Ocular Surface Squamous Neoplasia (OSSN)

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The Ocular Surface Squamous Neoplasia (OSSN) is a broad term including conjunctival intraepithelial neoplastic lesions (CIN) and invasive squamous cell carcinoma (SCC) of conjunctiva and cornea. CIN includes varying grades of dysplasia, ranging from mild, moderate, severe dysplasia to carcinoma in situ. Their importance lies in the fact that they can mimic benign lesions like pterygium or even chronic conjunctivitis. This condition has been known by various names like epithelioma, bowen's disease, epidermalization, dyskeratosis, conjunctival and corneal intraepithelial neoplasia, and ocular surface epithelial dysplasia. The term CIN, that is used today was derived from the terminology used in intraepithelial cervical malignancies. Lesions involving basal one third conjunctiva were classified mild, inner two third as moderate and full thickness lesions were called as severe dysplasias.

The term Ocular Surface Squamous Neoplasia (OSSN) was coined by Lee and Hirst which has three grades:

I. Benign dysplasia
   - Papilloma
   - Pseudoeplitheliomatous hyperplasia
   - Benign hereditary intraepithelial dyskeratosis

II. Preinvasive OSSN
   - Conjunctival/corneal carcinoma in situ

III. Invasive OSSN
   - Squamous carcinoma
   - Mucoepidermoid carcinoma

Epidemiology

Incidence of OSSN has wide geographical variations, it declines considerably with increase in latitude, and is thought to be more common in regions near equator. Males are affected more commonly than females. Average age of presentation is in sixth or seventh decade. Incidence is slightly higher in dark skinned Caucasians.

The average incidence of OSSN of conjunctiva and cornea was found to be 0.13/1 lac in tribal groups in Uganda by Templeton in a study in 1967, and 1.9/1 lac population per year in the Brisbane metropolitan area of Australia by Lee in 1992. In a recent study published in 2012, an incidence of 37.3 per 10 lac was reported for all eye cancers and 8.4 per 10 lac for SCC. Highest risk of OSSN is seen in older males, Caucasians and residents of lower latitudes (within 30° latitude to the equator). Patients with xeroderma pigmentosum and HIV develop OSSN at an earlier age.

All young patients with OSSN should be screened for HIV.

Etiopathogenesis

Although many etiological factors have been implicated those best understood are infection with human papilloma virus (HPV) and exposure to ultraviolet B (UV B) radiations.

Ultraviolet B radiation: Role of sunlight exposure as a major etiological factor is indicated by higher incidence in residents of lower latitudes, male sex (outdoor activity), in fair skinned individuals in those having history of actinic skin lesions and temporal lesions being more common aggressive than nasal lesions. UV-B causes pyrimidine dimer formation and damage to nucleotide excision repair which is responsible for DNA repair. It has also been seen to cause p53 mutation which can be seen in OSSN.

Xeroderma pigmentosum (XP) is an autosomal recessive disorder with defective DNA repair mechanism which predisposes to OSSN with aggressive clinical presentation at a younger age. OSSN has been reported as early as 3 years of age in a patient of XP.
Human papilloma virus: HPV 6, 11 has been associated with dysplasia and malignant lesions of conjunctiva and cornea. HPV 16, 18 has also been implicated in conjunctival intraepithelial neoplasias.

Human immunodeficiency virus: HIV infection is now established as a risk factor for the development of squamous cell neoplasia of the conjunctiva. OSSN can also be a clinical presentation of HIV in young patients. OSSN occurring in HIV patients are more aggressive and invasive that may require enucleation or even exenteration.

Other risk factors include chemical exposure (beryllium, arsenicals, petroleum products) cigarette smoking, vitamin A deficiency, and viruses like herpes simplex virus (HSV) type I.

Clinical Features

OSSN most commonly presents in the interpalpebral area near the limbus. Bulbar conjunctiva is most commonly involved but it can also involve palpebral conjunctiva. It may present with well defined margins or may be poorly demarcated as in diffuse variety making identification very difficult. Dilated feeder vessels are usually seen (Figure 1).

Patient may be asymptomatic or present with symptoms of chronic ocular irritation, foreign body sensation, redness. Rarely it may cause diminution of vision due to induced astigmatism.

Morphologically there are three types of lesions:

1. Gelatinous type (leukoplakic or papilliform): Commonest, placoid lesion with shiny velvety surface, and tufted vessels.
3. Diffuse variant: Shows radial growth pattern without well defined margin and may mimic chronic blepharocconjunctivitis. Corneal involvement in OSSN gives a ground glass appearance with well defined borders or a beaten metal appearance on retroillumination.

Histopathologically OSSN may be classified as mucoceridermoid, adenoid squamous, and spindle cell type according to the predominant cell type.

Differential Diagnosis

The differential diagnosis of OSSN includes pterygium, pinguecula, papilloma, keratoacanthoma, amelanotic nevus, malignant melanoma, dermoids, lymphoma, pseudoepitheliomatous hyperplasia.

Corneal lesions like pannus, keratinisation, epithelial basement membrane dystrophy, and herpes simplex virus keratitis also warrant consideration as differentials.

Diagnostic Modalities

Cytology: Desquamating corneal and conjunctival cells can be studied using exfoliative cytology which uses a cytobrush or platinum spatula for obtaining specimens; or impression cytology using cellulose acetate paper or biopore membrane. Smears thus obtained are stained by papanicolaou or giemsa stain after which dysplasia or metaplasia can be identified based on the cellular characteristics like nucleocytoplasmic ratio, pleomorphism, mitotic (Figure 1) loss of polarity.

Advantages

- Non invasive office procedure.
- Can be used to differentiate benign and malignant lesions.
- Can be used for surveillance for recurrence.
- Can be used as alternative to excision biopsy.

Disadvantages

- Unreliable for assessment of depth of invasion.
- Cannot differentiate between CIS and invasive carcinoma.
- Inadequate sampling like in cases with abundant surface keratin may yield false negative results.

Histopathology

- Gold standard.
- Excision biopsy for smaller lesions.
- Incisional biopsy for larger ill defined lesions.
Pre invasive OSSN can be classified as mild, moderate, or severe depending on the extent of dysplasia in the epithelium.

1. **Mild**: CIN grade 1 involves dysplasia in lower third of the epithelium.
2. **Moderate**: CIN grade 2 dysplasia involves middle third of the epithelium.
3. **Severe**: CIN grade 3 also called as carcinoma in situ where in dysplasia involves whole thickness of epithelium with intact basement membrane.

**Invasive carcinoma**: when basement membrane of epithelium is breached and cells infiltrate into stroma.

Complete pictorial documentation of the ocular surface with the lesion should be made on the Whatman's filter paper No. 16. Mention should be made of laterality and position of the lesion. Excised lesion with mucosal surface facing up, is to be placed on the filter paper with diagram with or without separate margins. Excised lesion mounted on the filter paper should be allowed to dry adequately (approx. 2–3 min) on the filter paper which causes adhesion of the tissue on the filter paper. This tissue on the filter paper is then submitted in 10% buffered formal saline and sent to histopathology laboratory.

**Anterior Segment Optical Coherence Tomography (ASOCT)**
- Non invasive.
- Disparity in reflectivity of normal and dysplastic epithelium is used.

OCT in ocular surface squamous neoplasia reveals epithelial thickening and increased reflectivity of the epithelium, and an abrupt demarcation from normal to abnormal tissue. Typically, there is sharp disparity in reflectivity of normal and diseased epithelium, allowing for exact localization of the tumor margins.

Newer ultra high-resolution, spectral- domain anterior segment OCT (UHR OCT) have a axial resolution of approximately 2um for evaluation of corneal pathologic features. The UHR OCT images of ocular surface squamous neoplasia may be helpful in the delineation of the tumor, and in the future may aid in the diagnosis as well as the ability to detect early subclinical recurrences.

**Confocal Microscopy**
Ocular surface cytological examination with in vivo confocal microscopy is a simple, safe, and relatively noninvasive diagnostic modality that can be used for the diagnosis and follow-up of patients with OSSN. In vivo confocal microscopy could help with the initial diagnosis of OSSN, identifying recurrences, monitoring of treatment and evaluating response to topical chemotherapeutic agents. In vivo confocal microscopy is capable to distinguish different stages of OSSN in all the cases. In vivo confocal microscopy is therefore a valuable tool in assessment of OSSN, especially in patients who are debilitated, terminally ill or cannot undergo invasive surgery. Confocal microscopes have a resolution of 4um.

**Limitation**: It can examine tissues to a maximum depth of 500um, therefore intra ocular extension cannot be detected.

**Management**
Although there is no agreed consensus regarding the management of OSSN, treatment of these tumors includes medical (topical and/or intralesional IFN-α2b, mitomycin C [MMC], 5-fluorouracil [5-FU]), surgical (simple excision and/or cryotherapy) or a combination of medical and surgical treatment options.

**Medical Management**

**A. Chemotherapy:**
Medical treatment of OSSN constitutes drugs like mitomycin-C (MMC) and 5 fluorouracil (5FU).

**Advantages**
- Inexpensive
- Treats whole ocular surface including dysplastic cells.
- Simple and reduced risk of limbal stem cell deficiency as compared to surgery.

**Disadvantages**
- Limited penetration in thicker tumors.
- Side effects on ocular surface and nasopharyngeal epithelium.

**Indications for chemotherapy:**
- Recurrence
- Diffuse lesion with clinically indistinguishable margins that cannot be removed completely by surgery.
- Positive edges after excision.
- Chemoreduction of large tumors before excision.
- Elderly debilitated patients who refuse or are unable to tolerate surgery.

MMC is used in concentration of 0.02-0.04% in cycles of 1 week treatment and one week off for 3-4 cycles. Drug free interval is given in between to allow for the growth and repair of normal healthy cells.

5FU 1% is used for 3-4 times a day continuously for 3-4 weeks or 3-4 times daily for 4-7 days with 30-45 days off and cycles repeated.
Special care is required while handling these chemotherapeutic agents and punctual plugs are recommended to protect the nasopharyngeal tissue.

Side effects of MMC include red eye, tearing, corneal erosions, punctuate epithelial keratopathy, pannus, dry eyes, limbal stem cell deficiency, tissue necrosis, cataract, punctual stenosis, and ectropion. 5FU have a similar side effect profile although these are less frequent when compared to MMC. These adverse effects can be avoided by close monitoring, proper patient education and punctal occlusion.

B. Immunotherapy

Immunotherapy particularly interferons have recently shown promising results in the treatment of OSSN. The IFN-α2b is low-molecular weight glycoprotein, produced by leukocytes, has antineoplastic and antiviral properties. It works through a number of mechanisms, like slowing the cellular growth cycle and promoting the body’s immune and antitumor response.

Topical IFN-α2b is preferred for OSSN, which are relatively thinner for complete tumour control (immunotherapy) while combination therapy with topical and injection IFN-α2b is used for partial reduction of thicker and extensive OSSN (immunoreduction).

IFN-α2b can be administered via topical drops, subconjunctival injections or intralesional injections. With drops, clinical resolution usually takes place with a mean treatment time of about 12 weeks. Subconjunctival injection combined with topical IFN-α2b for noninvasive OSSN has a faster time to resolution, about six weeks.

A typical regimen consists of topical IFN-α2b drops with a concentration of 1-3 million IU/mL, applied four times daily; or subconjunctival injections of 3 million IU/0.5 mL, administered weekly. Intralional IFN-α2b (10 million IU/mL) has been used in giant OSSN (≥6 limbal clock-hours).

Occasional flu-like symptoms and ocular surface irritation are sometimes seen in patients after treatment with IFNα2b but overall cytotoxic profile is better than chemotherapeutic agents. Cost of IFNα2b remains to be a major limiting factor for IFN alpha 2-b therapy.

Advantages
- Treats microscopic disease also that may be present throughout ocular surface.
- Can be used for tumors resistant to chemotherapy.
- Can be used for recurrent tumors.

Disadvantages
- Are more toxic than chemotherapeutic agents.
- Longer duration of treatment is required, therefore usually not started as first line of therapy.
- Cost of interferons remains a limiting factor.

C. Photodynamic Therapy

Photodynamic therapy (PDT) has also been tried for OSSN. PDT relies on the use of verteporfin, an intravenously applied, light-sensitive dye with a high affinity for abnormal blood vessels. When this photosensitizer is exposed to light of 689 or 692 nm, direct cell death and immune-mediated destruction of the adjacent tissue can occur. Barbazetto et al. have used 6 mg/m² body surface of verteporfin and a light dose of 50 J/cm² after the injection. PDT has shown very promising results in localized tumor regression and can be considered as a useful adjuvant for the treatment of patients with OSSN, especially when localized at the conjunctiva.

D. Other Nonsurgical Therapies

Alternative treatments have been used, including use of external beam radiation, strontium 90 radiation, dinitrochlorobenzene (an immunomodulator), urea, retinoic acid, anti-VEGF and phototherapeutic keratectomy with the excimer laser. All of these methods of treatment have been used with variable success rate and their role in OSSN is not well defined.

E. Combined Medical Treatment

In refractory OSSN cases, various chemotherapeutic agents can be used sequentially or as a combined treatment.

Surgical Management

Complete excision with adequate margins is the treatment of choice for most localized lesions. Alcohol assisted keratepitheliectomy and lamellar sclerokeratoconjunctivectomy can be done for corneal and infiltrative lesions.

‘No-touch’ Surgical Technique

Tumor resection is done under peribulbar anesthesia. Phenylephrine 2.5% drops are used to induce vasoconstriction, thus reducing perioperative bleeding and allowing better visualization of the corneal advancement of the tumor. A wide surgical excision is done to maximize the chances of complete removal. Dissection of all abnormal tissue with a wide surgical conjunctival margin of 3-4 mm is usually sufficient. Rose Bengal / Lissamine green staining is helpful to delineate the margins of the lesion. After outlining the borders of the tumor, 4-mm margins are marked with the help of calipers at the scleral edges. 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. The conjunctiva is lifted with forceps and incision is made with a conjunctival scissors. Initial tumor dissection is localized to the marked margins and any contact of the tumor with the surgical instruments is avoided to stop tumor seeding.
After completion of the dissection of the peripheral marked margins, the dissection is directed toward the center of the tumor. In the event of tumor adherence to the sclera, a partial thickness sclerectomy is performed with crescent knife. The use of absolute alcohol on the corneal side of the lesion to facilitate epithelial removal as one sheet i.e alchohleopithelectomy, is recommended. Once the lesion is removed en bloc, the specimen is marked in the proper orientation with sutures and then transferred to a piece of pencil-marked paper or the excised conjunctival specimen is placed on an absorbent paper and air-dried to prevent loss of orientation. The specimen is sent for histopathology in formalin. Conjunctival defect so created can be closed primarily (if less than three clock hours in diameter). Larger defects require either transpositional conjunctival flaps, free conjunctival flaps from the other eye, or amniotic membrane grafts. Frozen section can be used to assess the adequacy of excision, and is accurate in delineating horizontal tumor spread. Bunns modification of Moh’s technique of tumor margin surveillance may also be used. In this the free conjunctival edges are excised by 2 mm if residual tumor is evident even after excision of a 2 mm surgical margin.

Advantages
- Surgery is diagnostic as well as therapeautic it decreases tumor bulk.
- Provides specimen for histopathological examination.

Disadvantages
- High recurrence rate if surgery alone is used.
- Cannot be used in individuals who refuse surgery.

Complete removal of tumor is confirmed by histopathological examination of conjunctival margins which are sent separately. Negative surgical margin is the most important predictor for tumour recurrence. Recurrence rates are reported to range from 5% to 33% after negative margins to as high as 56% in those where margins were found to be positive21.

Cryotherapy applied to resected margins and at tumor base can be used as an adjunctive to surgery. It acts by causing ischaemic necrosis and direct destruction of the tumor cells. A nitrous oxide cryoprobe tip (2.5 or 5mm) is used to form an ice ball extending 2mm for conjunctiva, 1mm for episcleral tissue and 0.5mm for the cornea. A slow duration freeze with a slow thaw, repeated two to three times (freeze-thaw-refreeze) is recommended. It is important to include the limbal region during cryotherapy, and not apply the cryoprobe for more than three seconds.

Topical MMC in concentration of 0.02-0.04% can also be used intraoperatively.

Treatment of Recurrent OSSN

Recurrent OSSN is managed on the same management lines as the primary occurrence. However, a longer duration and/or higher concentration of Mitomycin-C may be required in cases which were treated and cured initially with Mitomycin-C. Secondly, recalcitrant cases have a higher probability to be resistant to Mitomycin-C and may eventually require surgical excision. In refractory OSSN cases, various chemotherapeutic agents can be used sequentially or as a combined treatment.

The patients with recurrent ocular surface squamous neoplasia can also be treated by triple combined therapy (excision of lesion with cryotherapy of limbus and conjunctival margin followed by Mitomycin-C 0.02% application at the time of surgery). It is very effective therapy for recurrent ocular surface squamous neoplasia. It is relevant for cases in large, poor countries where patients present late and are less likely to come for follow-up care22.

Prognosis

OSSN is a low grade malignancy with overall good prognosis and low incidence of lymph node or distant metastasis. Most significant prognostic factor for recurrence is presence of neoplastic cell in margins after tumor excision. Aggressive variants like muco-epidermoid and spindle cell carcinoma and OSSN in immunocompromised patients have a poorer prognosis.

References


