



## Treatment challenges associated with a superiorly located bulbar conjunctival mass—case report and review of the literature

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### ABSTRACT

**Purpose:** This report describes a recurrent case of ocular surface squamous neoplasia in a middle-aged and immunocompetent patient.

**Observations:** The summary of clinical presentation, workup, and medical and surgical intervention are described, followed by a brief overview of the treatment challenges associated with superiorly located conjunctival lesions.

**Conclusions:** In cases where topical chemotherapeutic drops cannot penetrate the lesion, the location of conjunctival lesions can sometimes pose a challenge. Hence, injections in such cases might be preferred. However, histopathology still plays a significant role in achieving a definitive diagnosis.

### 1. Introduction

The term ‘ocular surface squamous neoplasia’ (OSSN), introduced by Lee and Hirst in 1995, comprises intraepithelial dysplasia and squamous cell carcinoma of the cornea and conjunctiva. Typically, early lesions are found at the limbus, while in advanced stages, the tumor may extend to involve other structures, such as the eyelids and the orbit.<sup>1,2</sup>

Solar ultraviolet (UV) radiation, human immunodeficiency virus (HIV), and human papillomavirus (HPV) infections are well-known risk factors implicated in the pathogenesis of OSSN.<sup>3,4</sup> Typically, OSSN affects older males in their sixth decade; however, younger individuals can also be affected, especially in xeroderma pigmentosum (XP) or HIV patients.<sup>3–6</sup>

Histopathological evaluation of the lesion after an incisional or excisional biopsy is the gold standard for diagnosing OSSN.<sup>7</sup> Lissamine green and rose bengal stain can be used to assist in making the diagnosis and delineate the extent of the tumor.<sup>8,9</sup> However, there are no well-defined standards for diagnosis before the initiation of a topical treatment. Alternatively, imaging modalities such as ultra-high-resolution anterior segment optical coherence tomography (AS-OCT) are more important in diagnosing ocular surface lesions and their recurrences.<sup>6</sup> Furthermore, different imaging techniques are usually beneficial to rule out the tumor’s extension to adjacent structures.<sup>9</sup>

Treatment modalities for OSSN range from complete excision in focal and small tumors to administration of chemotherapeutic agents in diffuse and large lesions to a combination of both.<sup>7,10</sup> The standard of care for treating OSSN appears to have undergone dramatic changes in the last two decades. Topical agents such as 5-fluorouracil (5FU), mitomycin, and interferon-alpha 2b have been used successfully in OSSN treatment.<sup>11,12</sup>

The overall prognosis in OSSN is good. Modern treatment strategies are usually effective. The reported recurrence rates locally are around 5% and less than 2% metastasis to regional lymph nodes.<sup>7</sup>

### 2. Case report

In July 2018, a 54-year-old woman presented to King Khaled Eye Specialist Hospital with redness in the left eye that had been there for nine months, worsening over the last four months. The patient was a non-smoker with no history of atopy or immunocompromise. Her ocular examination revealed a visual acuity of 20/60 in the right eye and 20/400 in the left secondary to amblyopia. The slit-lamp examination showed a temporal conjunctival fleshy pink lesion extending from one o’clock to five o’clock positions along the limbus and extending superiorly with many prominent feeder vessels and an absence of leukoplakia. Also, anterior segment optical coherence tomography (AS-

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OCT) showed the classical finding of thickened hyper-reflective epithelium with an abrupt transition between abnormal and normal epithelium (Fig. 1 a and b).

Otherwise, the cornea, anterior chamber, lens, gonioscopy, and retina examination were unremarkable—no signs of atopic allergic conjunctivitis or cicatrizing conjunctivitis. Additionally, the inferior bulbar and palpebral conjunctiva were free of lesions. The right eye examination was completely normal.

Ultrasound biomicroscopy (UBM) and magnetic resonance imaging (MRI) with contrast, performed to assess for extension, revealed no local or orbital extension. The final impression was OSSN without orbit or lid extension.

First, the patient received a subconjunctival interferon injection of 10 million units and was started on MMC 0.02% drops for two months. Before treatment, plugs were applied for upper and lower puncta.

After one month of compliance to MMC 0.02% topical treatment, there was minimal change to the size and morphology of the lesion. Hence, the patient was started on an alternative therapy: a three-cycle topical 5FU course. In each cycle, the patient received 5FU four times a day for one week, followed by three weeks of no treatment. After the first cycle of 5FU, the examination showed significant improvement with only moderate conjunctival hyperemia. Examination using lissamine green staining revealed multiple residual foci from one to three o'clock (Fig. 2). After completing the third cycle of 5FU, the lesion had completely resolved; no staining was observed after applying the lissamine green stain. Examination of the cornea and other ocular tissues was unremarkable. All medications were stopped except lubricants.

The patient was followed up at three-month intervals for six months with no documented recurrences. Six months after the last follow-up, the patient presented to the emergency room complaining of reappearance of a similar lesion in the same location in her left eye. The biomicroscopy examination revealed an elevated and mobile papillomatous lesion measuring  $3 \times 4$  mm in maximal diameter with a feeder vessel involving the bulbar conjunctiva. No involvement of surrounding structures was observed. The inspection of the fornices revealed no lesions as well (Fig. 3 a). Recurrence of OSSN was the provisional diagnosis.

Additional workup was done to rule out any immunodeficiency, including levels of Complement C3, C4, immunoglobulins G (IgG), A (IgA), and M (IgM), and serology for Hepatitis B virus (HBV antigen and antibodies), Hepatitis C virus antibodies, and Human immunodeficiency

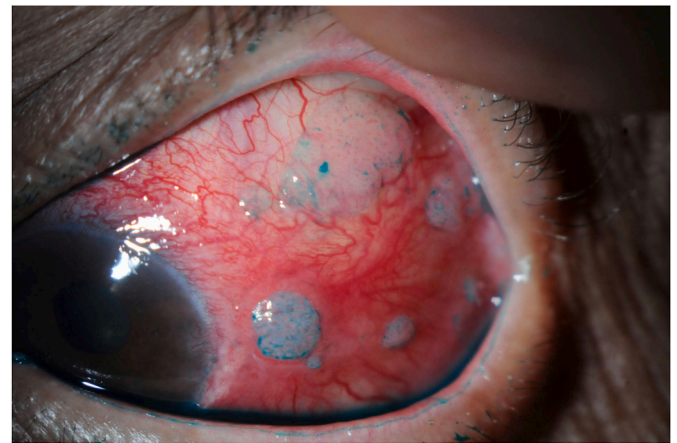


Fig. 2. Clinical picture showing multiple islands stained with lissamine green. This picture was taken during the topical 5-fluorouracil (5FU) course.

virus HIV 1,2 antibodies; all were within normal range. We performed a surgical excision of the lesion with a free margin using the no-touch technique. Additionally, cryotherapy was performed in a double freeze-thaw manner on the conjunctival margins. Absolute ethyl alcohol 99.7% and 0.02% Mitomycin C were applied to the scleral bed. After approximation and suturing of the conjunctiva, two layers of the amniotic membrane were used to cover the remaining defect using both Fibrin glue and sutures. An incisional lacrimal gland biopsy was taken as well. Finally, subconjunctival antibiotics and corticosteroids were injected and a Mega soft bandage contact lens was applied. The patient was discharged on topical antibiotics and corticosteroid drops.

The biopsy of the conjunctiva showed dysplasia involving the full thickness of the epithelium consistent with carcinoma in situ (Fig. 3 b). The examination of lacrimal gland biopsy revealed no evidence of malignancy.

### 3. Discussion

OSSN is the most common ocular neoplasm. Conjunctival OSSN is a well-differentiated tumor of low-grade malignancy.<sup>1</sup> Fortunately, the lesion grows slowly and seldom metastasizes. Rarely, OSSN can become potentially life-threatening when the lesion invades locally into the sclera, uvea, eyelids, and orbit and metastasizes to distant sites.<sup>13</sup>

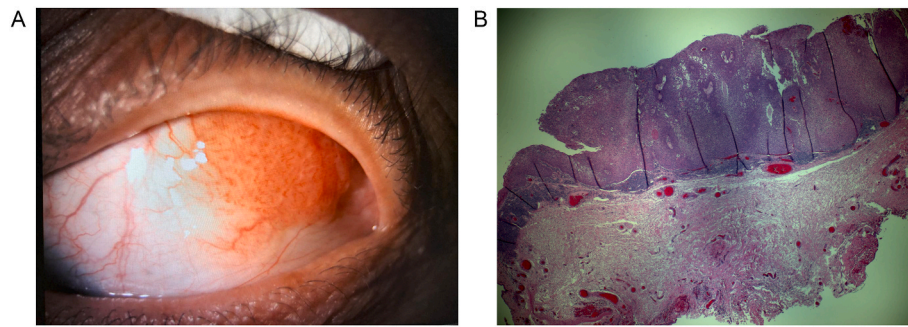
The agreed regimen to manage OSSN cases includes combinations of excision, cryotherapy, and topical chemotherapy such as 5-fluorouracil, mitomycin C, and interferon-alpha-2b.<sup>12,14,15</sup> Medical treatment is usually used for diffuse, multifocal lesions, lesions near the limbus, and recurrent disease. However, topical chemotherapeutic agents are subject to patient compliance, and a major drawback may be insufficient penetration of the drug into the tumor mass, especially in cases where the lesion is thick and the secondary ocular surface toxicity, which results in limbal stem cell deficiency (LSCD).<sup>16</sup>

In the beginning, our patient did not adequately respond to treatment trials with either MMC or interferon-alpha-2b chemotherapeutic agents. After receiving three cycles of 5FU, her lesion started to shrink in size and later completely disappeared. Follow-up is highly important since OSSN can recur many years after treatment. Additionally, follow-up is beneficial, especially in evaluating the efficacy and safety of the medications used. In this case, we used the AS-OCT and slit-lamp photos to monitor the patient's condition. The great advantage of AS-OCT is its ability to demonstrate in cases of OSSN a thickened hyper-reflective epithelium with an abrupt transition between abnormal and normal epithelium, thereby mimicking histopathological findings. Additionally, AS-OCT can be used to monitor tumor response to chemotherapy and assess prognosis.<sup>9</sup>

In this case, the lesion recurred a few months later. Recurrences have



Fig. 1. (a) Clinical picture showing diffuse gelatinous ocular surface squamous neoplasia temporarily in the left eye. (b) Anterior segment optical coherence tomography (AS-OCT) showing thickened hyper-reflective epithelium with an abrupt transition between abnormal and normal epithelium in our case.



**Fig. 3.** (a) The clinical photo shows an elevated papillomatous lesion involving the left eye's temporal bulbar conjunctiva. (b) The same lesion's biopsy showed dysplasia involving the full thickness of epithelium consistent with carcinoma in situ.

been reported with aggressive variants of the disease in immunocompromised individuals or those with atopic diseases.<sup>17,18</sup> However, our patient is immunocompetent and middle-aged adult, with no ocular surface disease or atopy. Therefore, consistent with this patient's clinical course, this case can be considered atypical.

The interpalpebral fissure is the typical location for OSSN.<sup>12</sup> However, in our patient, the lesion was located in the superio-temporal quadrant and extended further superiorly anterior to the lacrimal gland, adding additional challenges to treatment. Since the patient's clinical exam showed no signs of ocular surface disease or cicatrization, her MRI and other imaging modalities did not demonstrate any signs of extension of the mass to adjacent structures. Furthermore, the specimen was taken during surgery from the lacrimal gland and failed to show any tumor invasion. Therefore, we speculated that the reasons behind tumor recurrence in our patient might be related to the lesion's location where the drops were not reaching and penetrating the lesion properly. In such cases, injections might be preferred over drops. Additionally, the lack of a definitive diagnosis in the beginning was an issue in this case. For that reason, we opted to perform surgical excision of the lesion, and we sent the tissue for histopathological diagnosis.

Finally, as OSSN can present with the unusual course and atypical location, such as in our case, we expect that the debate about the pros and cons of surgical versus medical interventions for OSSN will continue.

#### 4. Conclusions

The location of OSSN can sometimes pose a challenge in cases where topical chemotherapeutic drops cannot reach the lesion; therefore, injections in such cases might be preferred. Histopathology still plays a very crucial role in achieving a definitive diagnosis. While evaluating conjunctival lesions, examination and investigational workup to rule out extensions to adjacent tissues should always be kept in mind and carefully looked for. Overall, eye care providers must individualize their treatment approach, considering patients' preferences, cost, and access to care when deciding on a treatment approach.

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NA.

#### Declaration of competing interest

None.

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