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Squamous Cell Carcinoma of the Eyelids: Review of Our Experience

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Abstract **Original Research Article**

Aim: To review the epidemiological and clinical features, management, and outcomes of surgical treatment of eyelid squamous cell carcinoma. ***Methods:*** A retrospective review of all eyelid squamous cell carcinoma treated between 2012 and 2019. ***Results:*** 21 cases were identified in 21 patients. Patient ages ranged from 7 to 70 years, with a mean age of 56 years. 14 patients were male and 7 were female. The lower eyelid was the site of origin for 13 tumors. Lesion size ranged from 2 mm to 36 mm with a median of 6 mm. Orbital invasion was found in two patients. No patients developed lymph node or distant metastases. Treatment was by complete excision with histological confirmation of clear margins. Exenteration was required in two patients. Mean follow up was 28 months. During the follow-up period, there was no recurrence or death reported. ***Conclusions:*** Eyelid squamous cell carcinoma is a relatively uncommon, but potentially fatal disease by orbital invasion or metastasis. However, if detected early and treated adequately, the prognosis is generally excellent.

Keywords: Squamous cell carcinoma, eyelids, orbit, excision, exenteration, molecular‑targeted therapies.

INTRODUCTION

Squamous cell carcinoma (SCC) is a type of invasive malignancy arising from the squamous cell layer of the skin epithelium [1]. It can be found in various locations on the body. In the ocular and periocular region, it can affect the conjunctiva, cornea, and eyelid skin. It is the second most common malignant eyelid tumor and represents around 5% of malignancies in the palpebral area [2].

It is potentially lethal by orbital invasion or metastasis and characterized by clinical polymorphism thus requiring early diagnosis and management. This study aimed to establish the epidemiological and clinical characteristics, treatment modalities and outcomes of surgical treatment of eyelid squamous cell carcinoma.

MATERIELS AND METHODS

A retrospective medical record review was conducted of all eyelid squamous cell carcinomas seen in the practice of the senior author (S.H.) in the 8 years from 2012 to 2019. Cases were identified by searching the practice records of the author and pathology laboratory computerised databases. Included were all lesions originating on the eyelids or canthi with a pathologically confirmed diagnosis of SCC. Exclusion criteria included lesions outside the orbital margin, and cases with less than 6 months of follow up. Each patient underwent a thorough history and clinical examination, and all follow up was performed by the senior author. The majority of lesions were treated with excision, while some were biopsied by the referring practitioner before definitive excision.

RESULTS

Patient ages ranged from 7 to 70 years, with a median age of 56 years. The youngest patient was 7 years old, but the majority of the patients (71,4%) were over 50 years of age (figure 1). Fourteen of the patients were male (66,7 %) and 7 were female (33,3%), (figure 2). One patient in the current study (The youngest patient) had a tumor diasthesis predisposing to epithelial malignancies, a xeroderma pigmentosum. Five patients (23,8 %) had recurrent eyelid lesions, previously treated elsewhere. The previous treatment was surgical excision in 3 cases and curettage in 2 cases. It was difficult to know for all these 5 cases whether these lesions represent recurrence of the original lesion, or the development of a metachronous lesion, for lack of initial histopathologic diagnosis.

Lesion size ranged from 2 mm to 36 mm with a median of 6 mm. The lower eyelid was the site of predilection, it was the site of origin for 13 tumors (61,9%), the media canthus for 5 tumors (23,8%), (table 1). Lymph node or distant metastasis was not observed in any patients. The surgical approach to SCC consisted of surgical excision with an average safety margin of 9.6 mm (with a median of 10 mm) in 19 cases, and orbital exenteration in 2 cases (table 2). The patients were followed-up for an average of 28 months (range, 18–42 months) after surgery. During the follow-up period, there was no recurrence or death reported.

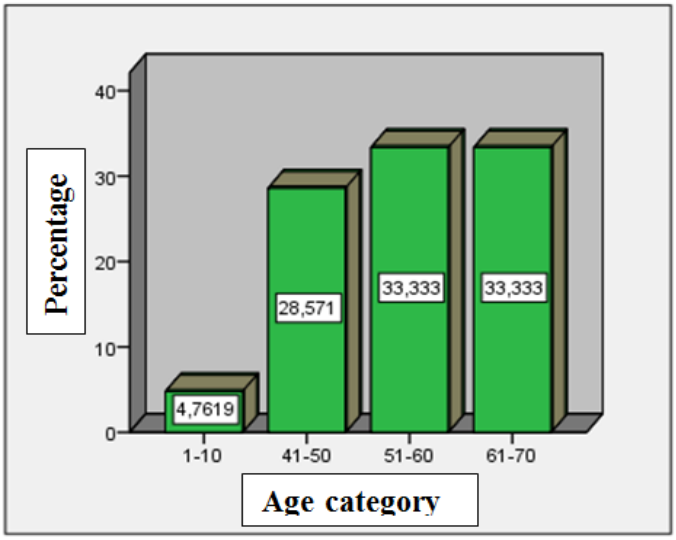

Fig-1: Patient age distribution (by years)

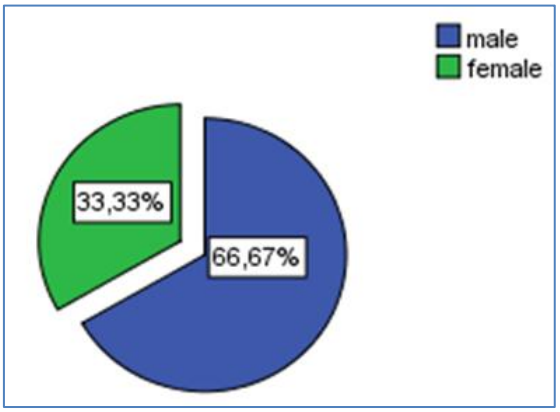

Fig-2: Distribusion by sex

Table-1: Site of lesion

Site	nombre of cases
Lower eyelid	13 (61.9%)
Medial canthus	5 (23.8%)
Upper eyelid	2 (5.9%)
Lateral canthus	1 (4.8%)

Table-2: Management options used

Treatement	nombre of cases
Excision with flap repair	13 (61.9%)
Excision with graft repair	6(28.6%)
Exenteration	2(9.5%)

DISCUSSION

The eyelids play an important role in the protection and maintenance of the eye. The eyelid skin is the thinnest in the body (less than 1 mm thick). It is very elastic and is well vascularized. The epidermis is composed of keratinized stratified squamous epithelium with an underlying basement membrane. The dermis contains a thin laye of connective tissue with an abundance of elastic fibers blood vessels, lymphatic vessels and nerves [3].

Approximately 5 to 10% of all skin cancers occur on the eyelid [4], in addition, other studies have revealed the rapidly increasing incidences of skin cancer and even malignant eyelid tumors [5-6].

However, SCC is relatively rare, it represents 3.4 to 12.6% of eyelid tumors. The reduced relative incidence of SCC is, in part, due to the recognition that a number of lesions can be confused with SCC like some Benign tumors such as keratoacanthoma, pseudoepitheliomatous hyperplasia, and inverted follicular keratosis [7].

The average age is 60 years (68 to 73 years) [8-10]. That of our series is 53, 7 years old, but it can occurs earlier in predisposed individuals like in patients with xeroderma pigmentosum or albinism. In our series the youngest patient was a child who was barely 7 years old and who was already being followed for xeroderma pigmentosum.

The manifest male predominance (66.7 % vs 33.3 %) may represent increased sunlight exposure by males, rather than a genetic predisposition.

SCC of skin has various risk factors and etiologies, including aging [11], chronic and excessive sun exposure [12], oil derivates and arsenic exposure,

Human Immunodeficiency Virus infection (HIV), xeroderma pigmentosum, albinism, old burns, chronic ulcers, and immunosupression. In our study, the most common risk factors were advanced age and sun exposure; 71,4% of the patients were over 50 years of age and 61.9% of patients had an excessive occupational sunlight exposure (> 6 h/d during the previous 10 years).

If SCC usually presents as an ulcerated lesion on an encrusted erythematous indurated and elevated base, the clinical types of carcinoma are variable and there are no pathognomonic characteristics [13]. In our study Lesions show a large spectrum of clinical appearances, including erythematous scaly patches, ulcerated lesions (figure 3), and nodular or papillomatous lesions (figure 4). The margin of the lesion may be well circumscribed in some cases, and ill defined in others. This wide variation in clinical appearances presents a great difficulty in differentiating SCC from some much more frequents skin cancers such as basal cell carcinoma. Numerous studies have confirmed the inaccuracy of preoperative clinical diagnosis. Donaldson M. J. had reported in a study that 62.7% of the SCC were clinically confirmed [14]. In another study Nixon R.L. had found that only 51% of the SCC were clinically confirmed [15]. The clinical diagnosis of basal cell carcinoma offers better results, Kersten obtaining a diagnostic accuracy of 92.8% [16]. All these figures prove the significant difficulty associated with the clinical diagnosis of eyelid SCC, and confirms the importance of histopathological examination, preferably by excisional biopsy, for all suspicious eyelid lesions.

Fig-3: Squamous cell carcinoma of the Lower eyelid presenting as a ulcerated lesion

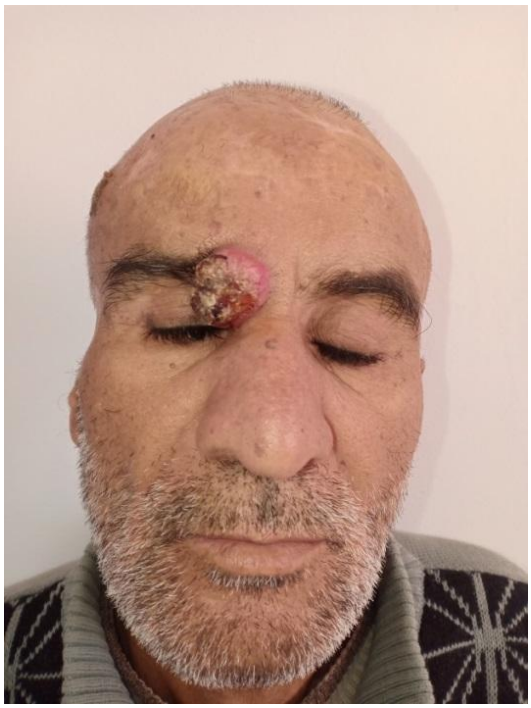

Fig-4: Squamous cell carcinoma of the upper eyelid presenting as a nodular lesion

The differential diagnosis of SCC includes basal cell carcinoma, keratoacanthoma, sebaceous gland carcinoma. Metastasis of systemic tumors to eyelids is not a very common occurrence, however, breast, thyroid, renal cell carcinomas and melanoma are known to spread to eyelids and may mimic SCC [17].

SCC typically manifests as a spectrum of progressively advancing malignancies, ranging from a precursor actinic keratosis to SCC in situ, invasive SCC, and finally metastatic SCC. It is considered as in situ when it is superficial to the basal membrane, and it is classified invasive when it extends deep to the basal membrane layer of the skin [18].

Excisional biopsy, is the gold standard to diagnose SCC as it can evaluate the depth and extent of invasion of the cancer. The histopathologic features of SCC depend on the degree of differentiation of the tumor. In well-differentiated tumors, the cells are polygonal with abundant acidophilic cytoplasm and hyperchromatic nuclei with various sizes and staining properties, dyskeratotic cells, and intercellular bridges. Poorly differentiated SCC shows pleomorphism with anaplastic cells, abnormal mitotic figures, little or no evidence of keratinization, and loss of intercellular bridges. Variants of SCC are spindle and adenoid SCC [19].

Orbital invasion is a serious and potentially fatal complication of SCC of the eyelide. SCC is responsible for approximately 10 % of carcinomas involving the orbit [20]. Delay in diagnosis is the critical factor in the orbital invasion. Clinical

presentations mimicking other lesions may retard the diagnosis. Risk of orbital invasion also increases when the initial lesion has been incompletely excised and is consequently prone to recurrences [21]. SCC may invade the orbit by direct extension [22], by perineural spread [23], or by metastatic spread.

Orbital invasion may also be associated with involvement of the orbital nerves, branches of the trigeminal and facial nerves, and cranial nerves. The involvement of cranial nerves may provide access to the cranial cavity [24, 25]. Spread is usually antegrade (i.e., toward the central nervous system) but may also be retrograde upon reaching a junction point such as the trigeminal ganglion [26].

In our study, orbital invasion was seen in two patients (5.9%), both required exenteration and both had a good result from surgery, and were recurrence free at 9 and 42 months after surgery. This is in line with other studies which have demonstrated that recurrence after orbital exenteration is rare [27].

SCC has the potential to metastasize to regional lymph nodes [28, 29]. The tumor may spread via the lymphatics to the submandibular nodes from the lower lid and medial canthus, and to the preauricular nodes if the tumor is in the lateral canthus or upper lid [30]. If the risk of metastases of the SCC exists it remains nevertheless relatively rare compared to others malignants tumors of the skin like melanoma. Szymanski reviewed 2517 cutaneous squamous cell carcinomas during a 25 year period and found only six tumors (0.23%) that had metastasized [31]. Lund [32], recorded six metastases (0.25%) from 2500 cutaneous squamous cell carcinomas. However, tumors arising in areas of previous radiation therapy or osteomyelitic cutaneous fistulas have a higher incidence of metastasis and mortality. SCC in areas of previous radiation damage have a metastasis rate of 20% [33].

Surgical excision is the treatment of choice for SCC of eyelid and in some cases may require grafts or flaps [34]. Published reports concerning the management of non-melanocytic malignant eyelid tumors show the strongest evidence for complete surgical excision using histology to verify tumor-free margins. Options include Mohs' micrographic surgery or excision with frozen-section control [35].

Radiation therapy is only reserved for patients for whom surgery is too dangerous. The promising, novel treatment option for patients with SCC is molecular targeted therapies. The best known targeted therapies include: Epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab, panitumumab, zalutumumab and nimotuzumab), EGFR tyrosine kinase inhibitors (gefitinib, erlotinib, lapatinib, afatinib and dacomitinib), vascular endothelial growth factor (VEGF) inhibitor (bevacizumab) or vascular endothelial growth factor receptor (VEGFR) inhibitors (sorafenib, sunitinib and vandetanib) and inhibitors of phosphatidylinositol 3-kinase/serine/threonine-specific protein kinase/mammalian target of rapamycin. There are also various inhibitors of other pathways and targets, which are promising and require evaluation in further studies [36].

CONCLUSION

Eyelid SCC is a relatively rare, but potentially fatal disease. It can be associated with important morbidity because these tumors are locally invasive and can metastasize, thus requiring early diagnosis and management to protect patients from serious and lethal complication such as invasion of the orbit and involvement of cranial nerves. This explains the need for histological examination of any suspicious lesion. Prevention through photoprotection is essential, especially in childhood and adolescence.

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