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Intraepithelial Carcinoma of the Limbus

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Abstract
Ocular neoplasms are uncommon. Of the ocular neoplasms, squamous epithelial tumours of the conjunctiva and cornea are rare. Ocular surface squamous neoplasia is categorized into carcinoma in situ and squamous cell carcinoma. Limbus which contains mitotically active stem cells is the most common site of ocular squamous epithelial neoplasia. These tumours have a varied clinical presentation and the diagnosis depends on histopathological examination. A 89 yr old male with history of discomfort in eyes for 15 days, clinically presented with leukoplakic limbal lesion. Biopsy of the lesion revealed intraepithelial carcinoma.
Keywords: *Intraepithelial carcinoma, Limbal stem cells, Bowen's disease.*

Introduction

The limbal epithelium, is the transitional zone between transparent cornea and opaque sclera. It contains pathway for aqueous humour outflow and is characterised by the palisades of vogt, an undulating network which harbours limbal stem cells. The limbal stem cells play an important role in differentiation of ocular tissues. They, characteristically have a slow turnover rate and high proliferative potential.

Ocular squamous epithelial tumours are divided into carcinoma in situ and squamous cell carcinoma. Squamous cell carcinoma exhibits features of invasion and metastasis. Carcinoma in situ also known as intraepithelial carcinoma and intraepithelial epithelioma, most commonly arises from the limbus. It extends slowly into adjacent corneal and conjunctival epithelium. The proliferative changes are usually confined within epithelium and varies considerably in its clinical appearance[1]. The clinical presentation usually varies, arising either as a thickening, leukoplakia or papilloma, rendering clinical diagnosis difficult[3]. Occasionally histological features resemble intraepithelial carcinoma of skin, termed as Bowen's disease or intraepithelial carcinoma of glans penis, described as Erythroplasia of Queyrat[1]. Complete excision of the lesion along with margins and histopathological examination of the biopsied specimen is essential to confirm the diagnosis.

Case History

A 89 yr old male presented with complaints of pain, redness and irritation of the left eye, for 15 days. On examination, the left eye showed bulbar conjunctival congestion with a well circumscribed, raised, whitish nodule measuring about 0.5 x 0.5 cm at 4'o clock position of the perilimbal region [Plate 1] . Right eye was normal. Visual acuity of both eyes were normal. The limbal nodule was excised. The histopathological diagnosis of the biopsied specimen was intraepithelial carcinoma. The patient showed good progress after surgery . On Regular follow up for one year, there is no evidence of recurrence or invasive disease [Plate 2].

Histopathology

Grossly, the limbal biopsy specimen received was a single tiny grayish white tissue piece measuring 0.5 x 0.5cm.

Histological Sections studied from the limbal biopsy revealed, squamous mucosal biopsy showing marked hyperkeratosis with a column of parakeratosis {figure 1}. Squamous epithelium was expanded and contained anaplastic cells {figure 2}. Few giant cells and occasional mitotic figures were also noticed {figure 5}. Basement membrane appeared intact {figure 3}. Histopathological features were consistent with the diagnosis of intraepithelial carcinoma of the limbus.

Plate 1: Clinical Picture of Limbal Nodule

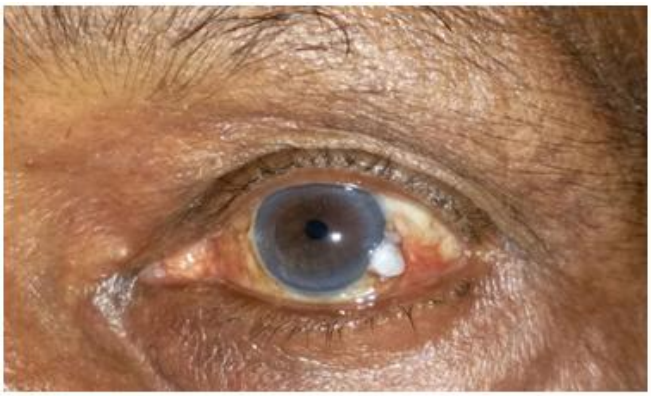

Plate 2: Clinical Picture after Surgical Excision

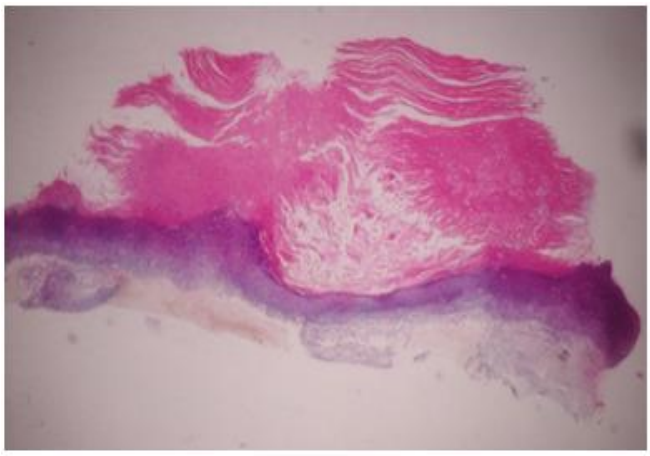

Figure 1: H & E stained (10X)
Squamous mucosal biopsy showing hyperkeratosis and focal parakeratosis

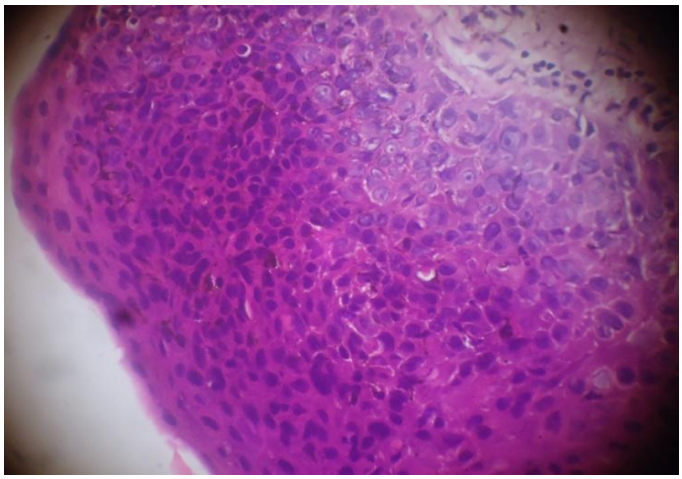

Figure 2: H & E stained (40X)
Showing markedly anaplastic tumor cells

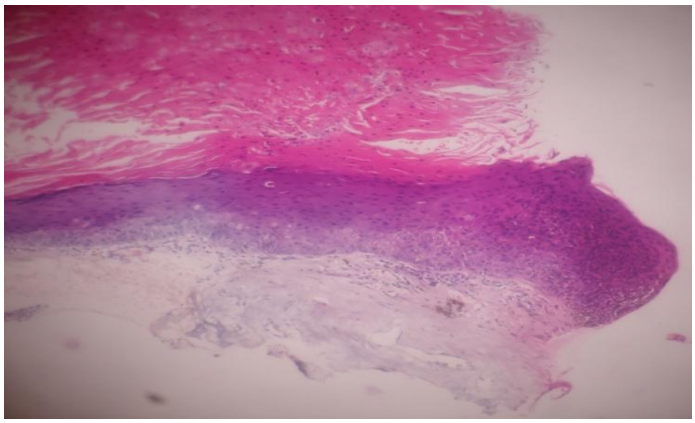

Figure 3: H & E stained (10X)
Tumors cells are confined within epithelium and the basement membrane is intact.

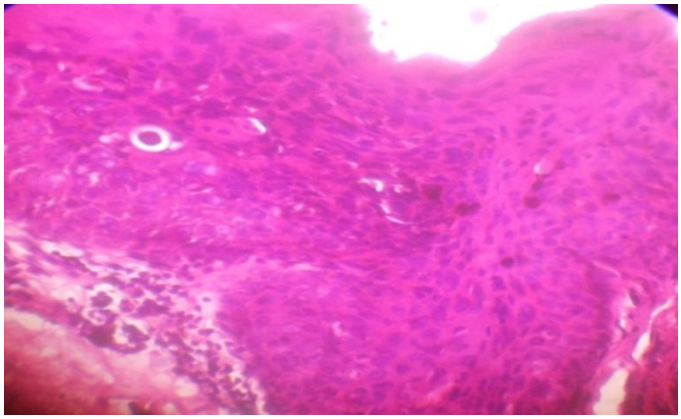

Figure 4: H & E stained (40 x)
Individual cell keratinization

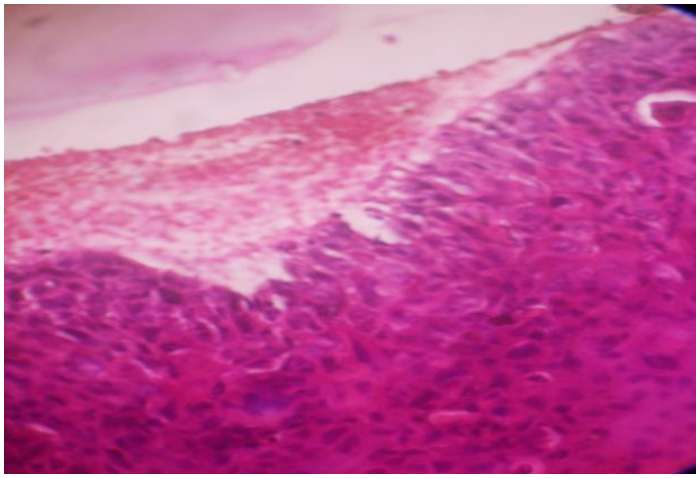

Figure 5: H & E stained (40 x)
Mitotic figures

Discussion

Tumors of the eye and ocular adnexa are rare. uveal melanoma and intraocular lymphoma are the most common ocular tumors. Ocular surface squamous neoplasia accounts to be the third most common ocular neoplasm. It is a broad term encompassing Conjunctival squamous cell carcinoma in situ and invasive squamous cell carcinoma[6]. Conjunctival squamous cell carcinoma in situ or intraepithelial neoplasia (CIN) is a rare and slow growing conjunctival neoplasm typically occurring in elderly and males. The incidence of this neoplasm is between 1 and 2.8 per 100 000 people per year and varies in different geographic regions[4]. The most common site of these tumors is interpalpebral area of the perilimbal conjunctiva[4]. The etiology is multifactorial with an interplay of multiple factors. There is an increased risk with history of exposure to ultraviolet rays, chemical carcinogens, tobacco, viral infections like HPV 16, 18 and immunosupression states. It may mimic benign corneal degenerations and may coexist with pterygium and pingecula. In younger individuals the most common predisposing factors are xeroderma pigmentosa and immunodeficiency states. Clinically, the lesion has varied presentations like nodular growth, gelatinous thickening, leukoplakia or papilliform lesions. The characteristic lesion is a vascularised gelatinous thickening of the conjunctiva, usually arising at the limbus and gradually extending to the cornea. The cornea is a thick transparent, non vascular structure of the eye. The anterior surface of the cornea is covered with a stratified squamous epithelium which is non keratinized and consist of five or more layers[7]. When the neoplastic squamous cells extend into the cornea, the corneal epithelium gets keratinized as a result of chronic irritation and adjacent neoplastic pannus formation, which metabolically supports these tumor cells. As a result, clinically it presents as a opacity[2]. Histologically, it is identified by, hyperkeratosis and parakeratosis. Microscopically, the intraepithelial carcinoma exhibit epithelial changes similar to invasive squamous cell carcinoma and can be differentiated only by the presence of an intact sub epithelial basement membrane. This intact basement membrane, confines the tumour cells within the conjunctival

epithelium, separating the epithelium and tumour cells from underlying substantia propria and stroma[7]. In invasive squamous cell carcinoma the cells invade through the basement membrane and involve the substantia propria. Corneal limbus is the site of ocular stem cells, which have high proliferative capacity and mitogenic potential. And also, the Bowman's layer of the cornea forms a natural barrier to prevent subepithelial cellular invasion and confines the tumor cells within epithelium[4]. Hence, neoplasms of this region remain confined within the epithelium for many years before there is an evidence of invasive growth. Intra epithelial neoplasia is managed by complete excision of the lesion along with margins, with or without cryotherapy. Radiotherapy, topical chemotherapy and immunotherapy has promising role in the management of recurrences and aggressive tumors .The recurrence of intraepithelial malignancies can occur over half of the cases and may occur years later. When recurrent, ocular surface squamous neoplasia's tend to involve more than half of the limbal stem cells. It may grow rapidly and become more invasive. Diagnostic modalities like Anterior segment optical coherence tomography, confocal microscopy and high frequency ultrasound helps in–vivo differentiation of intraepithelial carcinoma and squamous cell carcinoma; but the extent of invasion, variants, and prognosis cannot be made out[4]. Therefore, histopathological examination is the gold standard to diagnose various types and grades of ocular surface squamous neoplasia. It gives fair understanding about invasion and disease prognosis and thus helps in further management. Conjunctival impression cytology can also be used to diagnose flat limbal lesions and aids help in diagnosing recurrence.

Conclusion

Ocular surface squamous neoplasia has various clinical presentations. Both carcinoma in situ and invasive squamous cell carcinoma has similar clinical presentation, which makes the diagnosis difficult. Although, intraepithelial carcinoma is confined to the epithelium for many years, it can proliferate indefinitely and become invasive with high recurrence rate. The histopathological examination of the excised lesion is imperative for the appropriate diagnosis and to minimize recurrence and progression.

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