Squamous Cell Carcinoma of the Conjunctiva

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The stratified squamous epithelium of the conjunctiva can give rise to neoplastic lesions ranging from dysplasia to invasive squamous cell carcinoma (SCC), first described in 1860 by von Graefe, who called this lesion epithelioma [1].

■ Epidemiological Features

The incidence of SCC of the conjunctiva varies geographically from 0.02 to 3.5 per 100,000 [2, 3]. Recently a study of the geographical distribution of the disease found that incidence declined by 49% for each 10-degree increase in latitude, falling from more than 12 cases per million per year in Uganda to fewer than 0.2 cases per million per year in Great Britain [2]. The age of onset at latitude 30 degrees is younger than at latitude 45 degrees (57 years vs. 66.5 years) [4]. The disease is more common in men and among whites [5–7].

■ Pathogenesis, Risk Factors, and Associated Diseases

Conjunctival SCC tends to occur at the zone of transition of the ocular surface epithelium from conjunctiva to cornea (i.e., at the limbus). The corneoscleral-conjunctival limbus has been compared to the squamocolumnar junction of the uterine cervix, where cervical epithelium most commonly arises [4, 7]. Corneal epithelial stem cells, located most prominently at the crypts of Vogt in the limbal region, are capable of replacing lost or desquamated corneal epithelium. These stem cells are long-lived and have the potential for clonogenic cell division.
Exposure to ultraviolet (UV) light has been considered the main predisposing factor to the development of squamous cell carcinoma of the conjunctiva [2, 4–11], both because of its geographical epidemiological characteristics (see earlier) and because of its occurrence in patients with xeroderma pigmentosum [12–16].

Xeroderma pigmentosum is a rare genetic disease characterized by defective DNA repair [17]. UV irradiation of DNA can result in pyrimidine dimers that distort the DNA strand. In a retrospective study of 10 patients with xeroderma pigmentosum, conjunctival SCC occurred in 2 (20%) [18]. SCC of the conjunctiva in patients with xeroderma pigmentosum can be recurrent and invasive despite treatment.

The role of pterygium in the development of conjunctival SCC is unclear. Solar radiation is a risk factor for both conditions. SCC of the conjunctiva can arise (though rarely) from the epithelium of a pingueculum or pterygium [19, 20]. In one study, 60% of patients with carcinomas in situ (CIS) and SCC were found to have underlying collagen degeneration, and approximately 30% had contralateral pterygia [19].

Human papillomavirus (HPV) has also been implicated in the pathogenesis of conjunctival SCC [21–25]. The technology of polymerase chain reaction (PCR) analysis has greatly enhanced the sensitivity and specificity of detection of HPV genotypes. Using this technique, McDonnell and coworkers [24] detected the presence of HPV 16 DNA in 37 (88%) of 42 conjunctival biopsy specimens exhibiting dysplasia or frank conjunctival SCC. However, HPV also was present in tissue samples from the unaffected eye of 4 of 6 patients (67%) with unilateral conjunctival neoplasia. A recent study by Saegusa and coworkers [26] found HPV 16 DNA by PCR and by in situ hybridization methods in 12 of 16 papillomas (75%), in 2 of 4 specimens (50%) with dysplasias, and in 1 of 4 SCC specimens (25%). Thus, HPV probably does not by itself lead to the development of conjunctival SCC but may act in combination with other pathogenic factors.

Conjunctival SCC is associated with human immunodeficiency virus (HIV) infection [3, 27, 28]. SCC is the third most common malignancy associated with HIV infection, the tumor being found primarily in the oral cavity and rectum in HIV-infected individuals. A recent study of SCC of the conjunctiva in Uganda showed the incidence of the disease has increased sixfold, from 6 per million per year from 1970 to 1988, to 35 per million per year in 1992 [3]. This increase in incidence appears to be due largely to the epidemic of HIV infection in Uganda. Of the 48 patients with conjunctival SCC 36 (75%) were HIV-positive; 19% of the 48 controls was seropositive in this study.

Other potential etiological factors suggested by various studies include smoking [19], exposure to petroleum products [29] and chemicals such as trifluturidine [30] and beryllium [7], ocular surface injury [7, 31] and, possibly, herpes simplex virus type I [32]. A case of conjunctival SCC in
a patient with benign mucous membrane pemphigoid has also been reported [33].

## Clinical Findings

Clinically, distinguishing conjunctival SCC from dysplasia or CIS can be difficult. SCC of the conjunctiva characteristically is located in the interpalpebral region near the limbus, but it can occur in the fornical or palpebral conjunctiva or in the cornea. Pizzarello and Jakobiec [7] and Erie and colleagues [5] have described the tumor as being either gelatinous and velvety or papilliform (Fig 1) or leukoplakic (Fig 2), indicating keratin production. Most lesions are slightly raised and placoid, with characteristic surrounding tufted vessels (see Fig 1). Rarely, the lesion is pigmented and so it can be mistaken for melanoma [4]. The tumor has also been described in nodular (see Fig 2) and diffuse forms (Fig 3). The nodular type is circumscribed and can grow rapidly. The diffuse type probably reflects a radial intraepithelial growth pattern; this form is chronic and can masquerade as chronic conjunctivitis [4, 7, 34].

Figure 1  Gelatinous, papilliform squamous cell carcinoma of the conjunctiva.

Figure 2  Squamous cell carcinoma of the conjunctiva: nodular form with leukoplakia.
Diagnosis

Exfoliative Cytological Workup

Tissue specimens for exfoliative cytological workup, formerly obtained with a platinum spatula, are harvested with a cytobrush [35]. Malignant (as opposed to normal) cells vary in size and shape and are characterized by scanty cytoplasm and large hyperchromatic nuclei with coarse clumping of chromatin (Fig 4) [36, 37]. Multinucleate malignant cells and mitotic figures also are diagnostic of conjunctival SCC. Dysplastic cells are differen-
tiated from malignant cells by the presence of more moderate amounts of cytoplasm (Fig 5). A mixture of dysplastic and malignant cells is more typical of CIS, whereas SCC specimens exhibit more marked cytological aberrations and a background of necrotic tumor debris [36, 38]. However, cytological workup alone cannot accurately assess the extent of tumor invasion and cannot differentiate between CIS and invasive SCC [37].

In one study, exfoliative cytology detected the presence of carcinoma and identified the lesion as squamous in origin in 3 of 3 cases of SCC and in 5 of 6 cases of CIS [37].

**Impression Cytology**

Cellulose acetate filter-paper sheets are placed over the conjunctiva and removed for impression cytological evaluation of the cells removed by the filter paper. When removed, the paper lifts off the most superficial layer of the epithelium [39]. Dysplastic cells have enlarged, irregular, and hyperchromatic nuclei. CIS often is characterized by hyperkeratosis and, in some cases, by syncytialike cell groupings with irregularly arranged enlarged nuclei. In addition to these findings, SCC may show inflammatory cells and sheets of abnormal cells with macronucleoli. Impression cytology has a sensitivity of 77% for diagnosing SCC [40].
Other Diagnostic Methods

Weissman and coworkers [41] described the use of bromodeoxyuridine, a thymidine analog, to reveal increased suprabasal cell DNA synthesis. Patients with conjunctival SCC demonstrated increased conjunctival DNA synthesis.

Nucleolar organizer regions (NORs), which are genes coding for RNA, are seen as intranuclear black dots with silver stain. NORs have been shown to be more numerous in neoplastic lesions than in dysplastic lesions [42].

Histopathological Features

Epithelial dysplasia, CIS, and conjunctival SCC all belong to a single disease spectrum. Conjunctival and corneal intraepithelial neoplasia are referred to by multiple terms, including Bowen's disease, intraepithelial epithelioma, and dyskeratosis. Pizzarello and Jakobiec [7] classified these lesions as conjunctival intraepithelial neoplasia (CIN). Lee and Hirst [43] suggested the term ocular surface squamous neoplasia (OSSN) as an "umbrella" term to describe the spectrum of disease.

CIN histologically is characterized by a partial to full-thickness intraepi-
Figure 8  Tumor with predominantly polyhedral epidermoid cells with large nuclei and prominent nucleoli (H&E, × 250).

The neoplasia, whereas CIS has full-thickness involvement with loss of the normal surface layer. When invasion beyond the basement membrane occurs, the lesion has transformed to SCC (Fig 6).

Several atypical cell types of conjunctival SCC have been described [4, 7]. The most common cell type is small and spindle-shaped with elongated eosinophilic cytoplasm and elliptical, moderately chromatic nuclei without prominent nucleoli (Fig 7). Epidermoid cells are large polyhedral cells with large vesicular nuclei, prominent nucleoli, and eosinophilic cytoplasm (Fig 8). Clear cells have small hyperchromatic nuclei with scanty and clear cytoplasm. Occasionally, pigment granules are seen in these cells. Mucoepidermoid cells are cuboidal cells containing intracytoplasmic mucicarmine-positive droplets that are arranged in nests and cords, with secreted pools of mucin in the extracellular space. A mixture of cell types may be present in SCC lesions. Other cytological features include cellular pleomorphism, dyskeratosis, acanthosis, loss of polarity, and actinic change.

Variations of conjunctival SCC, such as mucoepidermoid carcinoma and spindle cell carcinoma, are more invasively aggressive [44–48]. Mucoepidermoid carcinoma is characterized by epithelial cells with intracytoplasmic mucinous elements (Fig 9). This lesion has a greater tendency to invade the globe and orbit and can recur rapidly after excision [44, 45].

Figure 9  Mucoepidermoid carcinoma of the conjunctiva with intracytoplasmic mucinous elements (H&E, × 400).
Spindle cell carcinoma is characterized by pleomorphic spindle cells that are arranged in spindles or fascicles (Fig 10). The pigmented variant of SCC of the conjunctiva is observed mainly in darkly pigmented individuals [49, 50]. The pigmentation results from the melanocytes interspersed among the squamous carcinoma cells. This variant is not more aggressive than the nonpigmented type.

**Treatment**

**Surgery**

Surgical excision is the most appropriate treatment for conjunctival SCC. Excision of the lesion with a surgical margin of 2 to 3 mm is recommended [7, 51]. Bowman’s membrane should be preserved if the tumor is contained in the corneal epithelium, as Bowman’s membrane may act as a natural barrier to tumor cell invasion into the corneal stroma [52, 53]. If tumor invasion extends beyond the corneal epithelium, a partial keratectomy is necessary. Frozen section of lesions has been used to assess the surgical margins and also is reliable for assessing horizontal tumor spread. However, frozen section is not sensitive or accurate for assessment of vertical tumor spread, as is suggested by the disparity between the determination of clean margins by frozen section and tumor recurrence [54].

Bunns and associates [55] have applied Mohs’ technique for cutaneous tumors in the surgical excision of conjunctival SCC. The tumor is resected with a lateral margin of 2 mm. The specimen is processed by permanent section within 24 hours. If margins are not free of tumor cells, the patient is returned for a reexcision of an additional 2 mm of the margin. The wound is allowed to heal by secondary intention. At 6 to 60 months of follow-up, no recurrences were noted among the 19 patients treated in the study by Bunns and coworkers [55].

Recurrence rates after excision range from 15 to 52% [43]. Recurrence is believed to be mainly a result of inadequate excision [5, 7].
colleagues [5] demonstrated a recurrence rate of only 5% (3 of 58) in cases with tumor cell–free surgical margins, as compared to a 53% (20 of 38) recurrence rate in those cases without tumor cell–free margins.

Tumors that exhibit intraocular or intraorbital invasion generally are managed with enucleation or exenteration, although occasionally excision of tumors showing intraocular invasion is successful. Char and associates [54] reported on a patient with recurrent conjunctival SCC with intraocular extension, which was removed with iridocyclochoroidectomy. Three and one-half years later, the patient’s vision was 20/30, with no signs of recurrence. However, apparent surgical clearance of intraocular tumor extension, even with frozen-section examination, may not ensure complete tumor excision. Glasson and coworkers [56] reported a case of recurrent conjunctival SCC 1 year after corneoscleral resection and iridocyclectomy; the patient required an exenteration.

**Radiotherapy**

Radiotherapy alone is not recommended in the treatment of conjunctival SCC but is employed as supplemental treatment in conjunction with surgery or in cases of a diffuse lesion for which excision would be too extensive [57, 58]. Strontium 90, a beta-radiation source, and gamma radiation using radium as a source, have both been employed. A review of 131 patients treated with surgical excision followed by radiotherapy from 1950 to 1985 showed that only 3 patients (0.02%) developed local recurrence [59]. Lee and Hirst [43], however, observed a much higher recurrence rate, with 7 of 18 patients who underwent excision and irradiation (39%) experiencing tumor recurrence. Potential complications of radiotherapy include conjunctivitis, dry eye, cataract, scleral ulceration, symblepharon, and corneal rupture.

**Cryotherapy**

Cryotherapy is used in combination with surgical excision. The recurrence rate after excision plus cryotherapy ranges from 7 to 22%, the average being 12% [43]. Pekşayar and coworkers [60] reviewed the results of this combination treatment in 22 eyes of 20 patients. In this study, the tumor was excised with a 2-mm conjunctival margin. A nitrous oxide cryoprobe was applied which extended 2 mm beyond the surgical margins for the conjunctiva, 1 mm beyond for the episcleral tissues and limbus, and 0.5 mm beyond for the cornea. The recurrence rate was 9% (2 of 22 eyes) at 5 to 12 years of follow-up. Side effects of cryotherapy include iritis, increased or decreased intraocular pressure, corneal scarring, sector iris atrophy, thermic inflammatory edema, ablation of the peripheral retina, and ectropion [60, 61].
Chemotherapy

Frucht-Pery and Rozenman [62] reported successful treatment, using mitomycin C, of corneal intraepithelial neoplasia involving the visual axis in 3 patients. Of the 3, two patients had histologically confirmed intraepithelial neoplasia. Topical mitomycin C, 0.02%, was administered four times daily for 10 to 22 days. The intraepithelial neoplastic lesions resolved within 9 weeks of treatment. At 4 to 12 months of follow-up, no recurrence was observed. Adverse reactions, including conjunctival hyperemia, ocular pain, and blepharospasm, resolved after mitomycin C was discontinued.

Clinical Course

Conjunctival SCC is a relatively low-grade malignancy [4, 5, 7, 51]. Intraocular invasion and metastasis are uncommon. Tumor cells invade intraocularly through the canal for perforating vessels at the limbus [63], and can spread to the trabecular meshwork, the iris, the ciliary body, and the choroid. Uveitis, glaucoma, retinal detachment, and scleral thinning might occur. Tabbara and colleagues [10] reviewed 10 cases of conjunctival SCC with distant metastasis. The initial sites of metastasis were parotid glands, submandibular and submaxillary glands, preauricular and cervical lymph nodes, lungs, and bone. The metastasis often results from delay in seeking medical treatment and is not necessarily associated with a poorer prognosis. Of the 10 patients reviewed by Tabbara’s group [10], only 1 died of distant metastasis at a follow-up of 6 to 48 months (mean, 18 months).

Tumor recurrence usually is a result of inadequate surgical margins. Most lesions tend to recur within the first 2 years [43]. Recurrent lesions usually are of the same histological grade as was the primary tumor.

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