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Conjunctival Intraepithelial Neoplasia – Clinical Presentation, Diagnosis and Treatment Possibilities

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1. Introduction

Conjunctival tumors are one of the most frequent tumors of the eye and adnexa. They comprise a large variety of conditions, from benign lesions such as papilloma to malignant lesions such as epidermoid carcinoma or melanoma which may threaten visual function and patient’s life if not diagnosed early. Although conjunctival tumors may arise from any type of the conjunctival cells, epithelial and melanocytic are the most frequent origins. Epithelial tumors account for a third to half of all tumors, with a higher prevalence in countries with larger actinic exposure. Approximately 40% of the tumors have an epithelial origin and 64.5% of them were pre-cancerous lesions (Saornil et al, 2009). The clinical differentiation between pre-cancerous benign and malignant lesions is difficult, requiring a biopsy for a definitive diagnosis.

Squamous neoplasia of the conjunctiva/cornea is a rare malignancy of conjunctival limbal stem cells, and the management of this malignancy may affect the ultimate outcome. The clinical distinction of squamous conjunctival neoplasia from other amelanocytic conjunctival tumors is based on certain clinical features of the tumor, and its correct management requires an understanding of normal anatomy and histology of the cornea and conjunctiva, as well as knowledge of the principles of tumor management.

Conjunctiva is a thin and flexible mucous membrane that extends from the internal surface of the eyelids to the fornix and anterior ocular surface up to the corneoscleral limbus. Histologically, conjunctiva is similar to other mucous membranes and comprises a non-keratinized stratified epithelium having two or more layers over the stroma formed by fibrovascular connective tissue containing vessels, nervous and lymphatic tissue. Basal layer of epithelium comprises melanocytes which produces melanine and inject it in the surrounding cells. Throughout the length of epithelium we can observe cup-shaped cells in charge of producing the mucoid component of the lacrimal film. These cells are called goblet cells.
1.1 Definition of Ocular Surface Squamous Neoplasias (OSSN)

Squamous cell neoplasia may occur as a localized lesion confined to the surface epithelium (conjunctival intraepithelial neoplasia) or as a more invasive squamous cell carcinoma that has broken through the basement membrane and invaded the underlying stroma (Shields & Shields, 2004).

Currently, the accepted term for the localized variety is conjunctival intraepithelial neoplasia (CIN). However, other authors prefer the terms dysplasia (mild, moderate, or severe) and carcinoma-in-situ. Where there are no longer normal surface cells then the process may be termed carcinoma-in-situ. Those cases where the cornea is invaded by the process are usually called conjunctiva-cornea intraepithelial neoplasia (CCIN). Squamous neoplasia constitutes the most frequent primary malignancy of the ocular surface.

1.1.1 Conjunctival Intraepithelial Neoplasia (CIN)

CIN is confined to the epithelium by definition. The term CIN was suggested in 1978, according with the general pathologic classification of intraepithelial tumors developed for cervical intraepithelial neoplasia (Pizzarelli & Jakobiec, 1978). CIN includes previous terms referred to this epithelial neoplasia such as: Bowen’s disease, Bowenoid epithelioma, intraepithelial epithelioma, intraepithelioma, dysplasia and carcinoma in situ (CIS).

Subjective symptoms referred by the patients include: foreign body sensation, redness, irritation, and a growth on the ocular surface (Giaconi & Karp, 2003).

Clinically, CIN appears as a fleshy, sessile or minimally elevated lesion usually at limbus in the interpalpebral fissure and less commonly in the fornical or tarsal conjunctiva (Shields & Shields, 2004). The limbal lesion may extend for a variable distance into the epithelium of the adjacent cornea. A white plaque (leukoplakia) may occur on the surface of the lesion due to secondary hyperkeratosis.

Fig. 1. Conjunctival intraepithelial neoplasia showing corneal invasion.

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1.1.2 Squamous Cell Carcinoma (SCC)

Squamous cell carcinoma is characterized by an extension of abnormal epithelial cells through the basement membrane to gain access to the conjunctival stroma (Shields & Shields, 2004). Clinically, invasive squamous cell carcinoma is similar to CIN; however, it may be larger and more elevated than CIN. Even though the cells of invasive squamous cell carcinoma gain access to the blood vessels and lymphatic channels, regional and distant metastases are both rather uncommon. Clinically it is very difficult to distinguish between CIN and SCC (Erie et al, 1986). In many occasions it is necessary to perform a biopsy.

1.2 Incidence

OSSN accounts for only 5% of all ocular malignancies (Lee & Hirts, 1995). CIN is the most common conjunctival malignancy (Grossniklaus et al, 1987). CIN occurred more commonly in pale-skinned groups than in more pigmented people, with an increased incidence in males (75%) vs females (25%), and a mean age of 60 years (Grossniklaus et al, 1987). OSSN associated with human immunodeficiency virus (HIV) is seen at younger ages (average 35 years), usually not in a bulbar location, and is more aggressive from a clinical point of view. Its incidence can vary from 0.13 to 1.9/100,000 inhabitants (Lee & Hirts, 1995), (Giaconi & Karpp, 2003), (Saornil et al, 2009). OSSN incidence varies geographically, increasing with closer distance to the equator. For example, Uganda has 1.2 cases/100,000 persons/year compared to the United Kingdom with less than 0.02 cases/100,000 persons/year. This might suggest a role of ultraviolet light exposure in the etiology of these tumors. US data indicate an incidence of 0.03/100,000 people/year, with a 6-fold increase in association with HIV infection (Sun et al, 1997), (Verma et al, 2008). The lesions are more common in males and elderly, with the majority occurring at the limbus. In Africa the incidence is changing. The tumor is more common, aggressive, more frequent in young persons, especially women (Ateenyi-Agaba, 1995). This is related with the coexistence of pandemic AIDS and exposition to the human papillomavirus (HPV) and ultraviolet radiations. Africa has the highest prevalence of HPV infection in the world (with more than 25% of women from 15 to 74 years affected), followed by South America (14.3%), Asia (8.7%) and Europe (5.2%) (Clifford, 2005). A study in the Kampala Cancer Registry in Uganda showed an increase from 6 cases of OSSN/1,000,000 persons per year between 1970 and 1988 to 35 cases/1,000,000 persons per year in 1992 (Ateenyi-Agaba, 1995). In Australia, a study found that 78.5% of affected people were male with a mean age of 60 years (Lee & Hirst, 1997). Similarly, another study in United Kingdom showed that the 77% were male, being 69% of them older than 60 years (McKelvie et al, 2002). Nevertheless, a study in Zimbabwe found that a 70% of patients were young women with a mean age of 35 years (Pola et al, 2003), while in South Africa mean age was 37 years (Mahomed & Chetty, 2002). A study in Tanzania showed that the 45.8% of 168 conjunctival biopsies were OSSN (Poole, 1999).

2. Etiologic factors for CIN

To date, CIN etiology remains unclear. The most probably explanation may be multifactorial causes. There are many known factors which may contribute to the development of these neoplasias.
Intraepithelial Neoplasia

recurrence rate in pathologic studies which revealed involved margins and a 5% recurrence rate when clear margins are confirmed (Erie et al, 1986). In extensive lesions, surgical excision is difficult, and additional procedures have been employed. Extensive resections in very extensive CIN may produce a limbal stem deficiency (Huerva et al, 2006). Adjuvant radiation has the potential complications of cataracts, scleral necrosis, corneal rupture, scarring of the cornea and conjunctiva, moderate to severe conjunctivitis, and loss of eyelashes (Giaconi & Karp, 2003). For those patients with extensive tumors or those tumors that are recurrent, treatment with topical mitomycin C, 5-fluorouracil, or interferon alfa 2b have been employed.

9.2 Topical chemotheraphy

Topical chemotherapy has a number of advantages over surgical approach. It enables to treat the entire ocular surface and is not dependent upon surgical margins. Primary treatment with a chemotherapeutic agent avoids potential complications of surgery, which can include scarring of the conjunctiva and cornea, limbal stem cell failure and incomplete excision of the lesion. Topical chemotherapics may be preferred over surgery by some patients, and when the patient refuse surgery, topical chemotherapics have been successfully used as primary treatment.

9.2.1 Topical mitomycin C (MMC)

For tumors with extensive involvement, where surgical removal bears significant risks for postoperative problems, topical MMC should have been considered for a long time. Topical MMC 0.02% or 0.04% 4 times daily in 7 to 14-day for two cycles (Shields & Shields, 2004) have been successfully employed for preoperative chemoreduction and to manage recurrent and residual tumors following surgical resection (Shields et al, 2002), (Frucht-Pery et al, 2002), (Shields et al,2005). MMC had been effectively used to treat primary CIN, with reported success rates between 85% (Wilson et al, 1997) and 100% (Frucht-Pery & Rozenmam, 1994), (Ramos-Lopez et al, 2004). Another large study has shown topical MMC to be an efficient treatment of most, but not all cases, of CIN. Tumor regrowth occurred in approximately 17% of cases (Frucht-Pery et al,1997). To avoid possible complications, the lacrimal punctal occlusion is mandatory during topical treatment. Chemoreduction with MMC cycles reduced the tumor size, especially in the surrounding thinner portions, and allowed for a subsequent limited surgical excision in all cases (Shields et al, 2005). Possible complications with topical MMC include superficial punctate epitheliopathy (Shields & Shields, 2004), conjunctival hyperemia, pain, allergy, corneal-scleral, melting disturbance of tear film stability, goblet cell loss, squamous metaplasia and limbal stem cells depletion (Frucht-Pery & Rozenmam, 1994), (Wilson et al, 1997), (Dogru et al, 2003), (Dudney & Malecha, 2004), (Khong & Muecke, 2006). Edema and endothelial apoptosis have been observed in experimental models (Chang, 2004). MMC toxicity seems to be dose dependent, occurring with the repetition of treatment cycles. Chemoreduction with topical MMC, followed by interferon alfa 2b (1 million IU/mL) 4 times daily, is an effective treatment in extensive CIN cases where surgical resection with safety margins is infeasible and corneal extension resection and the repetitive cycles of MMC adjunctive could cause a depletion of limbal stem cells and other commented side effects on the ocular surface (Huerva et al,
2006). In a follow-up of 18 months, topical Cyclosporine A (0.05%) combined with topical low dose of MMC (0.01%) four times a day for 12 weeks after positive margins following surgical excision showed no recurrence of the tumor (Tunc & Erbilen, 2006). In these cases Cyclosporine A has been employed by the antineovascular effect on the ocular surface.

9.2.2 5-Fluoracil (5-FU)

Other treatment options in the management of CIN include 5-fluorouracil (5-FU). However, compared with MCC, the experience with this alternative treatment is limited. Topical 1% 5-FU drops used 4 times daily for 2 to 4 days for each cycle and repeated at 30 to 45 day intervals have been reported. Following initial treatment, 4 patients were disease-free with a mean follow-up of 18.5 months. Of the 3 patients with tumor recurrence, 2 remained tumor-free following additional topical 5-FU treatment and 1 patient had a persistent tumor despite additional treatment with 5-FU and became tumor-free following treatment with topical MMC (Yeatts et al, 2000). No adverse reactions to pulsed treatment were reported. Another study using topical 1% 5-FU drops 4 times daily for 4 weeks in 8 eyes with recurrent, incompletely excised, and untreated conjunctival OSSN showed complete clinical regression at 3 months in all cases. OSSN recurred in 1 patient at 6 months but this was successfully treated with another course of 5-FU (Midena et al, 2000). Transient toxic keratoconjunctivitis that was noticeable with this treatment. Short-term complications include lid toxicity in 52% of patients, keratopathy in 11% and epiphora in 5% (Rudkin et al, 2010).

9.2.3 Interferon (INF) alpha 2b

Topical MMC and 5-fluorouracil have been used to reduce recurrence rates when used as an adjunct to surgical excision and as a primary treatment; however, their use can be associated with marked ocular surface toxicity. Topical (1,000,000 IU/ml four times a day) or subconjunctival INF alfa 2b (3 million IU/ml/ weekly) have been employed to treat CIN. In general, topical INF alpha-2b is well tolerated. Subconjunctival administration presents more side effects as flu-like symptoms (fatigue, fever, myalgias, malaise) and mild liver disturbances (Huerva & Mangues, 2008). Local conjunctival injection and follicular conjunctivitis are the most frequently reported side effects (Schechter et al, 2002) after topical administration. Redness and increase of CIN volume without ocular discomfort have been reported in a case (Huerva et al, 2007). Fine, diffuse, clear epithelial microcysts in the cornea after instillation of topical interferon a-2b have recently documented in other case (Aldave & Nguyen, 2007).

Topical INF alpha 2-b, sometimes combined with subconjunctival INF alpha 2-b, seems to be effective as primary treatment for CIN, in recurrent cases, and also in retreatment after recurrence when INF has been used previously for a short period of time (Huerva & Mangues, 2008). Approximately, 9% of CIN treated with subconjunctival and/or topical INF alpha 2b showed recurrences, and 33 % of them were successfully retreated with topical IFN alpha 2b (Huerva & Magues, 2008). Another one (16,6%) achieved complete remission after intraperioperative MMC (Hawkins et al, 1999). For INF alpha 2b topical treatment, the average time to complete tumor response is 11 weeks (range 2-59). For INF alpha 2b
subconjunctival and topical treatment, the average time to complete tumor response is 5.5 weeks (range 2-12), (Huerva & Mangues, 2008). Previous studies found the same observation (Karp et al, 2001). The time to clinical resolution using topical INF alpha 2-b was longer (11.6 weeks) that the combined intralesional and topical interferon (4.5 weeks), but that INF alpha 2b treatment involved fewer side effects. In general, it seems that the disadvantage with topical treatment is the long duration. We must emphasize the importance of long term follow-up for CIN patients because recurrences can occur anywhere from 33 days to 11.5 years (Tabin et al, 1997), although most recurrent CIN occurs within 2 years of initial excision (Schechter et al, 2005).

Many surgeons add adjunctive topical therapy to their surgical regimens for larger lesions (Stone et al, 2005). However, all sizes of lesions could be treated with topical INF alpha as the primary treatment because it is an effective, non-invasive treatment alternative to surgery that increases quality of life with low costs (Huerva et al, 2006), (Huerva et al, 2007), (Huerva et al, 2009). Actually, no clear consensus on the best way to manage the disorder has been established, because long-term, well designed studies are still needed. However, two recent studies have addressed the above questions and confirmed the effectiveness of this topical therapy for CIN. The first study (Schechter, et al, 2008) demonstrated total resolution of the tumor in 96.4% of cases treated with INF alfa 2b with a mean follow-up of 42.4 months. The second study (Sturges et al, 2008) demonstrated that topical treatment with INF and surgical excision have the same effectiveness as primary treatment for CIN for a mean follow-up of 35.6 months. The authors concluded that topical IFN alfa-2b and aggressive surgical excision can be considered equally effective as first choice for treating CIN. Topical INF alfa-2b has some advantages over conventional excision, including the reduction of risk to lose limbar stem cells secondary to surgical trauma and, thus, compromising the integrity of the ocular surface. This therapeutic mode can be recommended particularly for patients who reject any type of surgery, or mentally retarded patients in whom surgery is complicated as well as extended cases where an aggressive excision could cause the loss of limbar stem cells (Huerva, 2008).

Topical INF or subconjunctival INF remains a controversial issue. A recent report (Karp et al, 2010) concluded that subconjunctival 0.5 ml injection of 3 million IU IFN alfa 2b is a viable medical alternative for the treatment of ocular surface squamous neoplasia (OSSN) with a mean duration of follow-up of 55 months. The authors state that the advantages of perilesional INF alfa 2b injection include more rapid tumor resolution, ensured compliance, and perhaps more direct delivery to the tumor site when compared with topical INF drops. However, some patients may be apprehensive about receiving injections around the eye and may prefer eyedrops. A single weekly injection of INF may have better compliance than 4 eye-drops per day dosing for a mean of three months in many patients. Direct delivery to the tumor site may occur in well-localized lesions, while annular lesions or multifocal disease requires injection over the entire involved area, increasing the risk of conjunctival hemorrhage. By contrast, topical therapy is delivered to the entire ocular surface and has very good success rates. Topical therapy could be recommended for patients who reject any surgical procedure or those who are apprehensive about injections.
Weekly subconjunctival Pegilated INF alpha 2b might be an alternative in resistant cases of CIN or recurrent conjunctival papillomatosis avoiding a mutilating surgery (Tseng, 2009), (Karp et al, 2010).

9.2.4 Other treatment possibilities

Other treatment options in the management of conjunctival OSSN include topical retinoids, cidofovir and photodynamic therapy (PDT). Topical unguent of trans-reinoic acid (0.01%) showed complete resolution of CIN in 20% of cases, whereas 40% showed only partial response (Espana el al, 2003). This treatment may be then only adjuvant to surgery.

Regression of diffuse conjunctival CIN was demonstrated following a 6 week course of topical cidofovir eyedrops (2.5 mg/ml) with later residual lesion after surgical excision (Sherman et al, 2002).

Following PDT, using verteporfin, a complete clinical CIN regression, supported with angiographic evidence, has been reported at 1 month, without any recurrence for a mean follow-up of 8.6 months (Barbazetto et al, 2004). Likewise, histopathological evidence showing tumor regression following treatment with PDT in a patient with in situ CIN has been reported (Sears et al, 2008).

10. References


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Siganos CS, Kozobolis VP, Christodoulakis EV. The intraoperative use of mitomycin-C in excision of ocular surface neoplasia with or without limbal autograft transplantation. Cornea 2002; 21:12-16.


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 digestible, the book is illustrated with colorful images.

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