Ocular surface squamous neoplasia
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Abstract

Ocular surface squamous neoplasia (OSSN) is one of the most common ocular surface neoplasias encompassing preinvasive, carcinoma in situ and invasive squamous cell carcinoma. Since Lee and Hirst first coined the term in 1995 the classification of OSSN, investigations along with its treatment has undergone a lot of changes. Since it is commonly encountered in a clinician’s day to day practice it is important for an ophthalmologist to stay up to date with all the recent developments in OSSN. This review article aims to provide a detailed review of the current literature regarding the etiopathogenesis, clinical features, diagnostic and treatment modalities of OSSN as well as a brief overview of newer frontiers being explored. The authors’ experience of treating patients with OSSN is presented in detail in this review article.

Keywords: Ocular surface squamous neoplasia, interferon alpha 2b, mitomycin-c, plaque brachytherapy.

Ocular surface squamous neoplasia (OSSN) is a term that encompasses the spectrum of precancerous and cancerous epithelial lesions of the conjunctiva and cornea. The spectrum includes dysplasia, conjunctival intraepithelial neoplasia (CIN), and invasive squamous cell carcinoma (SCC). Previously it was called intraepithelial epithelioma, Bowens disease and Bowenoid epithelioma.

Lee and Hirst in 1995 first proposed the term ocular surface squamous neoplasia (OSSN) which included mild, moderate, and severe dysplasia, carcinoma in situ, and invasive squamous cell carcinoma (SCC). Table 1 shows Lee and Hirst’s grading of OSSN.

Table-1: Lee and Hirst’s grading of OSSN

<table>
<thead>
<tr>
<th>I. Benign dysplasia</th>
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</thead>
<tbody>
<tr>
<td>• Papilloma</td>
</tr>
<tr>
<td>• Pseudotheliomatous hyperplasia</td>
</tr>
<tr>
<td>• Benign hereditary intraepithelial dyskeratosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Preinvasive OSSN</th>
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</thead>
<tbody>
<tr>
<td>• Conjunctival/corneal carcinoma in situ</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Invasive OSSN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Squamous carcinoma</td>
</tr>
<tr>
<td>• Mucoepidermoid carcinoma</td>
</tr>
</tbody>
</table>

Both dysplasia and carcinoma in situ constitute the term Conjunctival Intraepithelial Neoplasia and are premalignant conditions whereas squamous cell carcinoma represents its progress into malignancy.

Epidemiology and incidence:

Prevalence of OSSN varies from 0.03-1.9 per million population depending on the geographic location. In a National Institutes of Health study, the incidence of OSSN in the United States was 0.03 cases per 100,000 persons. Lee and co-workers found the incidence to be 1.9/100,000 population per year in the Brisbane metropolitan area of Australia.

CIN accounts for 39% of all premalignant and malignant lesions of the conjunctiva and for 4% of all conjunctival
lesions. Unlike CIN, incidence of invasive SCC is of much lesser frequency, varying from 0.02 to 3.5/100,000 population.

75% of OSSN affect the men whereas 75% are diagnosed in older patients with the average age being 56 to 60 years and over 75% occur at the limbus. OSSN can also occur in young patients with HIV and Xeroderma Pigmentosa. They are most commonly seen in dark skinned Caucasians.3,4 The authors could not find any prevalence studies of OSSN in India or the Indian sub-continent.

Risk Factors and etiopathogenesis:

The various risk factors are summarized in table 2.

Table-2: Various risk factors of OSSN

1. Exposure to ultraviolet-B radiation.
2. Infection with human papilloma virus 16.
3. Exposure to petroleum products.
4. Heavy cigarette smoking.
5. Chemicals such as trifluridine, Arsenic, Beryllium Ocular surface injury.
6. Vitamin A deficiency.
7. Defective DNA repair in Xeroderma. Pigmentosum
8. HIV.

Etiopathogenesis:

Ocular surface DNA damage is probably mainly caused by solar UV radiation (UVR), although HPV is also hypothesized with supportive evidence to play a role in the etiopathogenesis of this condition. Fig. 2 shows the mechanism of DNA damage.

Viral hypothesis of etiology:

Scott et al demonstrated HPV 16 and18 Deoxyribonucleic Acid (DNA) and messenger Ribonucleicacid (m-RNA) in conjunctival intraepithelialneoplasia (CIN). HIV increases the oncogenic action of other viruses and a study from Botswana reported multiple oncogenic viruses (EBV, HPV, KSHV, HSV1/2 and CMV) in cases of OSSN and pterygium.25

Failure of DNA repair mechanisms (Fig.-2):

DNA damage activates checkpoint pathways that regulate DNA repair mechanisms in the different phases of the cell cycle.16 The molecular mechanisms that repair UVR-induced DNA damage include excision repair, mismatch repair, strand breaker pair, and cross-link repair.10

p53 suppressor system: P53, the guardian of the genome, protect cells from the effects of DNA damage. The primary responses include; cell cycle arrest at the G1-S checkpoint; irreversible withdrawal of cells from the cycle into programmed cell death.23

Vitamin A deficiency hypothesis:

S Gichuhi et al hypothesize that vitamin A deficiency has three effects; it compromises the integrity of the surface epithelium creating micro-abrasions for HPV entry, it leads to cell-mediated immunodeficiency, and dysregulation of stem cell differentiation.19

Classification of OSSN:

Fig.3 is a flowchart showing the morphological classification of OSSN.

The nodular type grows rapidly with a high incidence of metastasis to adjacent lymph nodes.
The **placoid type** are relatively long standing and less aggressive sub-type compared to the nodular type. It is further sub-divided into 3 different patterns of presentation.

- **Gelatinous**- Circumscribed gelatinous lesions are the most common.
- **Leukoplakic**- These are usually pre invasive.
- **Papilliform**- They are exophytic, strawberry like, with a stippled red appearance corresponding to its fibro vascular core. They are clinically benign.

The **diffuse type** is the least common and in the early stages presents as persistent redness of the conjunctiva. They are slow growing and mimic chronic conjunctivitis. It is difficult to differentiate between benign and malignant lesions in these cases.

Histologically OSSN can be mild, moderate, severe or CIN grade 1, CIN grade 2 and CIN grade 3. When dysplasia involves the lower one third of the epithelium it is called mild, dysplasia extending into the middle third is called moderate or CIN grade 2 and when the dysplasia involves the full thickness of the epithelium it is called severe or CIN grade 3.1,3,27,28,29

Tumour staging is assessed using the TNM (Tumour, Node, Metastasis) definitions, as stated in the American Joint Committee on Cancer (AJCC) recommendations. The eighth edition of the AJCC classification has been recently released, and the definitions for T1 and T2 differ from those in the seventh edition. The TNM staging suggested by the 8th AJCC is summarized in table 3.30

**Clinical features and diagnosis of OSSN:**

Ocular surface squamous neoplasia is mostly unilateral and is seen in middle aged and older male patients. Rarely, it is bilateral and in case of bilaterality it is associated with immunosuppression. It often presents with redness and ocular irritation. Vision is usually unaffected unless it encroaches the centre of the cornea. The tumor appears as fleshy or nodular, sessile minimally elevated lesion with surface keratin, feeder vessels, and secondary inflammation.1,3,1 In the study conducted by Shweta Walia et al the most common presenting feature was foreign body sensation with an ocular surface mass followed by redness and burning sensation. The duration of symptoms ranged from 2 weeks to 2 months or more than 6 months duration in their study.32

Corneal OSSN lesions are usually pre invasive, with a mottled, ground glass sheet appearance. They have sharply defined borders while the convex leading-edge spreads in an arc away from the limbus and often white dots are present over the grey epithelium. They are usually avascular. These lesions are typically indolent, slow growing and prone for recurrence.1,27,28,29,31

**Diagnosis of OSSN:**

The diagnosis of OSSN is mainly clinical as described above. All clinic tests and blood tests are supportive in nature. In contrast to treating other malignancies elsewhere in the body, treatment protocol of OSSN does not compulsorily mandate a histopathological diagnosis before starting of treatment. Only in clinically doubtful cases and diffuse type of lesions is an incision biopsy done first. Given that local lesions can removed without much morbidity or vision loss, the usual protocol is to directly go for excision biopsy after clinical diagnosis.
Table-3: TNM staging

<table>
<thead>
<tr>
<th>Tumor (T) category</th>
<th>Tumor criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td>Includes mild, moderate and severe dysplasia and carcinoma in situ, collectively referred to as conjunctival intraepithelial neoplasia</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor(&lt;5mm in greatest dimension) invades through the conjunctival basement membrane without invasion</td>
<td>T1 stage and beyond represent invasive squamous cell carcinoma</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor(&gt;5mm in greatest dimension) invades through the conjunctival basement membrane without invasion</td>
<td>Excludes tumours that invade cornea, intraocular structures, fornical conjunctiva, palpebral conjunctiva, tarsal conjunctiva, lacrimal punctum, canaliculi, plica, caruncle, anterior or posterior eyelid lamella or eyelid margin</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades adjacent structures(excluding the orbit)</td>
<td>Includes involvement of adjacent structure excluded in T2</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades the orbit with or without further extension</td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades orbital soft tissues without bone invasion</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades bone</td>
<td></td>
</tr>
<tr>
<td>T4c</td>
<td>Tumor invades adjacent paranasal sinuses</td>
<td></td>
</tr>
<tr>
<td>T4d</td>
<td>Tumor invades brain</td>
<td></td>
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<table>
<thead>
<tr>
<th>Node(N) category</th>
<th>Node criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastasis (M) category</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
For all practical purposes the lesion is treated as malignant until proven otherwise by histopathology. Rose Bengal staining of the lesion one of the best indicators of a high possibility that the lesion is OSSN. Histopathological examination following an excisional or incisional biopsy provides a definitive diagnosis and is the gold standard in cases of suspicious lesions.

Less invasive methods that can aid in the diagnosis of OSSN are

1. **Exfoliative cytology** - using a cytobrush is particularly suited as malignant cells have poor cell to cell adherence and tend to desquamate when located on the mucosal surface. Impression cytology using cellulose acetate paper (CAP) is as simple and inexpensive diagnostic technique with the added advantage of maintained cell-to-cell relationship but it cannot assist in the grading of epithelial dysplasia neither it can exclude micro-invasive growth, which requires a full thickness examination of the involved tissue.

2. **In vivo confocal microscopy** - non-invasive diagnostic method which helps with the initial clinical diagnosis of OSSN, estimation of recurrence, management of treatment, and evaluation of response to topical chemotherapeutic agents in patients with conjunctival and corneal squamous lesions. In vivo confocal-microscopy analysis can be reliable in predicting the grade of dysplasia. In addition, cytological examination can differentiate between invasive and in situ tumors.

3. **High resolution OCT** - A novel way to diagnose subtle or suspicious lesions is by performing an "optical biopsy" with the use of high resolution (5–10ìm) or ultra-high resolution (3–5ìm) spectral domain optical coherence tomography (HR OCT). It is particularly useful at detecting epithelial thickening and differentiating epithelial lesions from subepithelial lesions of the conjunctiva and cornea. It is non-invasive, non-contact and can be used for the initial diagnosis of OSSN, the detection of OSSN in the presence of concomitant ocular surface disease, and during the follow up of patients on topical treatments for OSSN.

**Differential diagnosis of OSSN:**

It is important to rule out the lesions listed below before making a clinical diagnosis of OSSN. Below is Table 5 showing the differentials to be kept in mind.

**Treatment of OSSN:**

Tables 6 depicts the treatment protocol followed at our centre by a single primary surgeon (RH).
The treatment of OSSN includes:

1. Surgical excision
2. Topical chemotherapy including immunotherapy
3. Radiotherapy.

1. Surgical excision—Complete surgical excision using a technique without touching the tumor called the "no touch" technique is the treatment of choice in suspicious malignant lesions covering less than/equal to 3 clock hours at the limbus and not encroaching onto the centre of the cornea. This surgical technique has been adopted by the single primary surgeon (RH) at our centre. The higher the number of clock hours of corneo-scleral limbal dissection, the higher is the chance of occurrence of LSCD (Limbal stem cell deficiency) as stated by Swathi Kaliki et al. AMG following surgical excision of OSSN is effective for reconstruction of the conjunctival and corneal surface. However, it is not an effective replacement for

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**Table-5: The differentials of OSSN**

- Pannus
- Actinic disease
- Vitamin A deficiency
- Benign intraepithelial dyskeratosis
- Pinguecula
- Pterygium
- Pyogenic granuloma
- Keratoacanthoma
- Pseudoepitheliomatous hyperplasia
- Malignant melanoma and nevi

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**Table-6: The treatment protocol followed at our centre by a single primary surgeon**

**Suspected OSSN 1-3 Clock Hours**

Excision biopsy with 2mm clear margins and cryotherapy with amniotic membrane grafting

Margins positive

Topical chemotherapy with Interferon/MMC with 3 monthly review till tumor resolves

Margins negative

3 monthly review and evaluation for tumor recurrence

**Suspected OSSN 3-6 Clock Hours**

Incision biopsy to evaluate invasiveness

**PRE-INVASIVE**

Start topical chemotherapy with Interferon/MMC

Monthly follow up to evaluate tumor resolution-if resolves completely, then follow up every 3 months

**INVASIVE**

Start topical chemotherapy to achieve reduction in size. Once achieved, surgical excision of residual tumour with clear margins and cryotherapy to base and margins.

Monthly follow up for evaluation

**Suspected OSSN >6 Clock Hours**

Incision biopsy to rule out invasion

**PRE-INVASIVE**

Start topical chemotherapy with monthly follow up until complete resolution

**INVASIVE**

Start topical chemotherapy, if complete resolution occurs then monthly follow up till one year

If partial resolution-enucleation/exenteration depending on ocular coats
limbal stem cells. Limbal stem cell deficiency can be reversed by limbal stem cell transplantation (LSCT). In the study conducted by Swathi Kaliki et al, additional plaque radiotherapy for invasive squamous cell carcinoma was performed in three cases, and this did not influence the status of limbal stem cells. This process is extremely useful in patients with a lesion covering more than 6 clock hours, unresponsive to immune-reduction where surgery is the ultimate resort.  

2. Topical chemotherapy—

Topical chemotherapy—with drugs like Mitomycin-C (MMC), Interferon alpha, 5 Fluorouracil (5FU) is an effective modality of treatment for OSSN.

The indications for using topical chemotherapy for treating OSSN is summarized in table 7.

Table 7: Indications for topical chemotherapy

- >3 quadrants of conjunctival involvement
- >180 degree of limbal involvement
- Clear corneal extension encroaching onto the pupillary axis
- Positive margin after excision
- Patient not fit for surgery

Topical interferon therapy

In 1994 Maskin was the first to report to report the use of topical interferon (IFN alpha-2b) in a multi-focal limbal OSSN. Karp reported complete resolution in five cases of OSSN measuring <8 mm with IFNa2b. Over the past decade several authors have reported the beneficial effects of IFNalpha-2b in the treatment of OSSN. Owing to a lesser toxicity profile, IFNalpha-2b currently seems to be the treatment of choice for wider and extensive OSSN involving >4 clock hours of the limbus.

Mitomycin-C (MMC) & 5-Flourouracil (5FU)

Advantages of MMC &5FU are its low cost. Topical 5FU was first reported for the treatment of premalignant lesions of the cornea, conjunctiva, and eyelid in 1986. Since then, several studies evaluated 5FU as a primary agent for OSSN, with a high frequency of resolution (average 91%, range 82%-100%). In a study conducted by Nandini Venkateswaran et al both 5FU and interferon were found to be viable and effective treatment modalities for OSSN, with a high frequency of clinical resolution and low recurrence rate in both groups. Conjunctival intraepithelial

Fig.-6: The schematic diagram with intra-op clinical photographs alongside depicting (A) and (a) Tumour mapping; (B) and (b) with or without alcohol assisted epithelectomy with 2mm margin; (C) and (c) Enbloc excision with 4mm conjunctival margin from visible lesion border with or without lamellar sclerectomy (0.2 to 0.3mm) without touching the tumor. After this, there needs to be a change of instruments; (D) and (d) Double freeze thaw cryotherapy with base cryotherapy; (E) and (e) amniotic membrane grafting being done.
neoplasia and milder forms of Squamous Cell Carcinoma can be treated with topical MMC (0.02–0.04%). The mechanisms of action, dosage and side effects of the topical chemotherapy agents are mentioned in table 8.

Topical or subconjunctival anti-VEGF and other modalities:
Studies conclude that topical bevacizumab is effective as a neoadjuvant therapy combined with surgical excision for the treatment of OSSN. It may be used before surgery.
to decrease the size of the lesion. Excision may be unnecessary in responsive patients. Topical treatment also seems superior to subconjunctival administration, especially for the treatment of the corneal portion of the tumor. Teng et al. evaluated the efficacy of subconjunctival ranibizumab for the treatment of refractory squamous cell carcinoma of the conjunctiva with corneal extension in four patients. Their results revealed that ranibizumab can decrease the size and vascularity of the tumors but complete disappearance of the tumor did not occur in any of the cases.

The topical options available are mentioned in Table 9. If there is a patient with recurrent or refractory OSSN and one has exhausted all the options, the biopsy specimen can be evaluated with a PCR-based test to assess for the human papillomavirus (HPV). These re-fractory cases may have an underlying infection that might be missed. When HPV is confirmed, the anti-viral drug cidofovir has shown very promising results.

3. Radiotherapy – is a time-tested old treatment modality whose role is now limited to extensive or diffuse lesions in conjunction with other methods. Though extremely effective, it causes significant ocular surface damage and dry eye, which is often permanent.

Reports of using plaque radiotherapy has been few in literature, Naseripour et al treated patients with recurrent conjunctival squamous cell carcinoma effectively with Ruthenium-106 plaque radiotherapys. Natalie Walsh Conway et al treated 11 consecutive patients with biopsy proven scleral or corneal stromal involvement from either melanomas or squamous cell carcinomas of the conjunctiva. They used iodine-125 plaque, the visual acuity and the IOP remained unchanged and no one had recurrence at the treatment site or distant metastasis.

Also, because of limitations in the stage 3 of the TNM classification, a new clinical based classification as well as treatment modality has been proposed by Meel R et al. The classification is mentioned in table 10.

Recurrence:

Reported recurrence rate of OSSN is 15-52%. Lee and Hirst reported a 17% recurrence after excision of conjunctival dysplasia, 40% after excision of CIS and 30% for SCC of conjunctiva. Recurrences are higher in case

### Table-10: New clinical classification

<table>
<thead>
<tr>
<th>Grade</th>
<th>Limbal involvement (clockhours)</th>
<th>Maximal basal diameter (mm)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1: OSSN with no invasion into ocular coats clinically and on imaging (ultrasound bio-microscopy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Less than equal to 3 clock hours</td>
<td>Less than equal to 5 mm</td>
<td>Surgical excision with margin control</td>
</tr>
<tr>
<td>B</td>
<td>&gt;3 to &lt; 6 clock hours</td>
<td>&gt;5 to &lt; 15 mm</td>
<td>Immunotherapy or immuno-reduction</td>
</tr>
<tr>
<td>C</td>
<td>More than equal to 6 clock hours</td>
<td>More than equal to 15 mm</td>
<td>Immuno-reduction</td>
</tr>
<tr>
<td>Grade 2: OSSN with invasion into ocular coats on imaging (ultrasound bio-microscopy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Excision + lamellar sclerectomy or Keratectomy + cryotherapy</td>
<td></td>
</tr>
<tr>
<td>Grade 3: OSSN with intraocular invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Enucleation</td>
<td></td>
</tr>
<tr>
<td>Grade 4: OSSN with intra-orbital extension (confirmed by CT scan or MRI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Orbital Exenteration</td>
<td></td>
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</tbody>
</table>
of inadequate excision margins and positive margins post-surgery occurring within two years of surgery. The main predictors of recurrence are adequacy of margins at initial excision, positive margins at the time of excision, histological grade of the lesion, corneal location, larger size (>2 mm), age, high proliferation index. The recurrence rate can be limited to less than 5% with protocol-based management. Plaque brachytherapy is used to control gross or microscopic residual tumors. More extensive orbital invasion requires orbital exenteration.

Management of different cases of OSSN at our centre

Case 1 (Fig.-7):
A 54-year-old male patient presented to us with history of a nodule at the nasal limbus associated with mild redness and foreign body sensation for 2 months. On examination the lesion showed staining with Rose Bengal following which he was taken up for surgical excision with 4mm clear margins cryotherapy and amniotic membrane grafting. The specimen sent for histopathology demonstrated moderate grade OSSN. At 6 months follow up he was in remission.

Case 2 (Fig.-8A-D, Fig.-9):
A 54-year-old male patient presented to us with history of severe conjunctival congestion, foreign body sensation and a nasal limbal mass extending from approximately 1'o clock to 7'o clock position.

Figure 7: (A) Nasal limbal mass with mild congestion at 9'o clock position; (B) Slit lamp image of the nasal limbal mass with multiple prominent feeder vessels and telangiectasia; (C) Immediate post-operative picture post surgical excision and cryotherapy along with amniotic membrane grafting; (D) 6 months post-operative picture showing complete resolution with no recurrence at follow up period of 6 months.

Figure 8: (A) At presentation the nasal limbal mass extending for approximately 6 clock hours with extension onto cornea and severe conjunctival congestion; (B) 2 weeks after initiation of treatment with topical interferon showing the lesion to be regressing; (C) 1 month after initiation of treatment, the redness and congestion has increased and the mass not showing further regression; (D) after 2 months the lesion is showing recurrence despite continuing topical interferon.

Figure 9: Histopathological picture of invasive squamous cell carcinoma showing the characteristic keratin pearls (arrow)

We treated him with interferon eye drops four times daily and with 2 perilesional booster injections in the first month. The mass showed slight resolution with decrease in
redness but after 2 months of treatment it didn’t show any further resolution. He was then treated with Mitomycin-C eye drops 0.04%, four times daily for 3 weeks but didn’t respond as expected. An incision biopsy was done which showed invasive squamous cell carcinoma with involvement of the ocular coats. Subsequently he underwent an orbital exenteration.

**Case 3 (Fig.-10A-E):**

A 40-year-old female patient presented to us with history of watering, redness and a white gelatinous mass over the right cornea for 6 months. On examination, a white elevated gelatinous mass covering 360 degree of the peripheral cornea excluding the centre. An incision biopsy was done which came out to be mild to moderate grade OSSN. She was given two perilesional interferon injections two weeks apart in the first month and treatment with topical interferon 1MIU/ml was started 4 times daily. She responded satisfactorily. She stopped treatment on her own after 4 months only to come back with a recurrence. Treatment with topical interferon was restarted and she responded favourably.

**Newer Frontiers**

In the study conducted by Chauhan S et al 45% of advanced OSSN cases displayed strong p16INK4a immunoexpression and were associated with poor disease outcome. Thus, p16INK4a overexpression is useful to segregate high-risk patients with OSSN presenting at an advanced stage. Once identified, these patients can be advised more aggressive treatment modalities. Sunlight-induced epigenetic alteration in p16INK4a plays an important role in the pathogenesis of OSSN. In a study done by Dilip Kumar Mishra et al, it is stated that stem cells expressing p63, c-Kit, ABCG2, and CD44 have a role in the progression of OSSN. The authors also concluded that the screening of cancer stem cells can be used to prognosticate the severity of OSSN and possibly its metastatic potential. Apart from this it will help researchers to come up with much more targeted therapy for OSSN.

**Conclusion:**

Ocular surface squamous neoplasia is, thus, classified into premalignant conjunctival intraepithelial neoplasia (benign dysplasia and carcinoma in situ) and malignant invasive carcinoma. With higher incidence of CIN compared to invasive lesions, it is important to pick up suspicious lesions and initiate early management. Though there are non-invasive investigations to help aid in diagnosis, only a true biopsy clinches the diagnosis. With the modern surgical techniques, the local recurrence rate is less than 5% and regional metastasis is also less than 2%. OSSN generally has a good prognosis except in mucoepidermoid or spindle cell variants and in immune suppressed patients.

**References:**


