Anil Radhakrishnan MS

Ocular Surface Squamous Neoplasia [OSSN] - A Brief Review

Introduction

Though conjunctival tumours are uncommon, their early diagnosis assumes great significance due to its malignant potential in a small minority.1,4 The term Ocular Surface Squamous Neoplasia [OSSN] presently refers to the entire spectrum of dysplastic, pre-invasive and malignant squamous lesions of the conjunctiva and cornea, indeed a wide spectrum.1,2,3,4.

Classification of OSSN

Benign OSSN - Papilloma
- Pseudoepitheliomatous hyperplasia
- Benign hereditary intraepithelial dyskeratosis

Preinvasive OSSN – lesions confined to epithelium
- Conjunctival / Corneal intraepithelial neoplasia
  - [Grade 1 – 3 depending on extent]

Invasive OSSN – Squamous carcinoma
- Mucoepidermoid carcinoma

Demographics

Though OSSN is not a common disease, it is the third most common ocular tumour after melanoma and lymphoma. Also, a lot of them may go unnoticed as they are asymptomatic and usually slow-growing. The prevalence of OSSN is more in tropical region and varies from 12 cases / million/ year in Uganda to 0.2 cases / million/ year in United Kingdom, possibly related to sunlight exposure. However Caucasian race is more predisposed to UV related skin damage, and also OSSN compared to pigmented race, especially those living at latitudes less than 30 degrees to the equator.1,4

Unsuspected OSSN was found incidentally in 9.8% of 538 consecutive samples of pterygia, which underwent a histopathological examination in Queensland, Australia, a geographical zone with a high incidence of UV related diseases like skin malignancy and pterygium, which suggests that true incidence of OSSN may be much higher.

The average age of onset of OSSN is 56 years, but is seen to be younger in populations living close to equator. Also the average age of patients with carcinoma-in-situ is seen to be 5 to 9 years younger than those with invasive carcinoma, suggesting progression of neoplasia.1,2,3,4

The two main risk factors are UV-B light and Human Papilloma Virus.5,2,4,10 The other risk factors are exposure to petroleum products, heavy cigarette smoking, chemicals such as trifluridine and arsenicals, ocular surface injury, vitamin A deficiency, and European ancestry.5,2,3,4,10,11

Clinical features

UV-B light causes DNA damage and formation of pyrimidinedimers. Failure or delay in repair can lead to somatic mutations and oncogenesis. UV radiation is known to be mutagenic for p53 [a tumour suppressor protein in the host, which regulates the cell cycle and functions as a tumour suppressor]. In patients with xerodermapigmentosa the incidence of OSSN is much higher and occurs at an early age, even in childhood.

Human Papilloma Virus [HPV] has a well proven causal relationship with cervical neoplasia. DNA of HPV -16 & 18 are found in upto 80% of cervical intraepithelial neoplasia [CIN – grade 2 &3] and 90% of invasive squamous cell carcinoma. HPV-6 & 11 are associated with benign genital warts and CIN-grade1. Similarly, HPV DNA has been isolated consistently from dysplastic lesions of conjunctiva and cornea. However it is likely that HPV requires another risk factor like UV-B light for oncogenesis.

Pathology

Papilloma – seen as papillary fibrovascular fronds covered by acanthotic epithelium. Adult papillomas show dysplastic features like nuclear enlargement and hyperchromatism, increased nuclear to cytoplasmic ratio, loss of polarity etc.

Preinvasive lesions are classified as mild, moderate or severe dysplasia, depending on the degree of involvement.

CIN grade 1 [mild dysplasia] - dysplasia confined to basal [lower]one-third of epithelium

CIN grade 2 [moderate dysplasia] – extends into middle third of epithelium

CIN grade 3 [severe dysplasia] – extending into upper third of epithelium. The basement membrane however is intact. Full thickness dysplasia of the epithelium as in cervical neoplasias also referred to as ‘ carcinoma in situ’ [Fig 1]. Evidence of chronic inflammation may be seen in substantiapropria.

Invasive OSSN / Squamous cell carcinoma– shows nests of neoplastic cells that have penetrated the epithelial basement membrane and spread into the underlying stroma[Fig 2]. Tumour cells may be well-differentiated or ill-differentiated. Two types of cells may be seen interspersed along with squamous cells - [1] spindle cells or [2] mucoepidermoid cells. The latter is notorious for intraorbital extension as well as early recurrence if left untreated.

Address for correspondence: Amrita Institute of Medical Sciences, Kochi
seen at or near the limbus, grayish-white in colour with a characteristic tuft of blood vessels in the interpalpebral fissure area. It can become fleshy with feeder vessels. Rose Bengal or Lissamine green staining can help in delineating the extent of lesion [Fig 3 & 4]. The corneal side of the lesion may be seen as an opalescence of the epithelium, slightly raised in comparison to adjacent normal epithelium the edges of which are usually sharply defined. It is best appreciated by retroillumination.

OSSN is a slow growing tumour of low-grade malignancy, which rarely metastasises. Three morphological types are described [1] Gelatinous [2] Leukoplakic [3] Papilliform type. In clinical practice, gelatinous type is the commonest. The gelatinous lesion can again be circumscribed, which are most common or a nodular variety, which has a propensity for rapid growth and diffuse variety, the least common, which can masquerade as chronic conjunctivitis with no obvious tumefaction.

The lesions are usually asymptomatic and are detected by chance. A few patients may present with redness, irritation or foreign body sensation. It is nearly impossible to categorise OSSN as benign or malignant based on clinical appearance alone. Larger lesions that are fixated to the underlying tissue are usually malignant.

Regional lymphadenopathy (preauricular nodes, submandibular nodes and deep cervical) should be looked for.

Diagnosis – A high index of clinical suspicion is necessary. An incision / excision biopsy is considered the ‘gold standard’ for diagnosis and planning further treatment.

Impression cytology with Biopore membrane has reasonably good accuracy but can miss about 20% of cases. However, it has a definite role in follow-up of lesions, after primary treatment, whether surgical or topical chemotherapy.
Figure 5 – OSSN with healthy conjunctival margins sutured to absorbent paper to maintain orientation before sending for histopathological examination

Treatment


Surgical treatment – A wide surgical excision is done to maximize the chances of complete removal. Rose Bengal / Lissamine green staining is helpful to delineate the margins of the lesion. A ‘no touch’ technique avoiding direct manipulation of the lesion, by holding the tissue at the healthy conjunctival borders is employed to prevent tumour seeding into new area\textsuperscript{2,4,13,14}. Shields et al recommend usage of absolute alcohol on the corneal side of the lesion to facilitate epithelial removal as one sheet – alkoholepithelectomy\textsuperscript{13}. The excised conjunctival specimen is placed on an absorbent paper and air-dried to prevent loss of orientation. Rather the best method would be to spread out the specimen and apply 3 or 4 sutures, marking both the conjunctival side and the corneal side. [Fig 5].The recurrence rate following surgical excision ranges from 15 – 52%\textsuperscript{2,11}. Erle et al\textsuperscript{11} found that if the excised tissue margins were free of tumour, the recurrence rate was only 5% in contrast to 52% recurrence, if lesions were incompletely excised [positive surgical margins on histopathological examination].

Though a slow growing tumour with remote risk of systemic spread, if undiagnosed and untreated, it is capable of orbital and intraocular spread requiring exenteration or enucleation.

Cryotherapy – is done in combination with surgical excision. It acts by freezing the tissue and also obliterating the microcirculation, resulting in ischemic infarction of abnormal tissue. Cryotherapy is applied to the base and edges of the conjunctival margin to reach both superficial tumour islands and deeply infiltrated tumour cells. The cryo probe [with 2.5 or 5 mm tip] is inserted underneath the edges of resected conjunctiva to form an iceball. The recommended technique is short duration freeze with slow thaw, repeated two or three times [freeze – thaw-refreeze ]. The duration of cryotherapy depends on the location – the iceball extending 2 mm for conjunctiva, 1 mm for episclera and 0.5 mm for the cornea. Limbal region should not be spared, but cryo application should be limited to 3 seconds to minimize the risk of limbal stem cell damage. If cryotherapy is combined with surgical excision, the mean recurrence can be brought down to about 12%\textsuperscript{2,3,15,16}.

Conjunctival deficit is closed primarily if it is small [ < 3 clock hours]. For larger defects amniotic membrane transplantation or conjunctival autograft may be done.

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\textsuperscript{2,3,17,18}.

Topical chemotherapy - Over the last decade topical agents have been used by various investigators to treat various malignant and premalignant conjunctival lesions viz primary acquired melanosis with atypia, conjunctival melanoma, OSSN and pagetoid spread of sebaceous cell carcinoma\textsuperscript{2,4,7,22-27}. Topical administration of chemotherapeutic agents can deliver high drug concentrations to the ocular surface with negligible systemic side effects. It is capable of treating small tumour islands on the surface, which may escape surgical excision. Also topical chemotherapy can be titrated according to clinical response. Two chemotherapeutic agents are commonly used – Mitomycin-C [MMC] and 5-fluorouracil.

Mitomycin-C [MMC] is an alkylating agent that binds to DNA, leading to irreversible cross-linking and inhibition of nucleotide synthesis, which is not cell cycle specific. Under aerobic conditions, intermediates of MMC also react with oxygen to generate free radicals, causing cytotoxicity via lipid peroxidation. MMC is toxic to both proliferating and non-proliferating cells, but more for the former. Topical use of MMC has been time-tested for glaucoma filtering surgery [to prevent fibrosis and consequent bleb failure], refractive surgery [to prevent stromal haze following surface ablation] and pterygium surgery [to prevent fibroblast cell migration and to induce apoptosis in Tenon’s capsule fibroblasts]. In OSSN mitomycin C is used in concentrations of 0.02% or 0.04% 4 times a day for 1 or 2 weeks. These cycles are repeated at 4 to 6 week intervals. As MMC is relatively unstable in solution, it has to be refrigerated and a new bottle dispensed for each week of treatment. Shields et al\textsuperscript{17,23} use a one-week–on and one-week-off technique and has reported good results.

5-Fluorouracil [5FU] an anti-metabolite, which inhibits thymidylatesynthetase during S phase of the cell cycle, preventing DNA and RNA synthesis in rapidly dividing cells because of lack of thymidine. In contrast to MMC, it is cell
cycle specific. Though the experience with 5FU is less in comparison with MMC, it is equally efficacious and better tolerated. Also it is stable in aqueous solution for at least three weeks, does not require refrigeration and is inexpensive.

With the existing scientific literature, it is clear that both mitomycin and 5-FU are effective for complete eradication of preinvasive OSSN in majority of patients when used as a primary treatment. The success rates for topical chemotherapeutic agents are comparable to other treatment modalities in preinvasive disease.

For invasive OSSN, these agents achieve chemoreduction or decrease in tumour size. Postoperative MMC application, have also been used by several authors as adjunctive therapy following primary excision of OSSN with good success. Chen et al reported no tumour recurrence in 27 cases with a mean follow-up of 27 months.

Special care is required while handling these chemotherapeutic agents and punctual plugs are recommended to protect the nasopharyngeal tissue. Pregnant women should avoid contact with these agents.

Ocular side effects of topical chemotherapeutic agents are ocular surface toxicity and epithelial defect formation, progression of cataract and punctual stenosis. No cases of corneal or scleral melting have been reported. An intact epithelium prevents deeper penetration, topical MMC or 5FU should not be given to any patient with a conjunctival or corneal epithelial defect.

Immunotherapy- Interferons are naturally occurring glycoproteins with antiviral and antitumour properties with clinical application in cutaneous malignancies. Successful outcome was reported in all the 6 cases of biopsy proven OSSN treated with a combination of intrallesional and topical interferon 2b. Larger studies with longer follow-up are required to cement its place as a treatment modality.

**Management**

Though topical chemotherapy has opened new vistas in the approach towards OSSN, with a proliferation of advocates of non-surgical management, there is a definite risk of undertreating islands of tumour cells in invasive neoplasias. Though there are no standard protocols, following has been suggested as a treatment guideline by Basti and Mascali.

[1] Suspected OSSN < 3 clock hours – Excision biopsy + base/edge cryotherapy + alcohol epitheliectomy is done. If the margins are free of tumour cells, quarterly follow-up for a year is recommended to confirm absence of recurrence. Thereafter 6 monthly follow-up should suffice. If margins are involved, topical chemotherapy should be added with monthly follow-up and quarterly Biopore impression cytology for a year to evaluate recurrence. If disease free for one year, 6 monthly follow-up is suggested.

**Figure 6 – Treatment plan for OSSN < 3 clock hours**

![Image](image1)

[2] Suspected OSSN 3 – 6 clock hours – As there is a risk of producing limbal stem cell deficiency, excision biopsy + cryotherapy is better avoided. A diagnostic biopsy is required. In pre-invasive lesions topical chemotherpay is likely to achieve tumour resolution. If invasive, surgery + cryotherapy is done after chemoreduction with 4 to 6 cycles of topical chemotherapy.

**Figure 7- Treatment plan for OSSN 3 -6 clock hours**

![Image](image2)

[3] OSSN > 6 clock hours – A diagnostic biopsy is required. In pre-invasive lesions topical chemotherapy is quite likely to achieve tumour resolution. If invasive, surgery + cryotherapy is done after chemoreduction with 4 to 6 cycles of topical chemotherapy. If there is no response to chemotherapy palliative radiotherapy or extensive surgery like enucleation / exenteration may be required.
Conclusion

Ocular Surface Squamous Neoplasia [OSSN] though an uncommon entity needs to be picked up early, as prompt treatment in early stages is usually curative. Though slow growing in nature, advanced invasive lesions may end up in mutilating surgery like exenteration. The advent of topical chemotherapy has indeed augmented the treatment armamentarium and has made a paradigm shift in the management of this condition in the last decade.

References