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Ocular Surface Squamous Neoplasia

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1. Introduction

The ocular surface is composed of the conjunctiva and the cornea. The conjunctiva is a mucous membrane which covers the globe and inner part of the eyelids. The morphology of conjunctival epithelial cells are nonkeratinized stratified epithelia which vary from cuboidal over the tarsus, to columnar in the fornices, to squamous epithelia on the globe. Goblet cells account for up to 10% of the basal cells of the conjunctival epithelia. The substantia propia of the conjunctiva consists of loose connective tissue. The cornea is a transparent, avascular tissue which acts as both the anterior eye wall and an optical media for light to enter the eye. The corneal epithelium layer is composed of stratified squamous epithelial cells and makeup about 5 % (0.05 mm) of the total corneal thickness. The corneal epithelial stem cells located at the basal layer of the limbal epithelia proliferate continuously and give rise to the superficial layer that subsequently differentiate into superficial cells. Regulation of cell growth and metabolism are critical to maintain an intact ocular surface and transparent cornea.

Primary tumors of the conjunctiva and cornea can be grouped into two major categories: congenital and acquired. The acquired lesions are composed of a variety of neoplasms which originate from squamous epithelia, melanocytes, and lymphocyte cells. Tumors of squamous epithelium occupy a large spectrum of lesions, ranging from benign lesions like squamous papilloma, to precancerous lesions which are confined to the surface epithelium (intraepithelial neoplasia or dysplasia, previously known as Bowen's disease). There are even more invasive squamous cell carcinomas that break through the basement membrane to the underlying substantria propia of the conjunctiva or corneal stroma.

The term ocular surface squamous neoplasia (OSSN) was first described in 1995 by Lee and Hirst to denote a spectrum of neoplasm originate from squamous epithelium ranging from simple dysplasia to invasive squamous cell carcinoma(SCC), involving the conjunctiva, the limbus, and the cornea.(Lee & Hirst 1995) Similar to cancer of cervix, it has a relative high recurrence after treatment and may metastasize. This tumor is considered as a low grade malignancy but invasive lesion can spread to the globe or orbit. This chapter highlights the epidemiology, etiologies and related factors, clinical manifestations, diagnostic tools, and standard care of management of these tumors. Squamous papilloma is also included as some conjunctival papilloma may have dysplastic potential.

2. Epidemiology and pathogenesis

OSSN is considered an uncommon disease with geographic incidences which vary from 0.2 to 3.5 per 100,000, with greater frequency near the equator. (Lee & Hirst 1995) It is the most common ocular surface tumor in many series.(Lee & Hirst 1995; Shields et al. 2004; Shields & Shields 2004) Prior to HIV pandemic, OSSN was noted to occur predominantly in the elderly for whom it was the third most common oculo-orbital tumor after malignant melanoma and lymphoma. (Lee & Hirst 1995) This tumor is rare in the United States, with an incidence rate of 0.03 per 100,000 persons, although the rate was approximately 5-fold higher in males and Caucasians (Sun et al. 1997).

Pathogenesis of OSSN has yet to be attributed to specific etiologic factors, the main associated factors being exposure to ultraviolet (UV) radiation, human papilloma virus infection, and human immunodeficiency virus (HIV) seropositivity.

2.1 Ultraviolet-B

Chronic exposure to UV–B radiation (290-320 nm) is an established cause of many eye diseases such as pingecular, pterygium, cataract, and age-related macular degeneration. (Taylor et al. 1992) Evidence from epidemiologic studies and worldwide cancer registries have confirmed that the incidence rate of OSSN increased with proximity to the equator, presumably from increased solar UV radiation. (Lee et al. 1994; Newton et al. 1996) One population-based cancer study found that the incidence of squamous cell carcinoma(SCC) of the eye declined by 49% for each 10 degree increase in latitude, falling from more than 12 cases per million per year in Uganda, to less than 0.2 cases per million per year in the UK. The incidence of SCC decreased by 29% per unit reduction in UV exposure. (Newton et al. 1996) There is considerable evidence linking cutaneous malignancy and UV exposure. (English et al. 1997) These lesions occur predominantly in sun-exposured areas of the skin. Lesions of OSSN are often found at the corneal limbus in the interpalpebral area, where sun-exposure is greater. The corneal limbus is a transitional area, from the conjunctival to corneal epithelial, analogous to the squamocollumnar junction of the uterine cervix which is prone to dysplastic change. The role of limbal stem cells in development of OSSN is controversial. These cells are long-lived and have great potential to clonagenic division. OSSN may arise from dysfunction limbal stem cells and from mutagenic agents such as UV radiation leading to mutations in the P53 tumor suppressor gene, also known as *TP*53 gene. One pilot case-control study found that the *TP*53 mutation was detected in 56% of cancer cases (SCC) and 14% of control. 50% of mutations were CC-TT transition which was a molecular signature of mutagenesis by solar UV rays. This prevalence was high compared to any cancer type (not exceed 6%), but matched that of skin cancer in subjects with xeroderma pigmentosum.(Ateenyi-Agaba et al. 2004) Solar elastosis was also found more frequently in pathological specimens from the conjunctival squamous cell neoplasia (53.3% of cases and 3.3% of controls). (Tulvatana et al. 2003) One immunohistochemical study showed that UV radiation may play a role as a stimulating agent in the expression of some proteolytic enzymes, such as matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), which are relevant to neoplasia. (Ng et al. 2008)

2.2 Human papilloma virus

Human papilloma viruses (HPV) are oncogenic viruses and their role in human cervical carcinoma is well-established, however, their role in OSSN is unclear. Nakamura demonstrated that 50% of squamous tumors of the ocular surface and lacrimal sac were associated with HPV. (Nakamura et al. 1997) Biopsy specimens together with analyses of archrival embedded tissue revealed that the low risk HPV type 6 and 11 were the most common types of viruses associated with conjunctival papilloma. (Sjo et al. 2007; Verma et al. 2008) The high risk HPV type 16 and 18 have also been demonstrated in conjunctival papilloma, however, both are commonly found in high grade dysplasia, or invasive squamous cell carcinoma of the conjunctiva. (Sjo et al. 2007; Verma et al. 2008) One study identified the DNA of HPV 16, 18, and mRNA from the *E6* region, which represented active transcribed viruses from all specimens of conjunctival intraepithelial neoplasia by using the PCR technique (n = 10). (Scott et al. 2002)

In contrast, several studies have failed to demonstrate HPV in malignant conjunctival epithelial tumors and suggested that HPV was not associated with malignant conjunctival lesions and posed other mechanism, such as UVB being more important to the etiology of these lesions. (Eng et al. 2002; Tulvatana et al. 2003; Sen et al. 2007; Manderwad et al. 2009) Thus, the association between HPV and OSSN is variable in different geographic areas, and perhaps depends on the method of detection used. (Eng et al. 2002; Sen et al. 2007; Guthoff et al. 2009; Manderwad et al. 2009)

2.3 Human immunodeficiency virus

OSSN is now recognized as an AIDS-related cancer and its incidence has increased with the HIV pandemic in Africa. (Porges & Groisman 2003) One study revealed that HIV was strongly associated with conjunctival squamous neoplasia in Africa with an odds ratio of 13 (HIV was positive in 71% of cases and 16% of controls). (Waddell et al. 1996) A case-control study of conjunctival SCC in Uganda demonstrated a 10 fold increased risk of conjunctival SCC in HIV-infected patients. (Newton et al. 2002) These tumors occurred at an earlier age in HIV-infected individuals and was often more aggressive than immunocompetent patients. OSSN may be the primary or only apparent manifestation of HIV infection in sub-Saharan Africa. (Spitzer et al. 2008) SCC can also involve other non-ocular sites such as the oropharynx, cervix, and anorectum.(Jeng et al. 2007) One study from the US found that there was an increased prevalence of HIV among patients with CIN who were younger than 50 years of age. (Karp et al. 1996) A HIV/AIDS Cancer Match Registry Study in the USA, however, demonstrated that the risk of conjunctival SCC was elevated regardless of HIV category, CD4 lymphocyte count, and time relative to AID-onset. The risk was highest with age≥ 50, Hispanic ethnicity, and residence in regions with high solar-UV radiation. (Guech-Ongey et al. 2008) Tissue analysis from OSSN specimens in HIV-1 patients identified multiple oncogenic viruses including HPV, EBV, and KSHV, suggested that these infectious agents may contribute to the development of this malignancy in HIV patients. (Simbiri et al. 2010)

2.4 Immunosuppression

Of note, OSSN shares some striking similarities to skin neoplasm. It is believed that localized immune suppression of the skin from sun damage may lead to increased

susceptibility to HPV infection, causing neoplasia. Additional risks have also been reported in immunosuppressed cancer patients and organ transplant patients. (Shelil et al. 2003; Shome et al. 2006) As well, there have been reports of OSSN after corneal grafts, which may partly be related to local immunosuppression, HPV, or possibly that neoplastic cells had been in the donor corneal epithelia at the time of transplantation. (Ramasubramanian et al. 2010)

2.5 Others

Other factors associated with this condition include old age, the male sex (Lee & Hirst 1995; Sun et al. 1997), and fair skin pigmentation (Lee et al. 1994; Sun et al. 1997), as well as heavy cigarette smoking (Napora et al. 1990), exposure to petroleum products (Napora et al. 1990), and some genetic conditions like xeroderma pigmentosum. The latter is an uncommon genetic disorder, where excessive reactivity to UV light-induced damage results in a more malignant course. It is common in early childhood with severe photosensitivity and photophobia. (Kraemer et al. 1987; Chidzonga et al. 2009) Long standing use of ocular prosthesis (Jain et al. 2010)and contact lens wear (Guex-Crosier & Herbort 1993) have also been implicated in the pathogenesis of OSSN, although evidence is scant.

3. Clinical manifestations

The clinical spectrum of OSSN varies from benign lesions like squamous papilloma, precancerous lesions like conjunctiva-corneal intraepithelial dysplasia (CCIN), carcinoma in situ, and invasive squamous cell carcinoma (SCC).

3.1 Conjunctival papilloma

Squamous papillomas are among the most common benign acquired lesions of the conjunctiva. There are two forms of conjunctival papilloma: pendunculated and sessile. Both have different etiology and clinical courses. A pedunculated conjunctival papilloma is a fleshy, exophytic mass with a fibrovascular core which gives rise to a stalk. (Fig.1) It often arises in the inferior fornix, but can be present on the tarsus or bulbar conjunctiva. This lesion is associated with HPV subtype 6 or 11 (Sjo et al. 2007), and often occurs in children. It can regress spontaneously, or may recur after surgical excision.

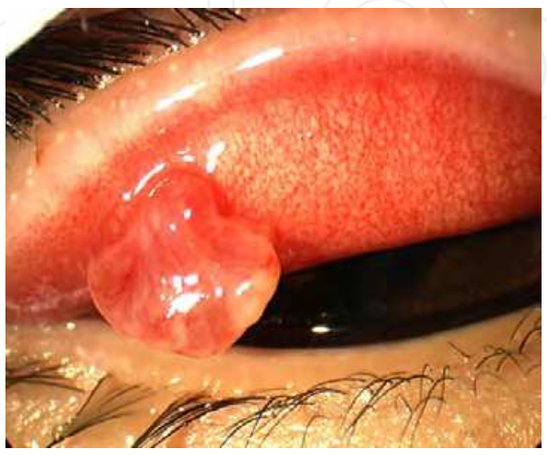

Fig. 1. Penduculate conjunctival papilloma arising from upper palpebral conjunctiva.

A sessile papilloma is more typically found at the limbus and has a broad base. The glistening surface and numerous red dots resemble a strawberry. (Fig.2) In contrast, a sessile lesion usually occurs in adults and more prone to dysplastic change. This lesion is related to HPV subtype 16 or 18. The latter oncogenic virus strains are strongly associated with human cervical carcinoma.

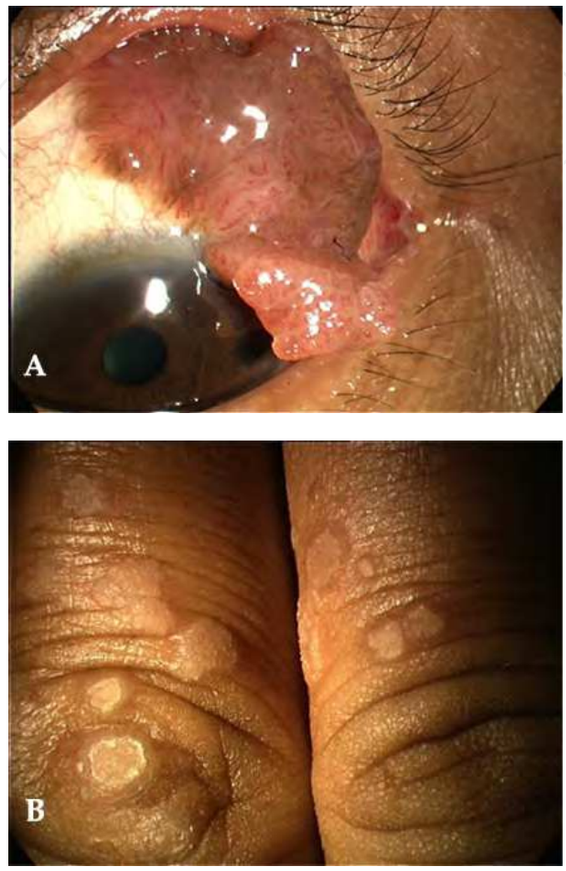

Fig. 2. A. Sessile mass arising from bulbar conjunctiva. B. Multiple papillomas involve skin of two fingers in the same patient.

3.2 Conjunctival-corneal intraepithelial neoplasia

The clinical symptoms are generally nonspecific, vary from asymptomatic to chronic irritation, redness, and varying degrees of visual involvement determine by the extension of lesions to the visual axis. Clinical patterns may be in a papilliform, as well as velvety, gelatinous, leukoplakic, nodular or even diffuse fashion. (Fig. 3-5) The lesions most commonly arise in the interpalpebral area of perilimbal conjunctiva, but are less common in the forniceal or palpebral conjunctiva. A white plaque (leukoplakia) may occur on the surface of the lesion, representing secondary hyperkeratosis, which results from squamous cell dysfunction. The conjunctival lesion is mobile with feeder vessels supplying the mass. These tumors may appear as slowly growing localized lesions that mimic benign conjunctival degenerations, and sometimes coexist with pterygia or pingecula. (Hirst et al. 2009) Sometimes, the lesions can have pigmentation and masquerade as malignant

melanoma. (Shields et al. 2008) (Fig.6) OSSN can be diffused or have bilateral involvement. (Fig.7) Corneal OSSN is usually an extension of conjunctival squamous neoplasia. Rarely, isolated corneal involvement has been reported with the potentially aggressive form. (Fig.8) Bowman's layer usually is a barrier to invasive lesions. (Cha et al. 1993)

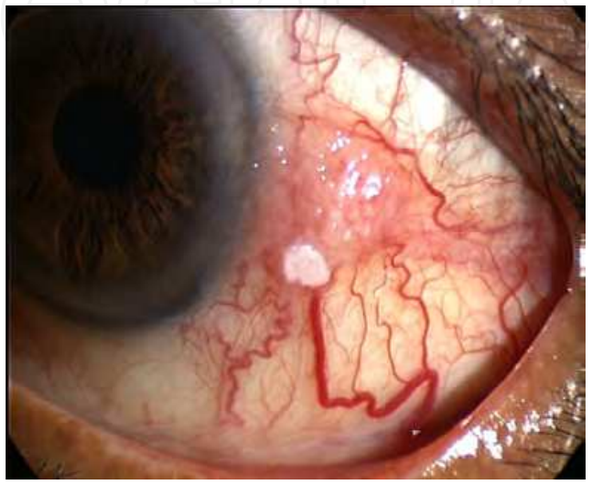

Fig. 3. Conjunctival intraepithelial neoplasia is present as a nodular mass with foci of leukoplakia on the surface of the lesion.

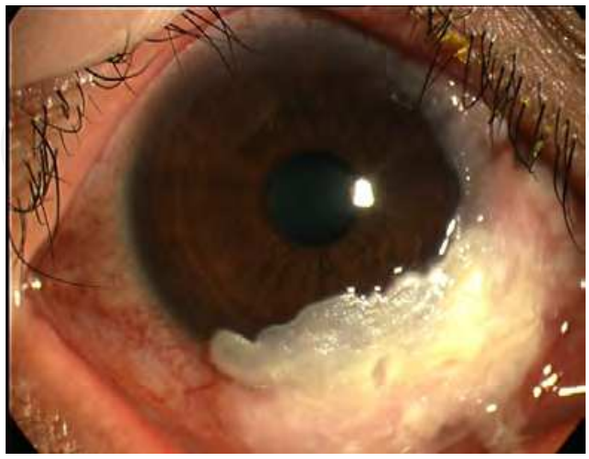

Fig. 4. Conjunctival-corneal intraepithelial neoplasia: a flat gelatinous mass with surface leukoplakia involves 2 quadrants of limbus.

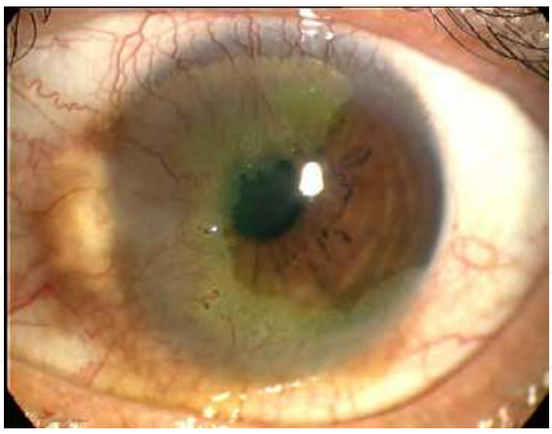

Fig. 5. Corneal intraepithelial neoplasia involving 270 degrees of the limbus (note vascular tuffs present on the mass)

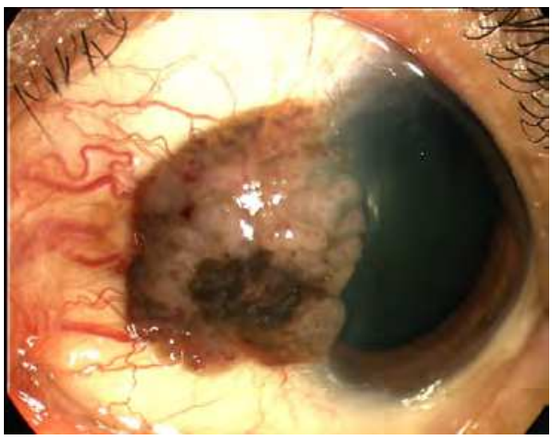

Fig. 6. Conjunctival-corneal intraepithelial neoplasia presents as a nodular mass with papillomatous pattern and hyperpigmentation (note feeder vessels are present).

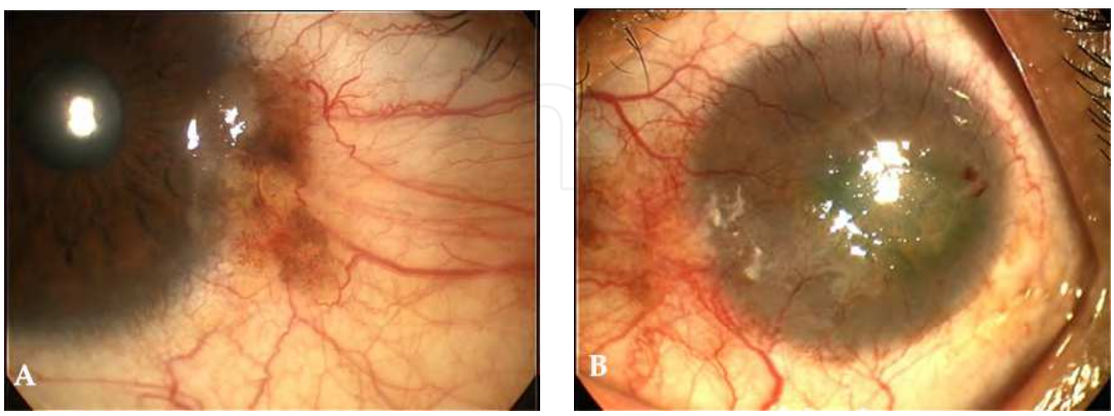

Fig. 7. Bilateral conjunctival-corneal intraepithelial neoplasia in an HIV-infected patient. A. Pigmented lesion with fibrovascular fond arising at the limbus. B. Diffused, flat lesion involving 360 degrees of the limbus (note central corneal epithelia defect is present in the photograph).

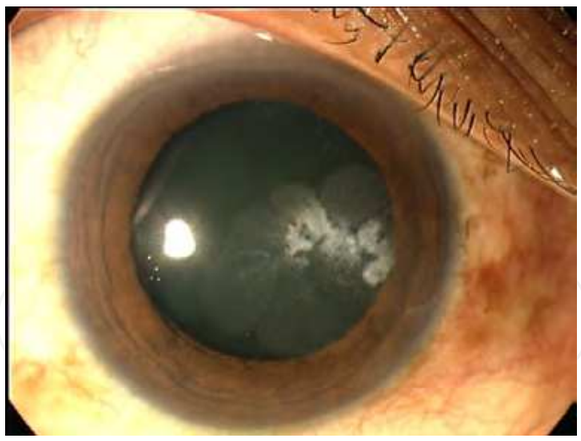

Fig. 8. Corneal intraepithelial neoplasia is present as a flat grayish mass with a fimbriated border and surface keratinization.

3.3 Squamous cell carcinoma

Squamous cell carcinoma is the final stage of this tumor where dysplastic epithelial invade beyond the basement membrane to the conjunctival substantia propia or corneal stroma. Clinically, invasive squamous cell carcinoma is generally larger and more elevated than CIN. (Fig.9) In practice, it may not be possible to distinguish invasive squamous cell carcinoma from intraepithelial lesion or carcinoma in-situ by using clinical features alone. However, an advanced lesion or mass that is immobile and fix to the globe should be suspected as an invasive lesion. A long term neglected mass or incomplete excised mass can invade through the globe or orbit. (Fig.10)

Local invasion is the most prevalent mechanism of tumor spread. Intraocular invasion may be associated with iritis, glaucoma, retinal detachment, or rupture of the globe. Metastases are rare, and the first site of extraocular involvement is regional lymph nodes.

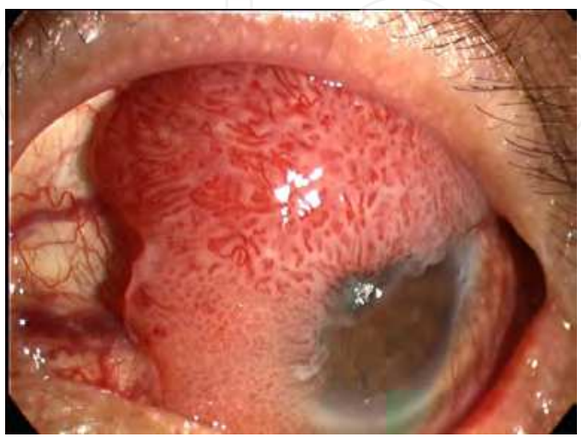

Fig. 9. Invasive squamous cell carcinoma involves two quadrants of conjunctiva and cornea (note papillary vascular pattern present on the mass with feeder vessels).

A rare variant of conjunctival squamous cell carcinoma is the mucoepidermoid carcinoma. Clinically, this tumor occurs in older patients and has a yellow globular cystic component due to the presence of abundant mucous-secreting cells within cysts. It tends to be more aggressive than the standard squamous cell carcinoma, thus deserves wider excision and closer follow-up. The spindle cell variant of squamous cell carcinoma is likewise aggressive. (Shields et al. 2007)

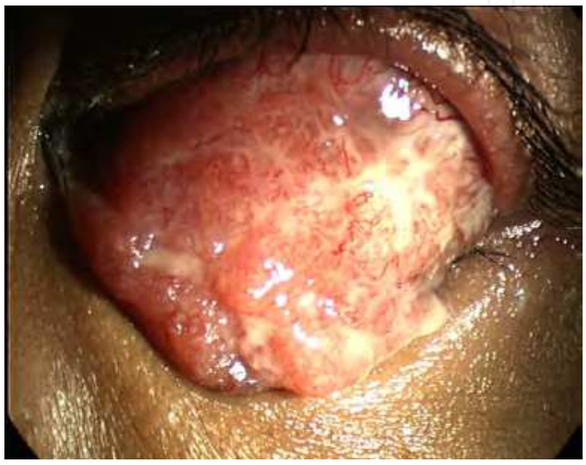

Fig. 10. An advanced squamous cell carcinoma involves the entire cornea and conjunctival surface with protrusions of the mass onto the lower eyelid.

4. Diagnosis and investigations

There are several points to cover before reaching diagnostic and management planning for OSSN, including clinical and pathologic findings, as well as the extension and complications of the tumors.

- Clinical feature of the lesion: morphology, size, site, surface, feeder vessels, and exact anatomical location whether it is conjunctival (move with conjunctiva when applying topical anesthesia with cotton tip applicator) or scleral involvement (fixed to the globe).
- Assessment of extension of the lesions
  - Intraocular invasion: perform gonioscopy to assess the invasion angle of the tumor. (Fig.11) Dilated fundus examination should be done to assess the intraocular invasion. In cases with media opacity, B-scan ultrasonography is helpful to assess sclera and intraocular spread.
  - Orbital invasion: by using CT scans or MRI scans, the accuracy and extension of the mass can accurately assess for the orbital or anterior eye involvement.
  - Regional lymph node spread: it is critical to assess the regional lymph nodes (preauricular, submandibular and cervical lymph nodes) as part of the clinical examination.

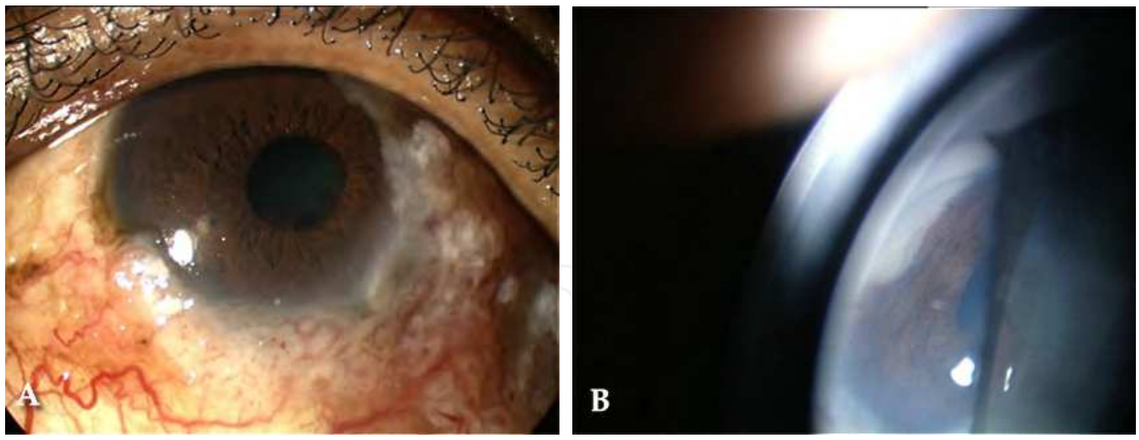

Fig. 11. Squamous cell carcinoma A. Diffused mass involves more than two quadrants of the limbus. B. Gonioscopic findings in the same eye show angle invasion by the mass.

- Pathologic diagnosis

  Since clinical appearance alone may not differentiate intraepithelial from invasive lesions, the gold standard for definite diagnosis is tissue histology, which can be performed by incisional or excisional biopsy. For relatively small tumors (≤ 4 clock hours of limbal involvement or ≤ 15 mm basal diameter), excisional biopsy is generally preferred to incisional biopsy. Larger lesions can be approached by wedge or punch biopsy. Incisional biopsy is also appropriate for conditions that are ideally treated with topical chemotherapy, or other treatments, such as radiation.

4.1 Histology

Histologic features of OSSN can be classified according to the presence of dysplastic cells originating in the basal cell layers which extend toward the surface. There are various patterns of dysplastic changes, ranging from the small squamous cells with increased nuclear-to-cytoplasmic (N/C) ratio, large squamous cells with hyperchromatic nuclei, and spindle cells bearing oval-shaped nuclei. The dysplastic cells contain abnormal nuclei either with nuclear pleomorphism or anisonucleosis. In addition, mitotic figures are increased and gradually pushed upward to the surface along with the degree of dysplasia. Many mitotic figures are abnormal. The histologic terms used to describe the OSSN include(Font et al. 2006):

- *Dysplasia*: dysplastic epithelial lesions of the conjunctiva and cornea divides into three grades based on the thickness of intraepithelial involvement. Koilocytes are rarely identified but suggestive for HPV infection when encountered. The thickness of involvement can be estimated using Periodic acid-Schiff (PAS) stain to demonstrate the presence of glycogen in non-neoplastic superficial squamous cells. Moreover, proliferating cell nuclear antigen (PCNA), Ki-67 and p53 immunostaining as well as argyrophillic nucleolar organizer region (AgNOR) staining may be useful for grading the dysplastic lesions as well as for correlation with clinical morphologic findings. (Aoki et al. 1998) Grading of dysplasia is described as:
  - Mild – less than a third thickness of the epithelium is occupied by atypical cells.(Fig.12A)

  - Moderate - within three quarters thickness of the epithelium is occupied by atypical cells.
  - Severe – nearly full thickness of the epithelium is occupied by atypical cells.(Fig.12B)
- *Carcinoma in situ*: full-thickness epithelial neoplasia with loss of the normal surface layer. (Fig.12C) Arborizarion of the proliferating blood vessels and extension of connective tissue along the neoplastic area may mimic the sessile papilloma.(Pizzarello & Jakobiec 1978)
- *Invasive squamous cell carcinoma*: the entire thickness of the epithelium has been replaced by the dysplastic cells and the basement membrane of the basal epithelial layer has been breached due to invasion of dysplastic cells into the substantia propia. Formation of cancer cell nests and single cancer cells with bizarre nuclei in the stroma is definitive of invasive carcinoma.(Tunc et al. 1999) (Fig.12D)

4.2 Cytology

Ocular surface cytology can be performed by two major techniques:first is exfoliative cytology by using spatula scrapings or a cytobrush to collect the sample, and second is impression cytology by using the collecting devices to collect the sample by contact with the surface of the lesions. The cytologic features of OSSN have been reviewed by several authors.(Lee & Hirst 1995)

- *Dysplasia*: Squamous cells with enlarged nuclei bearing fine to coarse granulation of the nuclear chromatins, irregular nuclear borders, scanty cytoplasm. The background is clean.
- *Carcinoma in situ*: Variable numbers of dysplastic cells with an admixture of intact and well preserved malignant cells. They are variable in size with scanty cytoplasm, usually < 1 nuclear diameter in width. The enlarged nuclei displays neoplastic features of hyperchromatism, irregular nuclear membrane thickening, or crusting of nuclear membranes. The other nuclear features include abnormal clearing or condensation of nuclear chromatins and large acidophilic nucleoli. However, background of the smear is clean.
- *Invasive squamous cell carcinoma*: Cytologic features of the SCC have been graded into two groups.
  - Grade 1-2: Marked cytologic aberration with bizarre malignant cell features including tadpole cells with cytolplasmic tails, fiber or spindle cells, hyperkeratinized cells with opaque refractile red or orange cytoplasm, and malignant nuclei.
  - Grade 3-4: Large or small cancer cells with scanty cytoplasm. Nonkeratinized cells maybe partially destructed cells, or complete loss of cytoplasm bearing large to huge pleomorphic nuclei. With deeper invasion and ulceration, tumor "diathesis" background- necrotic tumor cells, debris, blood, and leukocyte exudates are more prominent.

The advantages of cytology are a simple technique in diagnosis and follow-up after treatment in OSSN, particularly for detection of recurrences. However, some problems have been reported in exfoliative cytology techniques which may include a degree of uncomfort for the patient, problems with drying artifacts, problems with cellular overlap (difficult to interpret the specimens reliably) and non-localized lesions.

Impression cytology (IC) is a technique for collecting the superficial layers of the ocular surface by applying collecting devices. Commonly used are cellulose acetate filter paper with a pore size ranging from 0.025 – 0.45 micron or other materials (nitrocellulose filters, Biopore membranes, or polyether sulfone filters)(Calonge et al. 2004) so that cells adhere to the surface of the device and can be removed and processed further for analysis by a diversity of methods. IC represents a simple and non-invasive technique for both diagnosis and follow-up after treatment of several disorders of the ocular surface. The main advantages are that it allows relatively easy collection of epithelial samples with minimal

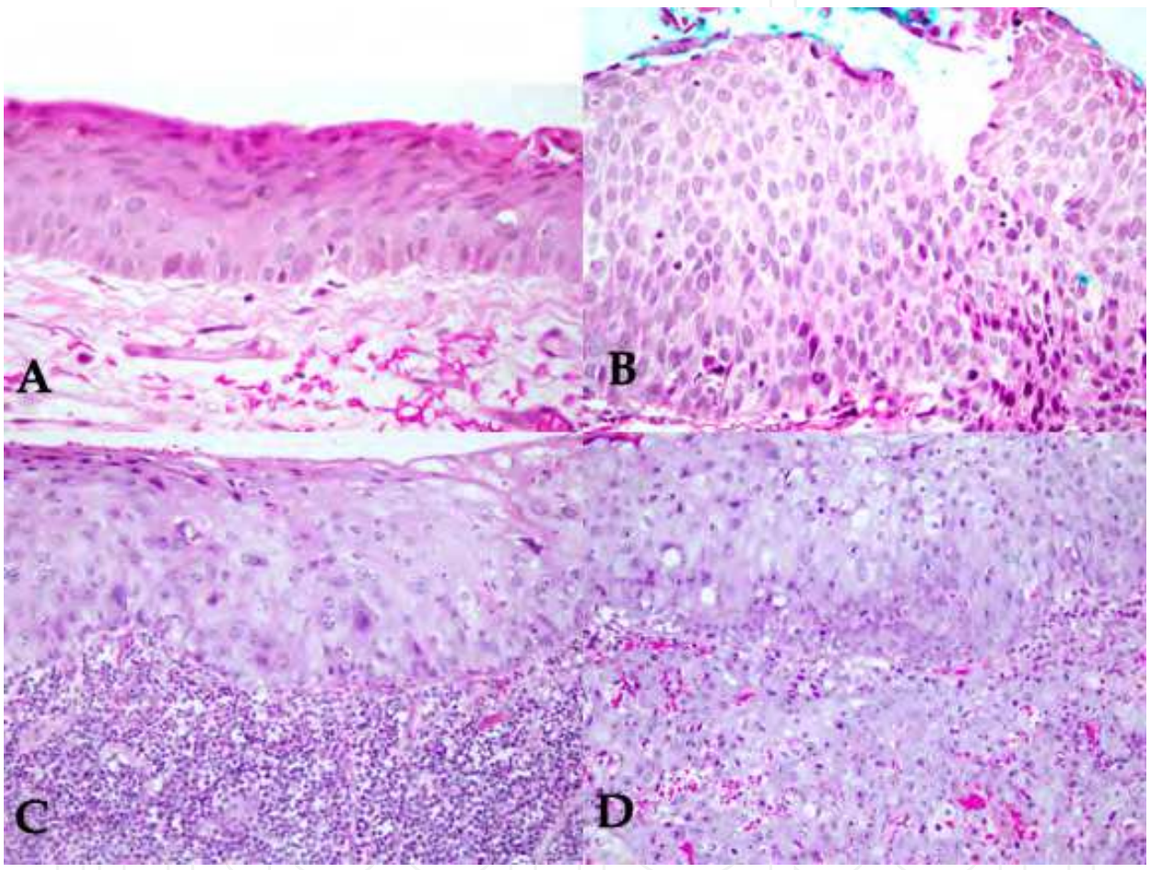

Fig. 12. Histologic features. A. Mild dysplasia; the basal cells are disordered with increased nuclear sizes and coarse nuclear chromatin. B. Severe dysplasia; the epithelial cells are varied in shapes and sizes with large pleomorphic nuclei. The surface cells are flattened with pyknotic nuclei. C. Carcinoma in situ: the entire thickness of the epithelium is composed of dysplastic cells bearing pleomorphic nuclei. Note the inflammatory reaction in the stroma. D. Invasive squamous cell carcinoma; the invasive nest in the stroma is composed of bizarre cells similar to those in the epithelium. The nuclei are plemorphic with thick nuclear membranes and prominent nucleoli (Hematoxylin and Eosin stain. Original magnification X40)

discomfort to the patient, can be performed on an outpatient basis, and allows more precise localization of the area being studied. In addition, a cell to cell relationship can be assessed, which allows one to see cells the way they exist in vivo.

Successful results of IC in diagnosis of OSSN in histologic-confirmed cases have been reported, with positive results of 77% - 80% of the cases.(Nolan et al. 1994; Tole et al. 2001) One study of ocular surface tumors found that IC had a positive and negative predictive value of 97.4% and 53.9%, respectively, when compared to histology.(Tananuvat et al. 2008) The limitations of IC are that, first, IC may be less sensitive for cases with keratotic lesions, because keratotic lesions are common in OSSN (68%) compared with a much lower incidence in cervical cancer. Second, IC may not distinguish carcinoma in situ from minimally invasive disease, because only the superficial cells are collected in the IC method. Therefore, a tissue biopsy remains necessary in cases with negative cytology.

At present, no cytologic criteria have been identified that reliably differentiate invasive carcinoma from in situ in IC samples. Squamous cell abnormalities may be classified into 4 groups, using a modification of the Bethesda system in cervical cytology(Solomon et al. 2002): (1) atypical squamous cells (ASC) (Fig.13 B); (2) low grade squamous intraepithelial lesions (LSIL), which encompass squamous papilloma and mild dysplasia(Fig.13 C); (3) high grade squamous intraepithelial lesions (HSIL), which encompass moderate to severe dysplasia and carcinoma in situ (CIS) (Fig.13 D-E); and (4) squamous cell carcinoma (SCC).(Fig.13 F) One series of OSSN found that SCC from cytology had a highest rate of correlation(91.7%) with histology followed by HSILs (45.5%), ASCs(42.9%),normal epithelia (33%), and LSILs (21.4%), respectively.(Tananuvat et al. 2008) Barros and coworkers used a scoring index modified from the Bethesda system which revealed a predictive index score of ≥4.5 represented the best cut-off point for diagnosis of SCC by using IC with a sensitivity of 95%, specificity of 93%, positive predictive value of 95%, and a negative predictive value of 93%.(Barros et al. 2009) However, the skill and the experience of cytologist are necessary for interpretation of the IC specimens.

4.3 Immunohistochemical analysis: Ki-67 proliferative index

Ki-67 nuclear antigen is expressed in all phases of the cell cycle, except the G0 phase. Ki-67 immunohistochemical analysis has been applied in the histopathologic diagnosis of malignant tumors. In normal cervical squamous mucosa, Ki-67 positive cells are found mainly in the parabasal layer. In cervical squamous intraepithelial lesions (SILs), the number of Ki-67 positive cells increased as the cell grading went from normal to low grade SIL(LSIL) to high grade SIL(HSIL). Similar findings have been reported in case of conjunctival SCC and intraepithelial neoplasia. One study compared tissue specimens obtained from SCC, CIN, and non-CIN (pterygium) lesions, revealed that Ki-67 proliferative index (Ki-67 PI) was significantly higher in SCC and CIN than in pterygium.(Ohara et al. 2004) In another study, the Ki-67 PI of CINs accounted for 20-48% which was significantly higher than non-CIN lesions (8-12%) and normal conjunctivae (8-12%). This study also showed that there was no statistical significance of P53-positive cells in CIN lesion compared to non-CIN lesions and normal conjunctiva due to the wide standard deviations. (Kuo et al. 2006) Therefore, Ki-67 PI may serve as a meaningful diagnostic marker for OSSN.

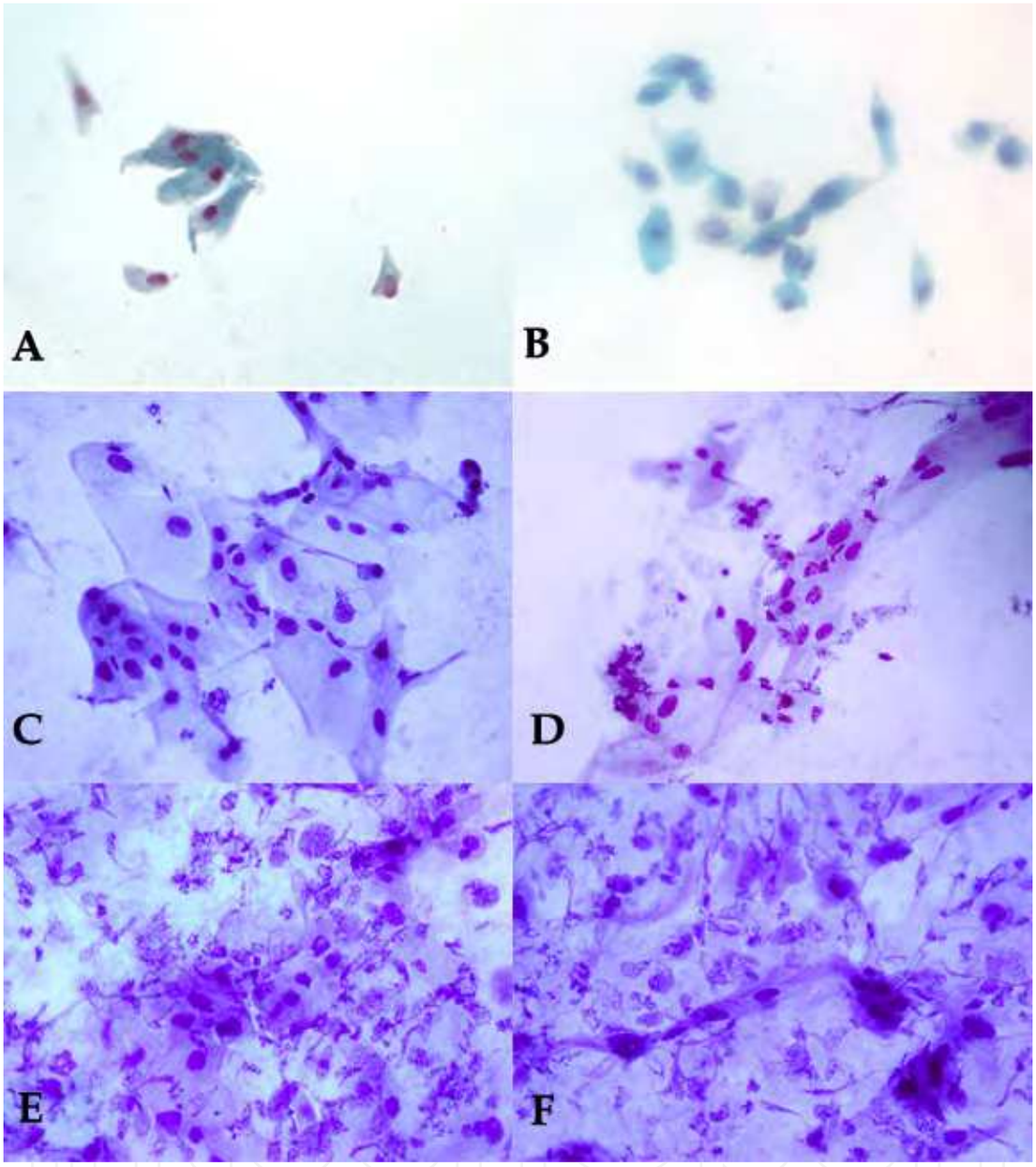

Fig. 13. Cytologic features from impression cytology specimens. A. Normal squamous cells with small nuclei and fine keratohyaline granules. B. Atypical cells with increased nuclear-to-cytoplasmic (N/C)ratio and glassy cytoplasm. C. Low grade corneal intraepithelial lesion; the dysplastic cells are varied in sizes with increased N/C ratio. They are similar to basal cells. Large polygonal squamous cells with small nuclei are also included. D. High grade corneal intraepithelial lesion; the nuclei are pleomorphic with coarse nuclear chromatins. E. High grade corneal intraepithelial lesion with inflammatory exudates on the background. The dysplastic cells cluster together with pleomorphic nuclei. F. Squamous cell carcinoma. The small and spindle cancer cells are aggregated together with the inflammatory background. Nuclear details are hardly noted as the cells overlap one another. (Papanicolaou stain. Original magnification X40)

4.4 Other investigation tools

Recently, in vivo confocal microscopy has proved useful as a noninvasive technique to investigate various ocular surface lesions including OSSN. Two studies found that confocal microscopic findings highly correlated with histologic features in CIN, thus provided real-time monitoring of the condition during treatment. (Alomar et al. 2011; Parrozzani et al. 2011)When compared to histology, however, there were some limitations. First, confocal microscopy provides en face images of cells compared to cross-sectional images from tissue histology. Second, fixation process required for histology results in shrinkage of tissue, therefore, morphometric comparison between living and fixed tissue have to be viewed in this context. Third, it is difficult to obtain in vivo confocal microscopic images and histologic images from exactly the same site of the tissue being examined.

The ultra high resolution (UHR) optical coherence tomography (OCT), a novel diagnostic technique for assessment of anterior eye segment lesions, was used for diagnosis and follow up after treatment of conjunctival-corneal intraepithelial neoplasia (CCIN) in a prospective case series. The UHR OCT images correlated well with the histologic specimens obtained from incisional biopsy before treatment. The UHR OCT was able to detect residual disease that was clinically invisible. The limitation of this machine was its capability to detect microinvasive lesions because the resolution of the current UHR OCT is approximately 2 micron, thus could not detect intracellular features. (Shousha et al. 2011)

Differential diagnosis

Because of the noninvasive nature of OSSN, the diagnosis is often missed or delayed. The patients' symptoms are sometimes treated as chronic conjunctivitis. Other conditions that are commonly mistaken include pterygium, pingecular, corneal pannus, viral keratoconjunctivitis, and corneal dystrophy.

5. Management

5.1 Conjunctival papilloma

Many conjunctival papilloma regress spontaneously. A pedunculated papilloma that is small, cosmetically acceptable and asymptomatic may be observed, although it may take months to years for spontaneous resolution. Larger and more peduculated lesions are generally symptomatic and of poor cosmetic acceptance, thus surgery adjunct with cryotherapy is recommended. A sessile papilloma must be observed closely. If there is any evidence of dysplastic change, excision with cryotherapy should be preformed.

Complete excision without manipulation of the tumor (no touch technique) is a crucial part of the surgical excision to minimize the risk of the virus spreading to uninvolved healthy conjunctiva. Double freeze-thaw cryotherapy is applied to the remaining conjunctiva to prevent tumor recurrence. An incomplete excision can stimulate growth and lead to a recurrence of the lesion and a worse cosmetic outcome. (Fig.14) Topical interferon- alpha 2b (Schechter et al. 2002; Kothari et al. 2009) and mitomycin C(Hawkins et al. 1999; Yuen et al. 2002) have been employed in the treatment of conjunctival papilloma. Immunomodulating agents such as oral cimetidine have led to regression of viral related papilloma. (Chang & Huang 2006)

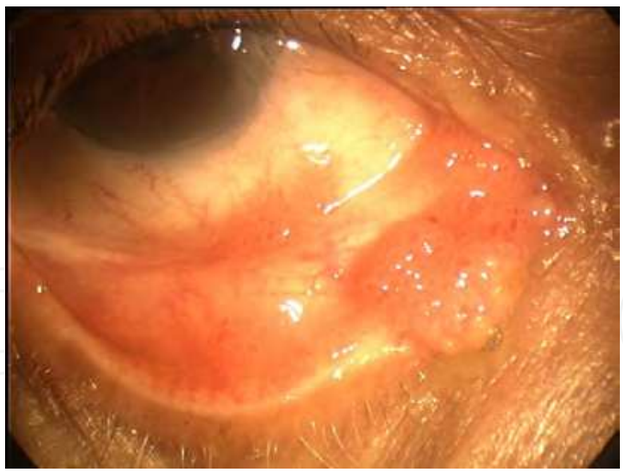

Fig. 14. Multifocal recurrence conjunctival papillomas involving lower palpebral conjunctiva, fornix, canruncle, and lower punctum after two previous excisions.

5.2 Preinvasive and invasive squamous neoplasia

5.2.1 Surgery

The management of OSSN varies with the extent of the lesion. The most accepted method of OSSN remains complete surgical excision. However, residual tumor cells left at the bordering tissue can induce tumor recurrence. Adjuvant therapies such as cryotherapy, alcohol abrasion, or topical agents are used in order to absolutely eradicate tumor cells from the ocular surface. Thus, the main treatment strategy is complete excision of the tumor with a wide surgical free margin followed by double freeze-thaw cryotherapy at the conjunctival margin and alcohol epitheliectomy for the corneal component. In case the tumor is adherent to the globe, a thin lamella of underlying sclera should be removed.

In order to decrease the chance of tumor recurrence, the standard surgical technique should be emphasized in all cases. The "no touch" technique purposed by Shield et al (Shields et al. 1997) is a widely accepted surgical approach as the conjunctival components, along with Tenon's fascia, should be excised with minimal manipulation of the tumor because cells from these friable tumors can seed into adjacent tissue. In addition, the surgery should be performed using microscopic techniques and the operative field should be left dry until after the tumor is completely removed to minimize spreading of tumor cells. Cryotherapy is thought to act through its direct destructive effects on cells, as well as the obliteration of microcirculation in the areas treated, resulting in ischemic infraction of the abnormal tissue. This is performed by freezing the surrounding bulbar conjunctiva as it is lifted away from the sclera using the cryoprobe. When the ice ball reaches the size of 4-5 mm, it is allowed to thaw and the cycle repeated. The complications that may occur from misuse of this technique or when the globe is accidentally frozen include cataract, uveitis, sclera and corneal thinning, and phthisis bulbi.

In cases of advanced tumors, the large conjunctival defect created by excision , particularly those over 4 clock hours, often require tissue replacement from a transpositional conjunctival flap, a free conjunctival autograft from the opposite eye, buccal mucosa graft, or amniotic membrane transplantation.

However, OSSN can be diffused or multifocal, with borders that are difficult to detect clinically, and there is also a chance for skipped areas from histopathologic examination. Reported recurrence rate after surgical treatment is significant (range between 15%-52%). (Lee & Hirst 1995; Tabin et al. 1997; Sudesh et al. 2000; McKelvie et al. 2002) Incomplete excision with positive surgical margins has been identified as a major risk factor for recurrence. (McKelvie et al. 2002) The more severe grades of OSSN appear to recur at higher rates. With adjunctive cryotherapy, the recurrent rate appears to be reduced (from 28.5% and 50% after simple excision, to 7.7% and 16.6% after excision with cryotherapy in primary and recurrence OSSN, respectively). (Sudesh et al. 2000)

The drawbacks of surgical treatment are complications resulted from the healing process, particularly in advanced lesions, including tissue granulation, symblepharon, pseudopterygium, diplopia from tissue shortening, blepharoptosis, limbal stem cell deficiency, and other complications. These surgical problems instigate further investigation into safer, alternative treatments.

5.2.2 Chemotherapy

Due to the relatively high rate of recurrence after surgical excision, various topical treatments have been advocated as a sole therapy for OSSN. Topical therapy offers a nonsurgical method for treating the entire ocular surface with less dependence on defining the tumor margin, potentially eliminating subclinical lesions. Topical treatment can offer a high drug concentration, avoiding systemic side effects. Furthermore, the increased cost, stress, pain, and trauma associated with surgical procedures are avoided. Topical medications have been used effectively for treating this condition comprised of mitomycin C (MMC), 5-fluorouracil (5-FU), and interferon, with MMC used most commonly by a group of external disease specialists. (Stone et al. 2005) These agents have been used as a sole therapy or a surgical adjuvant (preoperatively, intraoperatively, and postoperatively) for treatment of OSSN.

Mitomycin C

Mitomycin C (MMC) is an ankylating antibiotic that binds to DNA during all phases of the cell cycle leading to irreversible cross-linking and inhibition of nucleotide synthesis. When applied to conjunctival surfaces as a surgical adjunct, MMC has been shown to inhibit fibroblast cell migration, decrease extracellular matrix production, and to induce apoptosis in Tenon's capsule fibroblast. It is well known that chronic tissue effects from topical MMC administration can persist for many years after cessation of the treatment, thereby mimicking the effect of ionizing radiation. (McKelvie & Daniell 2001)

MMC has been widely used in glaucoma and pterygium surgery for its anti-fibrotic effect on subconjunctival fibroblast. The use of MMC for treatment of OSSN was first described in 1994.(Frucht-Pery & Rozenman 1994) Since then several case series using different concentrations and durations have been published. Common protocol ranges from topical MMC 0.02%-0.04% given four times a day to the affected eye for 7 to 28 days.(Fig.15) One case series demonstrated that even a smaller concentration of 0.002% of MMC was effective in treatment of primary and recurrent OSSN. (Prabhasawat et al. 2005) Several studies (similar to those used in fractionation of radiation in treatment of systemic cancers) preferred a cycle of 7 days in alternate weeks (1 week on and 1 week off) to allow cells of the

ocular surface to recover/repair. (McKelvie & Daniell 2001; Shields & Shields 2004) One randomized control trial found that MMC 0.04% eye drops used 4 times a day for 3 weeks was effective and caused early resolution of noninvasive OSSN. A relative resolution rate in MMC versus placebo was 40.87 and the mean time for tumor resolution in this study was 121 days, and there was no serious complication in midterm follow-up. (Hirst 2007) MMC has also been used as a surgical adjunct for OSSN: preoperative, to decrease the size of the extensive lesions before surgical excision (chemoreduction), intraoperative, and postoperative to decrease recurrences.(Kemp et al. 2002; Chen et al. 2004; Gupta & Muecke 2010)

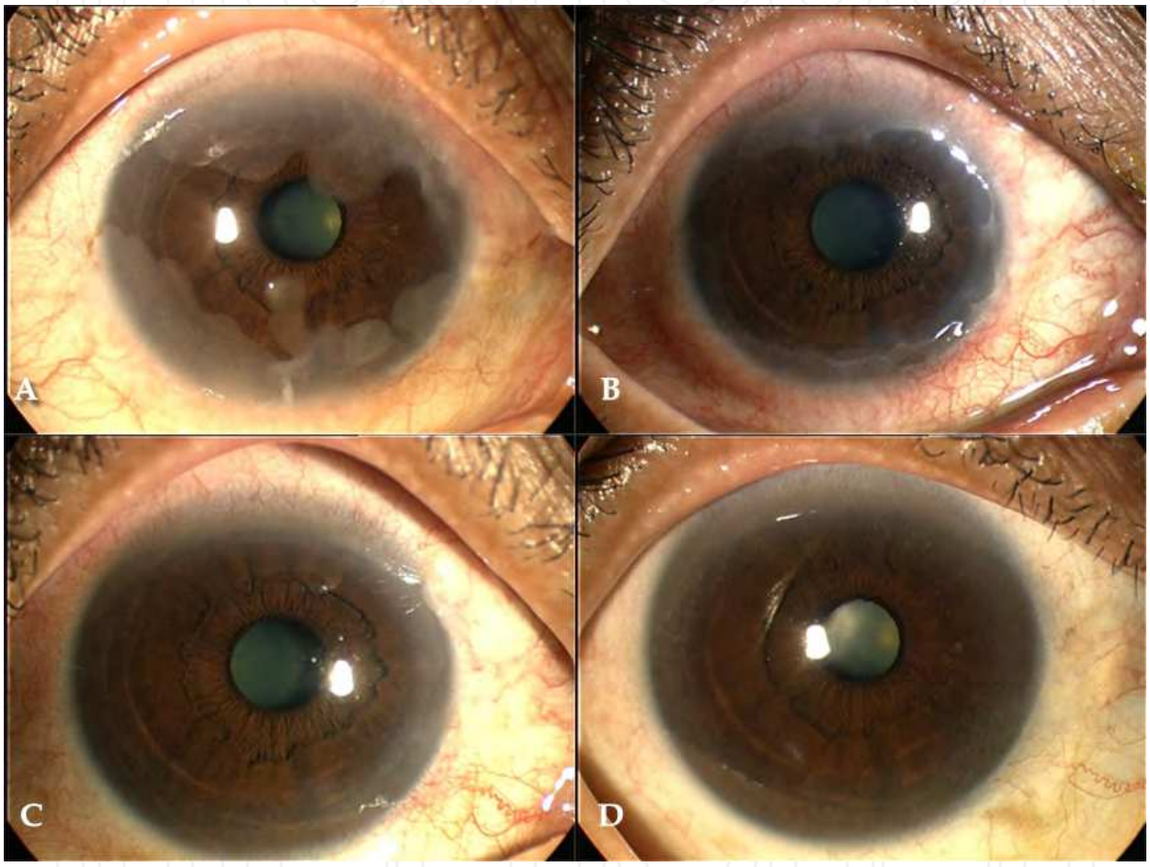

Fig. 15. Severe corneal intraepithelial neoplasia treated with mitomycin C 0.02% four times daily, alternating weeks: A. Appearance before treatment; B. Lesion partially resolved two months after treatment ; C. Completely resolved mass three months after treatment; D. Cornea is clear without recurrence eight years later.

Reported complications of MMC in treatment of OSSN included conjunctival hyperemia, punctuated epithelial erosion, and keratoconjunctivitis. A large retrospective series (n= 100 eyes) of ocular surface tumors treated with topical MMC 0.04% revealed that allergic reaction and punctual stenosis were two common complications. (Khong & Muecke 2006) Some of these side effects can be managed by stopping the medication and adding topical steroid three to four times daily. No significant changes were found on corneal endothelial cells after treatment with topical MMC 0.04% in a cyclic manner. (Panda et al. 2008)

However, MMC was found to have deleterious effects on endothelium cells after pterygium surgery, thus its judicious use and long term follow-up are mandatory.(Bahar et al. 2009) Even though common side effects related to topical MMC are self-limited, limbal stem cell deficiency appeared to be a significant long-term complication. (Dudney & Malecha 2004; Russell et al. 2011) Mckelvie and coworker reported the effects of MMC in treatments of OSSN on impression cytology; MMC appeared to produce cell death by apoptosis and necrosis. Cellular changes related to MMC mimic those caused by radiation-cytolmegaly, nucleomegaly, and vacuolation. These changes may persist at least 8 months after cessation of MMC therapy. (McKelvie & Daniell 2001) MMC-induced long term cytologic changes on the ocular surface have been demonstrated in another study. (Dogru et al. 2003) Serious complications of MMC such as scleromalacia, corneal perforation, cataract, glaucoma, and anterior uveitis have been reported in pterygium treatment and should be of concern if this agent is used in an open conjunctival wound or used excessively.(Rubinfeld et al. 1992)(Fig.16)

When MMC is prescribed as a treatment for OSSN, certain precaution should be taken. Patients and their families are advised to carefully handle the medication. Pregnant women and young children should avoid direct contact with the medication. Patients should be instructed to close their eyes for at least 5 minutes after instillation of MMC or punctal plugs are placed in both superior and inferior puncta to avoid nasolacrimal and systemic absorption of the drug. Since MMC is a chemotherapeutic agent, all residual bottles should be returned to the pharmacy for proper disposal.

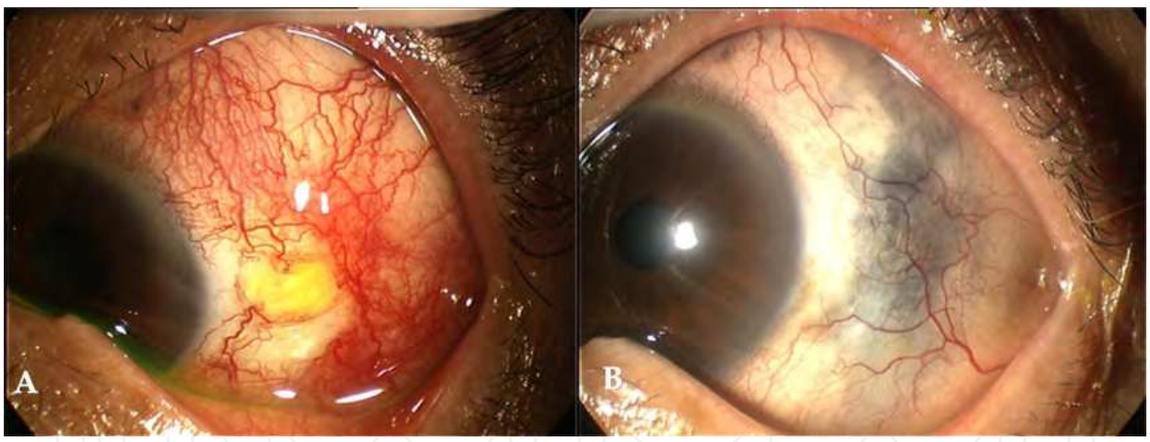

Fig. 16. A. Scleritis in eye with conjunctival intraepithelial neoplasia after excisional biopsy and postoperative mitomycin C. B. Scleral thinning in the same eye one year later after scleritis resolved.

5-Fluorouracil

Similar to MMC, topical 5-fluorouracil (5-FU) has been used to inhibit subconjunctival fibroblasts in glaucoma surgery. 5-FU is an antimetabolite used to treat many epithelial cancers because of its rapid action on rapidly proliferating cells. It acts by the inhibition of thymidylate synthetase during the S phase of the cell cycle, preventing DNA and RNA synthesis in rapidly dividing cells because of a lack of thymidine. Pulse 1% topical 5-FU in cycle of 4 days "on" followed by 30 days "off" until resolution of the lesion was a well-

tolerated and effective method in treatment of OSSN, alone or as an adjunct to excision or debulking therapy. (Yeatts et al. 2000; Al-Barrag et al.; Parrozzani et al.; Rudkin & Muecke) Local side effects associated with topical 5-FU, such as lid toxicity, superficial keratitis, epiphora, and corneal epithelial defect have been reported. (Rudkin & Muecke 2011) By using confocal microscopy, there was no long-term corneal toxicity associated with 1% topical 5-FU compared to the controlled eye. (Parrozzani et al. 2011)The advantages of this agent are its few side effects, plus the medication is inexpensive, easy to handle by both medical personnel, as well as the patients.

Interferon

Interferons (IFN) are a group of proteins that bind to surface receptors of target cells, triggering a cascade of intracellular antiviral and antitumor activities. Systemic interefon-alpha has been used in treatment of hairy cell leukemia, condyloma acuminate, Karposi's sarcoma in AIDS, and hepatitis (both B and C). Recombinant topical IFNα-2b (1 million IU/ml) 4 times a day has been used effectively in treatment of primary OSSN. (Sturges et al. 2008) The antiviral effects of IFNα-2b may explain why it may be less effective as a primary treatment for lesions not linked to HPV infections. Topical IFNα-2b has been used effectively in management of recurrent or recalcitrant lesions where surgical excision or MMC have failed. (Holcombe & Lee 2006) This agent is well tolerated and does not markedly damage the limbal stem cells. Subconjunctival/perilesional IFN-α-2b (1-3 million IU/ml) has also been used effectively for treatment of both primary and recurrent OSSN. (Nemet et al. 2006; Karp et al. 2010) Topical instillation of IFN appears to be associated with few side effects, such as follicular conjunctivitis and conjunctival injections, which appeared to completely resolve after cessation of the medication. (Schechter et al. 2008) There was a report of corneal epithelial microcyst after topical administration interferon identical to that which had been reported with systemic interferon therapy. (Aldave & Nguyen 2007) Subconjunctival IFNα-2b has been associated with transient fever and myalgias , similar to systemic applications.

Topical chemotherapeutic agents have demonstrated acceptable efficacy in treatment of OSSN. Comparison of these three drugs for treatment of noninvasive OSSN reveals that MMC is the most effective (88%), followed by 5-FU(87%), and IFNα-2b (80%). MMC has the highest rate of side effects, perhaps because MMC is the most frequently used topical agent. IFNα-2b is the least toxic, however, it is the costliest of the three agents. (Sepulveda et al. 2010) The relative indications of using topical treatments in OSSN are: 1) >2 quadrants conjunctival involvement, 2) > 180 degree limbal involvement, 3) extension into the clear cornea involving the papillary axis, 4) positive margin after excision, and 5) patient unable to undergo surgery. (Sepulveda et al. 2010) However, some clinicians prefer surgical excision as an initial treatment of invasive lesions if the extension is less than 6 clock hours of involvement, because this provides confirmation of the diagnosis with little cosmetic disfigurement if properly performed.(Shields et al. 2002) When topical agents are considered as a treatment regimen of OSSN, they should be used with caution as long-term effects on the ocular surface of the eye, as well as the adjacent eyelids and nasolacrimal drainage system, have not yet been completely defined.

Other treatment modalities in management of OSSN include plaque brachytherapy with Iodine-125 (Walsh-Conway & Conway 2009), beta-radiation therapy, gamma radiation, and

immunotherapy with dinitrochlorobenzene (DNCB). (Lee & Hirst 1995) Aggressive treatments such as enucleation or exenteration are considered in cases with ocular or orbital invasion. (Shields & Shields 2004)

6. Clinical course

OSSN is a slow growing tumor; however in neglected cases it can invade the globe and orbit and may lead to death. It has a potential for recurrence after treatment. In a series of OSSN, both intraepithelial and invasive lesions, it was found that sclera involvement occurred in 37%, orbital invasion 11%, and no metastasis or death was related to the tumors. (Tunc et al. 1999) In a series of 26 conjunctival SCC, intraocular invasion occurred in 11% of the patients, corneal or sclera involvement 30%, and orbital invasion 15%. Exenteration was required in 23% of cases, and 8% died of metastatic diseases. (McKelvie et al. 2002) Predicting factors related to significantly increased tumor recurrence include old age, large diameter lesions, high proliferation index (Ki-67 score), and positive surgical margin. (McKelvie et al. 2002)

A long-term study of CCIN also found that the recurrence rate after surgery was higher in cases with positive surgical margins than those with free margins (56% versus 33%). Timing for recurrence ranged from 33 days to 11.5 years after primary treatment, and those with incomplete excision recurred earlier than those with free margins. (Tabin et al. 1997) The slow growth of recurrent tumors and evidence of late recurrence 10 years after surgery warranted the need to have annual patient follow-ups for the remainder of their lives.

OSSN in immunosuppressed individuals seem to have an aggressive course in contrast to a relatively benign clinical course in classic OSSN.(Masanganise & Magava 2001; Gichuhi & Irlam 2007) The tumors often grow rapidly and have a tendency to invade the globe or orbit. This problem is exacerbated by poor health care facilities, and patient compliance, which are often present in HIV endemic areas. Management with standard approaches with these patients is often associated with higher rates of recurrence and intraocular or orbital invasion. Thus, treatment regimens may need a wide excision with a histological analysis of the margin, as well as other adjuncts such as cryotherapy, topical chemotherapeutic agents to prevent local recurrence, intraocular or orbital invasion, and metastasis. In addition, it is crucial for every HIV patient to have a detailed eye examination at presentation and maintain a close follow-up to detect recurrent disease early in its course.

7. Conclusion

OSSN is a spectrum of diseases ranging from simple dysplasia to invasive carcinoma. This lesion is considered a low grade malignancy, but its invasive counterpart can spread to the globe or orbit. It is the most common ocular surface tumor and its incidence varies in different geographic locations. The main risk factor is UV-B exposure as its incidence increases in areas close to the equator. Other important risk factors are the human papilloma virus and human immunodeficiency virus. However, it is unclear whether host factors (e.g. genetic factors and HIV-related immune impairment) or characteristics of the ocular surface epithelia may also be part of the etiopathogenesis of OSSN. Symptoms range from none at all to severe pain or visual loss. Clinically, these tumors most commonly arise in the interpalpebral area, particularly at the limbal region. Early diagnosis and management decrease the risk of locally aggressive and can improve the patients' prognosis for local

control and preservation of vision. In clinical practice, OSSN is generally evaluated by tissue histology. The developments of pre-operative diagnostic techniques such as impression cytology are of value in diagnosis and follow-up after treatment. Surgical excision adjunct with cryotherapy combined with alcohol abrasion in cases of corneal involvement are the main treatment strategy. Recurrence rates are higher for more severe grades of OSSN and have been related to the adequate of surgical margins at the initial excision. The standard management care of OSSN appears to shift toward topical chemotherapy such as MMC, 5 FU, and interferon as a sole therapy, or a surgical adjunct, particularly in diffused or un-operable cases. These alternative treatments continue to evolve despite a paucity of long term results in published literature. Invasive disease may cause intraocular or orbital involvement with eye loss, and occasionally may lead to death. Recurrence after initial treatment is variable and warrants life-long follow-up in all case of OSSN.

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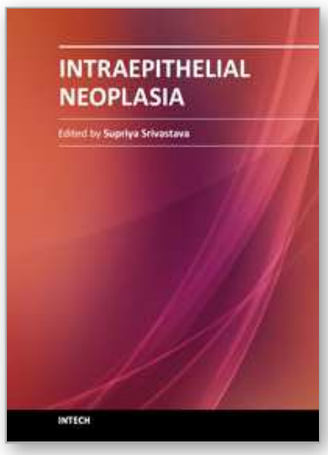

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The book "Intraepithelial neoplasia" is till date the most comprehensive book dedicated entirely to preinvasive lesions of the human body. Created and published with an aim of helping clinicians to not only diagnose but also understand the etiopathogenesis of the precursor lesions, the book also attempts to identify its molecular and genetic mechanisms. All of the chapters contain a considerable amount of new information, with an updated bibliographical list as well as the latest WHO classification of intraepithelial lesions that has been included wherever needed. The text has been updated according to the latest technical advances.This book can be described as concise, informative, logical and useful at all levels discussing thoroughly the invaluable role of molecular diagnostics and genetic mechanisms of the intraepithelial lesions. To make the materials easily digestive, the book is illustrated with colorful images.

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