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Eyeing victory with 5fu: Ocular surface squamous neoplasia: A case report

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Abstract
We report a case of ocular surface squamous neoplasia (OSSN) in a 66-year-old female presenting with a fleshy mass on the temporal aspect of the left eye for four months, accompanied by redness and foreign body sensation. Her best corrected visual acuity was 6/24 in the right eye and counting fingers at half a meter in the left eye. Examination revealed a leukoplakic, lobulated, immobile lesion measuring 4x3 mm on the temporal bulbar conjunctiva, characterized by hard consistency and abnormal vascularity. The both eye showed nuclear sclerosis grade 1-2 and a normal fundus.
CT orbit revealed lobulated lesion involving infero-medial aspect of anterior surface of sclera showing contrast enhancement with no obvious deeper extensions and negative HIV test. She was treated with Topical 1% 5-fluorouracil 4 times daily for 1 week followed by 3 weeks off-treatment followed by. Excisional biopsy, followed by application of mitomycin C and cryotherapy and later with amniotic membrane graft on her left eye. Histopathological report revealed moderately differentiated invasive squamous cell carcinoma that extended horizontally and deeper into the surgical margins. During the 6-month follow-up visit, no clinical evidence of recurrent squamous cell carcinoma was observed.

Keywords: Conjunctiva, ocular surface, neoplasia, mitomycin C, 5FU

Introduction
Ocular surface squamous neoplasia (OSSN) is an important pathological entity for clinicians since it closely mimics common conjunctival and corneal surface pathologies like pinguecula, pterygium, conjunctival granulomas, and cysts. OSSN can have purely conjunctival involvement, purely corneal involvement, or conjunctival tumors extending over the cornea. The malignancies can range from conjunctival intraepithelial neoplasia (CIN) to squamous cell carcinoma. The frequency of cases of OSSN documented worldwide is 0.03-1.9 cases per 100,000 people with countries located close to the equator having the maximum incidence [2]. However, currently there has been a changing trend with cases of OSSN rising in varied geographical locations like India. The etiology of OSSN is multifactorial. Various studies have implicated human papillomavirus (HPV), ultraviolet B (UVB) light rays, human immunodeficiency (HIV) 1 and 2 viruses, and Hepatitis B and C as the most common associations [1, 2]. The various predisposing factors are chronic cigarette smoking, use of petroleum products, hypopigmented hair and eyes, xerophthalmia (vitamin A deficiency), chemicals like arsenic and beryllium, ocular surface trauma.

Case Details: A 66 year old, female came to OPD with chief complaints of growth in the temporal aspect of LE since 4 months, associated with foreign body sensation and redness since 4 months. No complaints of itching, pain.
Patient is a known case of hypertensive since 7 years on TAB AMLONG 5MG 1-0-0
Patient is a known case of diabetic since 7 years and on Oral Hypoglycemic Drugs And On Insulin.
Not a known case of TB/EPILEPSY/BA.
No history of spectacle usage.
No ocular trauma or surgery.
O/E: Uncorrected visual acuity of OD: 6/36, OS:CF ½ M
On Slit lamp examination her left eye showed: A leukoplakic, lobulated, immobile lesion of 4x3mm on temporal bulbar conjunctiva, with abnormal vasculature.
The anterior chamber (AC) was clear.

Intraocular pressure was 12 mm in both eyes.
OU showed NUCLEAR SCLEROSIS Grade 1-2 and Normal fundus study. Indirect ophthalmoscopy and B-scan showed no intraocular extension.

Clinical Course
The patient's clinical presentation strongly suggested squamous cell carcinoma. HIV testing returned negative, and a CT orbit revealed lobulated lesion involving the inferomedial aspect of anterior surface of sclera showing contrast enhancement with no obvious deeper extension. Patient is treated with topical 5-Fluorouracil 1% administered topically 4 times daily for 1 week followed by a drug holiday of 3 weeks. One month after topical treatment, the patient underwent an excisional biopsy of the left eye, followed by cryotherapy, intraoperative application of mitomycin C, treatment with absolute alcohol, and the placement of an amniotic membrane graft. Histopathological analysis confirmed the presence of invasive, stratified squamous epithelium with full thickness severe dysplasia. Individual tumor cell or polygonal in shape with hyperchromatic nucleus showing prominent nucleoli having moderate amount of eosinophilic cytoplasm. During the 4-month follow-up appointment, corrected visual acuity in the left eye was CF 4 M and no signs of recurrent squamous cell carcinoma. By the 10-month corrected visual acuity had improved to 6/60.

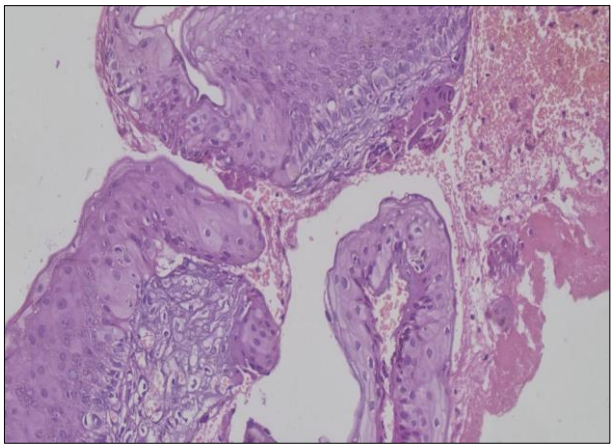

Fig 1: 200X (H&E)- Microscopy showing stratified squamous epithelium with full thickness severe dysplasia. Individual tumor cell or polygonal in shape with hyperchromatic nucleus showing prominent nucleoli having moderate amount of eosinophilic cytoplasm

Discussion
Ocular Surface Squamous Neoplasia (OSSN) is a term encompassing a range of neoplastic conditions affecting the squamous epithelium of the ocular surface, including the conjunctiva and cornea. These conditions span from benign squamous papillomas and conjunctival intraepithelial neoplasia (CIN) to malignant carcinoma in situ (CIS) and invasive squamous cell carcinoma (SCC). Although relatively rare, OSSN holds clinical significance due to its potential to cause substantial ocular morbidity, including visual impairment, and the risk of metastasis if left untreated.
The reported incidence of OSSN varies globally, ranging from 0.03 to 1.9 cases per 100,000 individuals [3]. Despite its infrequent occurrence, OSSN is considered the most common malignant tumor of the ocular surface, especially in regions with high levels of ultraviolet (UV) radiation exposure. It is typically diagnosed in middle-aged and older adults, with a higher prevalence in men, likely due to increased exposure to sunlight and outdoor activities.
OSSN is classified based on the degree of epithelial dysplasia and the extent of stromal invasion. The main categories include:

- **Squamous papillomas:** Which are benign lesions with minimal epithelial dysplasia.
- **Conjunctival Intraepithelial Neoplasia (CIN):** Which consists of dysplastic epithelial cells confined to the epithelium and can progress to carcinoma in situ (CIS) if left untreated.
- **Carcinoma in situ (CIS):** A full-thickness epithelial lesion without stromal invasion.
- **Invasive SCC:** The most aggressive form, where malignant cells breach the basement membrane and infiltrate deeper ocular tissues, leading to potential complications.

This spectrum of disease underscores the importance of early detection and appropriate management to prevent progression to invasive SCC, which may result in significant ocular complications.
In 1995, Lee and Herst classified Ocular Surface Squamous Neoplasia (OSSN) into three categories:

1. **Benign dysplasia:** Non-cancerous growths like papillomas or mild changes in the cells.
2. **Preinvasive OSSN:** Early-stage cancer (carcinoma in situ) where abnormal cells are still only in the surface layer, not spreading.
3. **Invasive OSSN:** Cancer that has spread into deeper layers, including squamous cell carcinoma and mucoepidermoid carcinoma.

The management of Ocular Surface Squamous Neoplasia (OSSN) includes two primary modalities: surgical excision and topical chemotherapy.

- Surgical excision, performed using the no-touch technique along with base cryotherapy, remains the traditional treatment of choice. However, in this patient, surgical intervention was deferred due to uncontrolled blood glucose levels, which elevated the risk of postoperative complications.
- Although effective, surgical excision carries the inherent risk of developing iatrogenic limbal stem cell deficiency (LSCD), a significant concern that may compromise ocular surface integrity. As a result, topical chemotherapy has gained increasing favor as an alternative treatment modality. Topical chemotherapy offers several advantages, including a reduced risk of LSCD, lower cost, and decreased morbidity. Furthermore, it has the potential to prevent recurrence by targeting neoplastic cells that may not be visible clinically, thus offering more comprehensive coverage of the ocular surface.

Topical Chemotherapy Agents
Several topical chemotherapeutic agents are available for the treatment of OSSN, including:

1. 5-Fluorouracil (5-FU)
2. Interferon alpha-2b (IFN-2b)
3. Mitomycin C (MMC)

- Mitomycin C (MMC), while proven to be effective, is associated with a higher incidence of side effects, such as pain, redness, severe epitheliopathy, and limbal stem cell deficiency. These side effects may lead to discontinuation of treatment. Other potential adverse effects include punctal stenosis, conjunctivitis, photosensitivity, and allergic reactions. MMC can be used as neoadjuvant, adjuvant or primary therapy. It can used in two concentrations of 0.02 or 0.04%, both dosed four times a day [3-7].
- In contrast, 5-FU has a more favorable side-effect profile, which made it the preferred treatment option in this case. Its lower risk of severe complications compared to MMC enhances patient adherence to the treatment regimen.

Mechanism of Action and Benefits of 5-FU

The use of 5FU for the management of OSSN was first described by De Keizer in 1986 [8].

- 5-FU is a pyrimidine analog that inhibits thymidylate synthase, thereby impairing DNA and RNA synthesis, which results in an antineoplastic effect. It is a well-established antimetabolite used in the treatment of various cancers, including skin, colon, and breast cancers.
- Histopathological analysis of tumors treated with 5-FU reveals characteristic cytoplasmic vacuolation and pyknotic nuclei in the keratinocytes, which are indicative of effective cytotoxicity. Additionally, 5-FU possesses anti-inflammatory properties, which may help reduce fibrosis and scar formation.
- Studies utilizing *in vivo* confocal microscopy have demonstrated that 5-FU is selectively effective against OSSN, with no long-term pathological changes observed in the corneal cells, including the endothelium, epithelium, stroma, and sub-basal nerve parameters.
- 5-FU has been used in ophthalmology as an adjuvant therapy in a variety of surgical contexts, including glaucoma, vitreoretinal, and pterygium surgeries. It has also been employed in the topical treatment of OSSN since 1986, further supporting its established role in ocular oncology.

Rationale for Using 5-FU

In light of the patient's uncontrolled blood glucose levels and the potential risks associated with other chemotherapeutic agents, 5-FU was chosen as the treatment of choice. Its proven efficacy, favorable side-effect profile, and reduced risk of serious complications such as limbal stem cell deficiency made it the most appropriate option for managing OSSN in this case. Parrozzani *et al*. [9] conducted a study where 5FU 1%, cycled 1 month on 1 month off, was used as primary therapy for OSSN in 41 patients. They had complete tumour regression in 83% of cases with a mean of 1.5 cycles [9]. They also found that multi-focality ($p = 0.023$) and tumour thickness >1.5 mm ($p = 0.045$) were associated with a poorer response to therapy [9]. They had a mean follow-up period of 105 months and a 12% recurrence rate. Venkateswaran *et al*. [10] compared the efficacy of IFN and 5FU. They used a dosing schedule of 5FU 1% four times a day for a week with a 3-week drug holiday, and IFN 1 million IU/ml four times a day until resolution [10].

Take Home Points

- HIV testing is mandatory in young patients with ocular surface squamous neoplasia.
- It's important to keep in mind that even those with XP who receive enough sun protection may yet experience vitamin D deficiency, so they should regularly take supplements.

Conclusion

This case highlights the successful management of OSSN with topical 5-Fluorouracil (5-FU) followed by surgical intervention, leading to no recurrence during the 6-month follow-up. Early detection and appropriate treatment are critical in managing OSSN, as it can progress to invasive squamous cell carcinoma. The use of 5-FU demonstrated efficacy with fewer side effects compared to other treatments, emphasizing its value in treating ocular surface squamous neoplasia, particularly in patients with comorbidities like uncontrolled diabetes.

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