised and showed no signs of recurrence. Intraocular pressures measured at 11:08AM using Goldmann applanation tonometry were 13 mm Hg OD and 12 mm Hg OS, which were achieving the goal IOP of 14 mm Hg OD/OS. The reduction in IOP was attributed to the medication changes that had occurred at the initial examination and improved patient compliance.

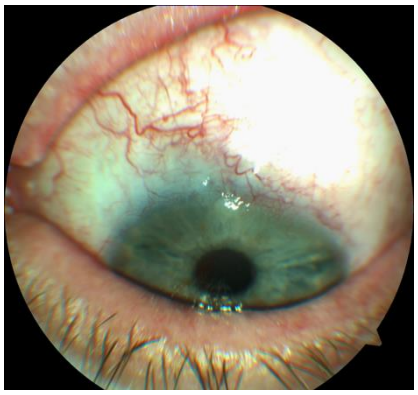

Figure 6: an anterior segment image OS. The image displays the resolution of the CIN III/III lesion following excision and cryotherapy

The patient was instructed to continue the current course of action with his topical interferon alfa-2b qid OS, discarding the bottle every 14 days. The patient was educated on keratitis and the high risk for limbal stem cell deficiency given his surgical history. The patient was educated that surgical procedures (with and without cryotherapy) can cause ocular surface toxicity, cicatricial conjunctival changes, and limbal stem cell deficiency. The keratitis was the cause of his reduced visual acuity and was related to the interferon alfa-2b use, and he was given a prescription for preservative-free artificial tears to be used qid OS. Strict instruction was given to separate drops by 10 minutes to avoid any diluting effects. The patient declined dilation, and an undilated viewing showed stable findings. A follow-up appointment was scheduled for one week for an anterior segment check OS.

EYE CLINIC VISIT #3

The patient presented to the VA eye clinic for an anterior segment check. Corrected visual acuity was 20/20- OD and 20/70-2 OS with habitual correction. There was no improvement with pinhole OS. External evaluation had not changed.

Anterior segment evaluation of OD and OS were the same as the previous visit. Intraocular pressures were measured using Goldmann applanation tonometry at 12 mm Hg OD and 11 mm Hg OS, which were under his goal IOP (14 mm Hg OD/OS). The patient declined dilation, but the undilated viewing showed stable findings.

The patient was instructed to continue the current course of action with his topical interferon alfa-2b qid OS, discarding the bottle every 14 days. The patient was instructed to use the preservative-free artificial tears as needed OS, paying special attention to separating drops OS by at least 10 minutes to avoid dilution. The patient was instructed to continue care with his ocular oncologist as scheduled, and he was scheduled for a six month return to the VA eye clinic for an anterior segment check.

DISCUSSION

The bulbar conjunctiva is a common location of conjunctival tumors and lesions. The surface consists of non-keratinized stratified squamous epithelial tissue atop the basement membrane with loose lamina propria below, which helps keep the conjunctiva attached to the episclera-sclera complex.[1,4]

Conjunctival tumors and lesions are often separated into two large groups: congenital and acquired. Shields et al. reported that congenital conjunctival tumors in the United States account for 2% of the total biopsied conjunctival lesions.[2] Acquired conjunctival tumors and lesions are further subcategorized into different types based on their origin.[1] Ocular surface tumors are derived from epithelial, melanocytic, and lymphocytic cells, and surface epithelial, melanocytic, and lymphoid tumors are the three most common categories of acquired conjunctival tumors.[1-2] Shields et al. reported that 11% of patients presented with premalignant and malignant epithelial conjunctival lesions, 53% presented with a melanocytic conjunctival lesion, and 8% presented with a lymphoid conjunctival lesion.[2] Interestingly, 13% of patients in the study were diagnosed with a non-neoplastic conjunctival lesion, where 22% of those patients had a final diagnosis of pingueculum, and 13% had a final diagnosis of pterygium.[2]

As a whole, conjunctival lesions affect men and women about equally; however, certain types will predominantly affect males.[2] Conjunctival squamous cell carcinoma, papilloma, conjunctival nevus, and pingueculae or pterygium tend to affect males at a much higher rate.[2,3] Conjunctival lesions typically appear unilaterally; however, lymphoid tumors are unique in that they appear bilaterally 37% of the time.[2,3] Conjunctival lesions predominantly present in Caucasian populations.[2] Shields et al. reported 89% of the conjunctival lesion patients in their study were Caucasian.[2] The bulbar conjunctiva is ultimately the most common area of conjunctival lesion development.[2] Seventy-five percent of all conjunctival tumors originate at the bulbar conjunctiva, and the nasal and temporal aspects of the bulbar conjunctival were the most affected with a frequency of 31% and 33% respectively.[2] Conjunctival epithelial tumors frequently present at the limbal or extralimbal regions, 65% and 28% of the time respectively.[2] Melanocytic tumors appear on the bulbar conjunctiva in 79% of the case. Lymphoid tumors appear in the fornix or on the bulbar conjunctiva, 37% and 33% of the time respectively.[2]

Ocular surface squamous neoplasia is a catch-all term that includes lesions originating from corneal and conjunctival epithelium, including squamous papilloma, conjunctival intraepithelial neoplasia, and SCC.[1,3-5] OSSN has an incidence of 0.02-3.5 per 100,000.[1] A study within the Department of Veterans Affairs from March 1, 2007 to March 1, 2012 found 28 confirmed cases of OSSN out of 24,179 patients in a Miami area/South Florida Veterans Affairs Hospital population.[10] The prevalence was measured at 0.1%, and the risk factors determined for this population were similar to those previously listed.[10] If a pterygium was present, the patient had a 16-fold risk increase of OSSN development.[10] There is a greater frequency of OSSN in individuals who reside closer to the equator because of increased ultraviolet (UV) light exposure.[1,6] Interestingly, according to Gichuhi et al., 16° south is the latitude with the highest incidence.[4] Other risk factors include: older age, light skin pigmentation, tobacco smoker, occupational petroleum exposure, human papilloma virus (HPV) infection, human immunodeficiency virus (HIV) seropositivity, xeroderma pigmentosa, and vitamin A deficiency.[1,3,4,6,7] HIV testing should be considered in younger patients with OSSN presentations, especially those with a feeder vessel observed.[5] Interestingly, the ATP-binding cassette subfamily B member 5 (ABCB5) gene is upregulated in cases of OSSN and could possibly be involved in the development of the condition.[11] The ABCB5 gene was observed in several cancer cells, though its purpose is not well understood at this time.[11]

Squamous papillomas appear as benign sessile or pedunculated lesions that tend to appear near the limbus and have the potential to spread to the cornea.[1] Sessile papillomas tend to appear in adults and are commonly associated with HPV 16 and

18. Typically, these lesions will appear on the bulbar conjunctiva and will have a broad base from which a fibrovascular frond spreads.[1,12] Recurrence of this type of lesions is possible. Pedunculated lesions tend to appear in children and are associated with HPV 6 and 11. They generally appear in the inferior fornix and have a narrow base and many fronds. Recurrence of pedunculated lesions is much higher than sessile lesions, which are commonly found in adults. The reported recurrence rate of squamous papilloma in general is 6-27%.[1]

Interestingly, Tulvatana et al. did not find enough evidence in their study to conclude that HPV is a risk factor for OSSN.[6] HPV association can be considered non-conclusive, though, because a study by Scott et al., demonstrated the presence of HPV 16 or 18 being found in each of their CIN subjects.[7]

CIN has an incidence of 1.9-2/100,000.[7,12] They present as gelatinous lesions that typically appear in fair-skinned individuals 60-70 years old.[1,12] The lesion can show leukoplakia (otherwise known as keratinization), and generally have a sessile appearance.[1,12] CIN has varying grades and levels of dysplasia. Mild dysplasia, or grade I, ranges from 33% to 50% of corneal or conjunctival epithelial involvement. Grade II involves more than 50% of the corneal or conjunctival epithelium and is considered moderate dysplasia. Grade III, commonly called carcinoma in-situ (CIS), has an incidence of 39%. CIS is severe dysplasia involving the entire epithelial thickness but without penetration of the basement membrane.[1,12,13]

SCC is considered invasive, as the cells have penetrated the basement membrane.[1] SCC has an incidence of 0.02-3.5 per 100,000.[3] SCC displays an exophytic growth pattern, which is a pattern of growth that occurs in the interpalpebral fissure (as opposed to endophytic growth, which is another growth pattern, where the other surrounding tissues of the cornea, sclera, globe, and posterior orbit can become involved).[1,12] Othman reported intraocular invasion occurring 2-15% of the time and orbital invasion occurring 12-16% of the time.[1] SCC metastases are seen in about 1% of cases.[12]

Clinical observations can assist with determining severity of the lesion. Similar to other suspicious lesions of the body, size, shape, and consistency are important to document. The presence of a feeder vessel may indicate a more advanced ocular surface lesion. The anatomical location of the lesion provides useful information about the lesion. The clinician can determine if the lesion is wholly within the conjunctiva or fixed to the globe by simple physical manipulation of it.[1] Gonioscopy provides the clinician with information regarding intraocular angle and posterior cornea involvement and is important in cases where the lesion shows corneal involvement. Using B-scan or magnetic resonance imaging with

gadolinium using 2 mm slices may offer additional information in cases of deep ocular or periocular metastatic lesions. Lymph nodes should be routinely checked for any possible involvement while keeping in mind that metastasis is rare. Preauricular and cervical lymph node involvement may be present in cases of advanced malignancy. Impression cytology, a process that allows for collected cells to be studied histologically, is another tool that can be useful in screening patients; it has a high positive predictive accuracy of 97.4% but a negative predictive accuracy of 52.9%.[1]

Mittal et al., reported 142 microns as being the differentiating thickness measurement between pterygium and OSSN with high sensitivity and specificity.[14] The average thickness in OSSN is measured at 346 microns, and the average pterygium thickness is measured at 101 microns.[28] Anterior segment OCT imaging can assist with the measurement through the use of the caliper function.

Traditionally, the gold standard treatment of OSSN lesions involves surgical excision using a no-touch method demonstrated by Shields.[8,9] The technique does not use balanced salt solution for surgical irrigation with the intent to avoid spreading tumor cells associated with the OSSN lesion to other locations on the globe. The no-touch technique involves creating a 4 mm clinically tumor-free area. Absolute alcohol and cryotherapy are used during the surgical process.[1,15] Reconstruction of the cornea may require lamellar keratoplasty, as had occurred in this case report, or conjunctival grafts.[1] The literature reports variable recurrence rate of OSSN lesion (widely due to its dependence on positive or negative margins). Peksayar et al. lists a recurrence rate of 30-40% following surgical excision. Nanji et al. lists a recurrence rate of up to 56% with positive surgical margins.[1,16] Even OSSN excisions with negative surgical margins have a recurrence rate of up to 33% and as low as 5%.[1,9] Li et al. report a 7.1% recurrence rate at 1 year, 2 years, and 5 years following excision and cryotherapy treatment.[9] In extreme cases of advanced and aggressive ocular or orbital invasion, enucleation or exenteration may be required.[15]

Following excision of the OSSN lesion, the use of an amniotic membrane (such as the brand, Prokera®) may be considered for use to assist with the reconstruction of the damaged ocular surface.[17] An amniotic membrane in an excision situation provides the removal zone with a covering while helping to reduce inflammation, vascularization, and scarring by limiting fibrosis that would otherwise occur.[1,17]

While the traditional treatment plan for OSSN lesions involves excision, removal, and biopsy, topical treatments either in conjunction with the no-touch method, or as single therapy, have emerged. Topical options include: mitomycin C, 5-

fluorouracil (5-FU), and interferon-α2b. Mitomycin-C is an alkylating antibiotic, which essentially damages DNA during all cell-cycle phases and causes irreversible cross-linking and nucleotide synthesis inhibition.[16,18] Rapidly dividing cells are most sensitive during mitomycin-C use.[1] Topical mitomycin-C comes in two concentrations, 0.02% or 0.04%, with differing dosing schedules.[1,16,18] Ocular toxicity is commonly reported with mitomycin-C use and includes keratitis, conjunctival hyperemia, ocular allergy, and general irritation.[1,16,18] Use of 0.02% mitomycin-C appears to be related to decreased toxicity.[18] Mitomycin-C monotherapy has demonstrated complete resolution in up to 90% of patients.[18,19] 5-FU is an antimetabolite pyrimidine analogue, which inhibits DNA & RNA synthesis.[16,18,19] 5-FU comes in a 1% concentration.[16,18] Ocular toxicity is reported with the use of 5-FU, including hyperemia and keratitis; however, the toxicity-related issues are not as severe as mitomycin-C use.[16,18,19] In a study by Joag et al., 82% of patients treated with 5-FU monotherapy showed completed resolution.[19] Interferon-α2b is created from systemic interferon-α, which has approval by the U.S. Food and Drug Administration to treat chronic hepatitis B and C, condylomata acuminata (HPV-related), malignant melanoma, follicular lymphoma, autoimmune deficiency syndrome-related Kaposi's sarcoma (1 or 27 AIDS-defining condition), and hairy cell leukemia.[1,16,18] Interferon-α2b is a glycoprotein molecule, which shows antiviral and antitumor activity by acting on cell surface receptors through a poorly understood mechanism of action.[1,16,18] Topical interferon-α2b is concentrated to 1 million IU per ml.[1,16] Galor et al. showed no clinical advantage to using 3 million IU per ml instead of 1 million IU per ml.[20] Compared with mitomycin-C and 5-FU, interferon-α2b shows little ocular toxicity-related side effects, though keratitis can occur.[1,16,18] Interferon-α2b can be used as dual-therapy in an injection delivery system plus topical treatment, as was used in this case report.[16] Shields et al. reported tumor control in 95% of patients when interferon-α2b is used as monotherapy or combined with surgical excision.[21] Karp et al. and Kusumesh et al. showed complete CIN resolution with monotherapy use of topical interferon-α2b.[22,23] The use of interferon-α2b when combined with surgical excision may improve outcomes, especially in cases where a negative tumor margin may be difficult to achieve.[22,24,25]

A study from Moon et al. reported on a cost comparison between interferon-α2b and surgical excision. The interferon-α2b presented an average of two more visits than the surgical group. An average cost increase of $12,612 for surgery compared to interferon-α2b was noted. The cost of office visits was higher in the medical group because many of the visits in the surgical group were covered within the global period. Using Medicare allowance, there was no statistical difference between the surgical and topical options.[26] Joag et al., reports cost of $190 per

month for mitomycin-C, $240 per month for interferon-α2b, and $40 per month for 5-FU.[19]

Mitomycin-C and 5-fluorouracil, two drops that are used in cases of OSSN, have been related to limbal stem cell destruction and subsequent deficiency. The limbal region contains stem cells that are responsible for corneal epithelial integrity, providing for regeneration of those cells. These cells are susceptible to permanent damage causing a condition referred to as limbal stem cell deficiency (LSCD). In cases of LSCD, conjunctival cells begin to replace corneal cells. The cornea may also show signs of ulceration, scarring, neovascularization, or non-resolving epithelial defects. When staining with fluorescein, a vortex pattern may be observed along with a poor, unbalanced tear film, corneal erosion, and corneal filaments. Surgical procedures with limbal involvement (such as trabeculectomy and removal of conjunctival lesion with corneal involvement) also pose a risk to limbal stem cells because mitomycin-C is commonly used. Treatment ranges from the use of preservative-free artificial tears in mild cases of LSCD to limbal grafts in very severe cases of LSCD where entire limbal integrity is compromised. Taking advantage of the vault provided by a scleral lens may also benefit a patient suffering with severe LSCD as it will afford the opportunity for a healing environment.[27]

CONCLUSION

This case demonstrates the role of case history, clinical observations, and proper referral in the diagnosis and management of a suspicious conjunctival lesion. It is important for the clinician to remember that clinical observation can assist with determining severity of the lesion. Gonioscopy can provide the clinician with information regarding intraocular angle and posterior cornea involvement. It is important to perform gonioscopy in cases where the lesion shows corneal involvement. Additional testing such as B-scan, anterior segment OCT, and MRI can provide additional information about the invasiveness of such lesions. Similar to other suspicious lesions of the body, size, shape, and consistency are important to document. The presence of a feeder vessel may indicate a more advanced ocular surface lesion. The anatomical location of the lesion provides useful information about the lesion. The clinician can determine if the lesion is wholly within the conjunctiva or fixed to the globe by simple physical manipulation of it.[1] Depending on the surgeon's preference, excision and cryotherapy, topical monotherapy, or a combination treatment may be used in these cases. Prognosis is favorable in most cases if treated early and there is limited recurrence.

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