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Review Article

Recent updates on the management of ocular sebaceous gland carcinoma

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ABSTRACT

Ocular sebaceous gland carcinoma (SGC) is a relatively rare, slow growing, but most aggressive and life-threatening tumor. It accounts for around 1% of all cutaneous malignancies. In Caucasians, SGCs are rare accounting for 1-5.5% of eyelid malignancies with a high incidence rate (28-60%) reported in the Asian population. In most SGCs no obvious etiology has been identified but few cases are associated with Muir-Torre syndrome. The dysregulation of several cell signaling pathways has been reported in tumorigenesis of SGC. Recently genome sequencing of periocular SGC revealed several gene mutations like TP53 and RB1 genes. Ocular SGC is known as the 'great masquerader' as it mimics several benign and inflammatory conditions like chalazion and chronic blepharitis/ blepharoconjunctivitis which may be responsible for delayed diagnosis and high mortality. Clinico-pathologically ocular SGC can be broadly categorized into nodular and pagetoid subtypes. The latter is more aggressive and associated with a high rate of lymph node metastasis and recurrence hence requiring aggressive multimodal treatment. More aggressive features associated with poor prognosis include involvement of both eyelids, infiltrative growth pattern, multicentric in origin with a pattern of spread to surrounding structures like pagetoid spread, vascular, lymphatic and orbital invasion. Although wide surgical excision with tumor-free margin is the gold standard treatment for the localized nodular type of ocular SGC, but the management of advanced-stage disease, invasive or aggressive lesions and recurrence is challenging and often needs a multidisciplinary approach that can reduce the mortality rate in patients with SGC. In this review article, we report recent research in molecular pathogenesis, clinicopathological features, the importance of TNM staging, sentinel lymph node biopsy, map biopsy and immunohistochemical evaluation of tumor markers like p^{53},Ki-67, bcl-1, and p^{21}. We also emphasized the treatment of ocular SGC, i.e. surgical excision & reconstruction, topical therapy, neoadjuvant chemotherapy, targeted therapy, and radiation therapy.

1. Introduction

Sebaceous gland carcinoma (SGC) is an uncommon, slow growing tumor. It is the most aggressive and lethal malignant tumor after cutaneous malignant melanoma. The tumor is predominantly seen in the periorbital region. Ocular SGC is relatively rare in the western population (4-5% of all eyelid malignancies) while in the Asian-Indian population, it is the most common eyelid

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malignancy accounting for 28-60%.[1–5] SGC of the eyelid tends to occur in the 6th -7th decade of life and it predominates in females.[6] Clinically, it masquerades as benign and inflammatory conditions like chalazion and chronic blepharitis or blepharoconjunctivitis which may lead to delay in diagnosis, metastasis and poor prognosis.[7] It may involve fornicial and bulbar conjunctiva with diffuse thickening of the eyelid and caruncle area. A high rate of recurrence (9-36%) and nodal metastasis (17-28%) have been reported.[8] The diagnosis and management of ocular SGC is often challenging because of its masquerading and aggressive nature. In this review we highlight the latest diagnostic techniques ,treatment & therapeutic options based on existing literature.

2. Origin and Clinical Patterns of Ocular SGC:

Sebaceous carcinoma develops from some specific glands and periorbital area including the gland of Zeis, meibomian glands, glands associated with hair follicles, caruncle, conjunctiva, and sebaceous glands with the eyebrow. The gland of Zies is a unilobular sebaceous gland located on the margin of the eyelid that produces an oily substance, during abnormal conditions, this gland gives rise to 10% of sebaceous carcinoma.[9] The meibomian glands (tarsal glands) are exocrine glands located along the rim of the eyelids (Figure 1). The meibomian glands are abundantly present at the upper lid (63%) as compared to the lower lid (27%) hence SGC of the eyelid is more profound at the upper eyelid. The incidence of sebaceous carcinoma arising from caruncle is very low, reported to be around 5-10%.[9]

SGC is the most aggressive tumor of the eyelid and associated with a high mortality rate, thus its early & accurate diagnosis and appropriate treatment are important. Sebaceous carcinoma of the eyelid is the most notorious tumor which can masquerade as a benign condition (“masquerade syndrome”) like chalazion, chronic blepharitis / blepharo conjunctivitis & keratoconjunctivitis , etc., often resulting in difficulty or delay in diagnosis.[10]This in turn can increase the chances of local recurrence, metastasis, and death. Ocular sebaceous carcinoma has a varied clinical presentation. The most common presentation is a painless, sessile / nodular yellowish tumor involving the eyelid margin (from the gland of Zeis)with loss of eyelid architecture and cilia (Figures 1 and 2). SGC may sometimes grow outward and become pedunculated with keratinization and also possess a cutaneous horn-like appearance.[11,12] Less commonly, SGC may ulcerate and have an appearance like squamous cell carcinoma / basal cell carcinoma. The second most common manifestation is a diffuse pseudo-inflammatory lesion that is marked as a diffuse unilateral thickening of the eyelid (Figures 4 and 5). This presentation is more likely to extend to the epithelium of nearby structures such as the cornea and conjunctiva. The lack of a typical nodular appearance causes the clinician to suspect an inflammatory condition.[13,14] It is also suggested that SGC must be ruled out in unilateral blepharitis in an elderly patient that does not respond to standard treatment, and thus a biopsy is indicated. SGC may develop as a gradually progressive yellowish-red mass involving the medial canthus. (Figures 5 and 6).[15] Often SGC may originate as a sebaceous cyst of the eyebrow. Caruncular SGC is uncommon. (Figure 7). Primary sebaceous carcinoma is rarely found in the lacrimal gland,[16,17] rather seen as extensive invasion of eyelids, conjunctiva, cornea, and anterior orbital tissue.[15]

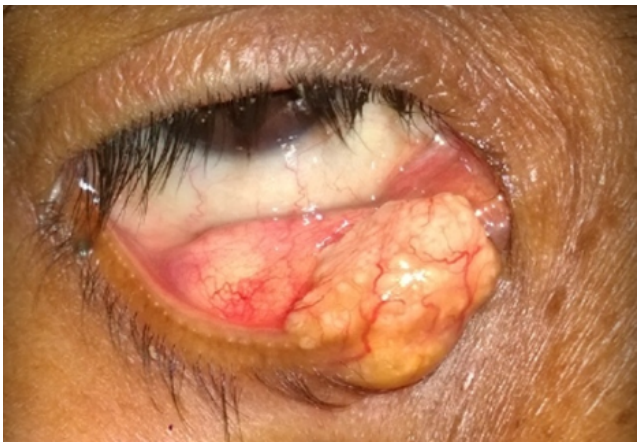

Fig. 1: Large nodular type of sebaceous gland carcinoma arising from meibomian glands of the right lower eyelid involving the medial aspect of the lid. Note irregular yellowish mass with loss of cilia and multiple telangiectatic vessels.

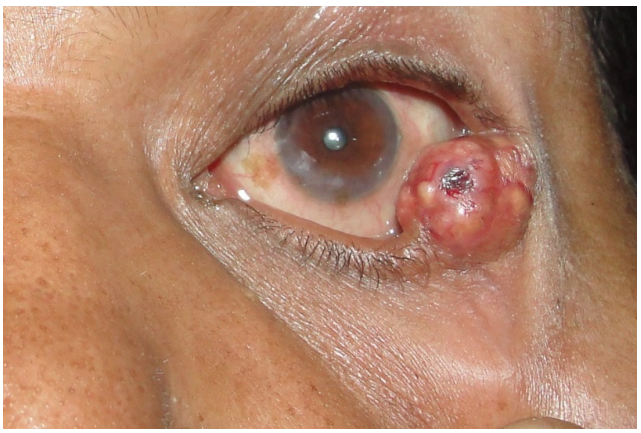

Fig. 2: Nodular sebaceous carcinoma arising from the lateral aspect of the tarsus of the left lower eyelid.

American joint committee on Cancer (AJCC) recommendation defined TNM (tumor node metastasis) to access the tumor staging. AJCC classification on the recent staging of SGC based on the eighth edition is given below in Table 1:[18]

Table 1: JCC cancer staging manual giving details on each part of the TNM system for eyelid cancer (eighth edition)

Primary Tumor (T)	**Definition**
TX	Primary tumors cannot be evaluated
T0	No primary tumor
Tis	Refers to carcinoma in situ
T1	Size of tumor ≤ 10 mm in diameter
T1a	No invasion of the tarsal plate or eyelid margin
T1b	Invasion of tumor in the tarsal plate or eyelid margin
T1c	Involvement of tumor in the full thickness of the eyelid
T2	Tumor size > 10 mm but ≤ 20 mm in diameter
T2a	No invasion of the tarsal plate or eyelid margin
T2b	Invasion of tumor in the tarsal plate or eyelid margin
T2c	Involvement of tumor in the full thickness of the eyelid
T3	Tumor size > 20 mm but ≤ 30 mm in diameter
T3a	No invasion of the tarsal plate or eyelid margin
T3b	Invasion of tumor in the tarsal plate or eyelid margin
T3c	Involvement of tumor in the full thickness of the eyelid
T4	Tumor invading the orbital, facial, and ocular structure
T4a	Tumors invading the intra-orbital and ocular structure
T4b	Tumors invading the lacrimal sac, nasolacrimal duct, brain and erosion of bony orbital walls, or those with paranasal sinus
Lymph Node (N)	
NX	Regional lymph nodes cannot be evaluated
N0	Refers to no regional lymph node metastasis
N1	Regional lymph node metastasis < 3 cm in diameter
N1a	Metastasis based on clinical evaluation or imaging
N1b	Metastasis proved by histopathology
N2	Regional lymph node metastasis > 3 cm in diameter with involvement of bilateral and contralateral lymph node
N2a	Metastasis based on clinical evaluation or imaging
N2b	Metastasis proved by histopathology
Distant Metastasis (M)	
M0	No distant metastasis evaluated
M1	Metastasis to other body parts

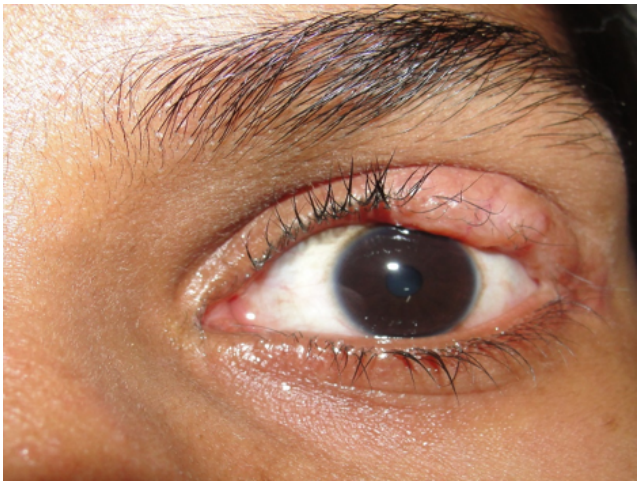

Fig. 3: Diffuse thickening of the lateral half of left upper eyelid with irregular loss of cilia due to sebaceous gland carcinoma in a 40 year male.

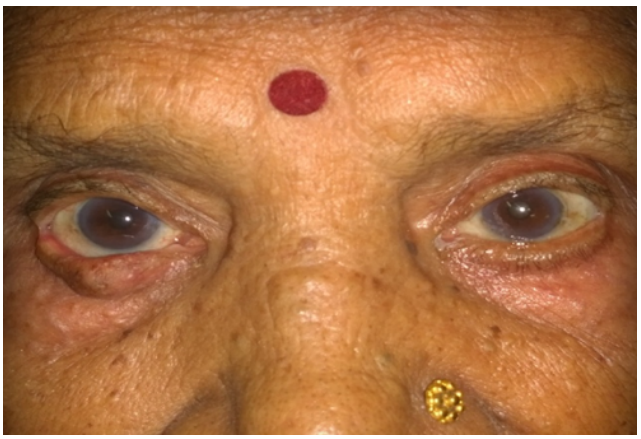

Fig. 4: Nodular swelling with diffuse thickening of right lower eyelid due to sebaceous gland carcinoma in 70-year female.

3. Tumor spread

Diagnosis and management of ocular SGC is always challenging mainly due to its masquerading nature and tendency to spread beyond its primary site of origin. It can spread through local invasion, regional metastasis and distant metastasis. SGC tends to have a multicentric origin and pagetoid invasion. It has been reported that 18% of advanced sebaceous carcinomas are having multicentric origin.[16,19] Eyelid sebaceous carcinoma can locally invade the adjacent orbital soft tissue, lacrimal system, and intracranial contents. Regional metastasis of ocular SC occurs via lymphatic spread in about 30% of cases.[20,21] The SC of the upper eyelid tends to metastasize to preauricular lymph node (Figure 8) & parotid gland while lower eyelid carcinoma tends to metastasize to submandibular and cervical lymph nodes.[22,23] The majority of the deaths

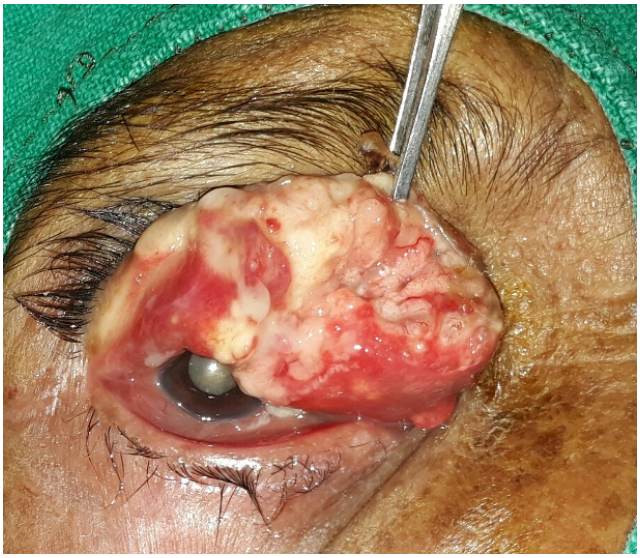

Fig. 5: Advanced ulcero-nodular sebaceous gland carcinoma of the medial half of left upper eyelid with extensive involvement of medial canthus and infero-medial bulbar conjunctiva.

Fig. 6: Advanced ulcero-nodular sebaceous gland carcinoma of the medial half of left upper eyelid with extensive involvement of medial canthus and infero-medial bulbar conjunctiva .

associated with ocular SC is due to distant metastasis. The most common organs involved are the brain, liver, lung bone etc.

4. Pathology

4.1. Histopathology

A gross specimen of eyelid biopsy of SGC may have a yellow appearance due to the presence of lipids. Microscopic histopathologic examination is the gold standard in confirmation of SGC. Normal Sebaceous gland presents as a peripheral border of basaloid cells

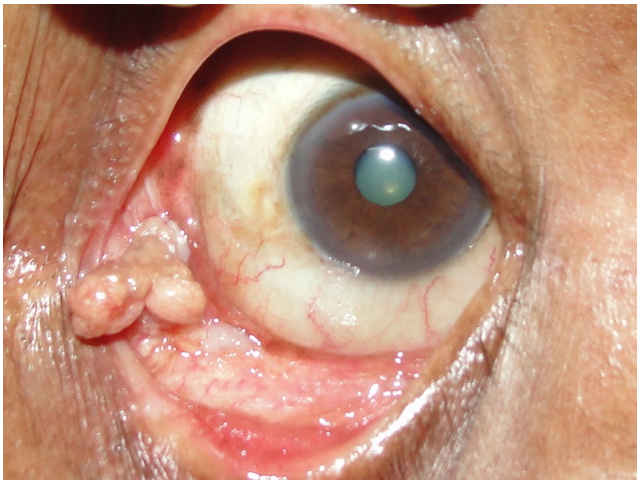

Fig. 7: Multilobulated pedunculated mass arising from left caruncle that was histopathologically proven as sebaceous gland carcinoma.

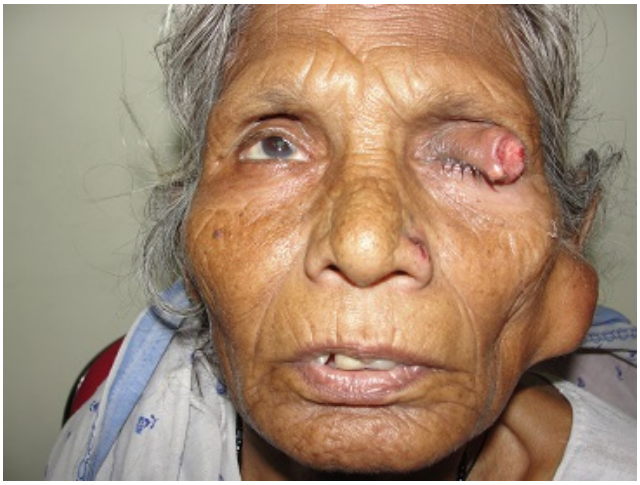

Fig. 8: Ulcero-nodular type of sebaceous gland carcinoma of the left upper eyelid with pre-auricular lymph node metastasis in a 70-year-old female.

which after maturation became lipid-laden cells. In SGC there is a loss of the normal maturation architecture of the gland. SGC is characterized by pleomorphic cells with prominent vacuolated or clear cytoplasm, vesicular nuclei with prominent nucleoli, and numerous mitosis(Figures 9 and 10). The intracytoplasmic lipid vacuoles can be demonstrated by oil red O or Sudan IV Stains. The four histopathological patterns of SGC are (i) Lobular (ii) papillary (iii) Comedocarcinama and (iv) mixed type.[16,22,24] The lobular pattern is most frequent and characterized by peripheral normal-looking, sebaceous gland architecture, and control well differentiated lipid- producing cells (Figure 11). Rao et al reported a comedocarcinoma variant characterized by large central necrosis surrounded by peripheral viable

cells.[25] However papillary pattern mostly present as small conjunctival tumors having papillary projections with sebaceous differentiation. Histopathologically SGC can be classified as well-differentiated, moderately differentiated and poorly or undifferentiated type.

Rao et al also described infiltrative features of SGC categories as minimal, moderate and highly infiltrative patterns. Minimally infiltrative type tumors are predominantly composed of lobules with minimal stromal invasion while highly infiltrative type have diffuse infiltrating cords of tumor cells in the stroma. Higher degrees of stromal infiltration is associated with a high mortality rate.

Cavanagh et al described the multicentric origin of SGC and which is also an important cause of misdiagnosis[26] Another causes of misdiagnosis is its ability to exhibit intraepithelial spread reported in about 39% patients, which may be Bowenoid, pagetoid and mixed pattern.[23,27,28]

Imprint cytology of tissue and fine needle aspiration cytology of lymph node may suggests earliest pathological diagnosis of SGC (Figure 12).

4.2. Immunohistochemistry

Missed histopathological diagnosis on light microscopy is very common with in the case of poorly differentiated SGC. Insufficient biopsy specimens also lead to misdiagnosis. In such conditions, immunohistochemistry helps in diagnosis. Sinard et al used immunohistochemistry to differentiate SGC from other eyelid cancer.[29] SGC is immunoreactive to epithelial membrane antigen (EMA), Cytokeratin Cant-C-K-S & ant-CK-15). Ber-EP4 and Adipophilin (ADP) are more sensitive marker of lipid droplets in SGC than oil red O.[30] Basal cell carcinoma never express EMA. An EMA –positive, Ber-EP4-positive immune-staining supports diagnosis of SGC while EMA-positive, Ber-EP4-negative supports squamous cell carcinoma and EMA-negative, Ber-EP4-positive result supports basal cell carcinoma. (Figures 13, 14 and 15). SGC expresses high p53 and Kil17 (proliferation markers) and decreased expression of DCL-2 and p21 in serum (anti-apoptotic markers).[31] Recently it has been demonstrated that SGC is highly positive for androgen receptor (AR) Immunostaining AR may be a reliable marker of sebaceous differentiation(Figure :14).[32–34] Monoclonal antibodies like BRST -1 and CAM52 are positive in most of the SGC cases.[29,35]

4.3. Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) can be done to identify occult or sub clinical, microscopic nodal spread of SGC. SLNB or strict node surveillance has been recommended for large tumors (> 10mm size), T2b or worse tumors, suspected lymphadenopathy, tumors having poorly differentiated histology and tumors having perineural invasion.[36–38] In SLNB technetium- labeled sulfur colloid is used as a tracer molecule that reaches local lymph nodes through the lymphatic system. The site of tracer collection can be detected by a handheld gamma probe. The single or multiple nodes containing tracer are then excised for histopathological examination.

4.4. Conjunctival Map Biopsy

Ocular SGC tends to show microscopic pagetoid spread leading to diffuse eyelid and conjunctival involvement. In such cases, it is difficult to visualize tumors grossly. Conjunctival map biopsies (CMB) are recommended to determine the extent of the tumor and to decide the definitive treatment for SGC having diffuse conjunctival involvement.[39–41] Shield C.L. advised pretreatment and post-treatment conjunctival map biopsy while treating SGC by topical mitomycin C.[42] In CMB 10-14 biopsies should be taken from bulbar conjunctiva (superonasal, inferonasal, superotemporal and inferotemporal quadrants), on the tarsal conjunctiva (medial, lateral and mid portion) of both eyelids and from plica semilunaris.[43] Careful labeling and numbering of each biopsy should be done before submitting the specimen for histopathological examination.

5. Molecular basis of sebaceous gland Carcinoma:

The molecular basis of tumorigenesis of sebaceous gland carcinoma (SGC) is very little known. Muir-Torre Syndrome (MTS) often associated with SGC and other visceral malignancies, occur due to genetic alterations. MTS have a germline mutation in the DNA mismatch repair (MMR) gene and commonly absent MMR proteins are MLH1, PMS2, MSH6, and MSH2.[44,45] The cell signaling pathways that have been dysregulated in SGC are many like TP53, Went / β-catenin, p21/WAFT1 and Sonic hedgehog (Shh) pathway etc.[46] Kim et al reported a higher incidence of lymph node and distant metastasis in SGC associated with the activation of Wint and Shh singling pathways.[47] Bladen JC also observed Hedgehog (Hh) upregulation specially Gli2 more in SGC than BCC.[48] Kumar A et al found dysregulation of two major pathways in meibomian gland carcinoma of the eyelid: MAPK (mitogen-activated protein kinase) and JAK/STAT(Janus kinase / signal transducers and activators of transcription) by microarray analysis.[49] Tumor suppressor gene p53 helps in maintaining cellular integrity and differentiation. The presence of mutational inactivation of the p53 genes may lead to the progression of SGC and has been associated with a poor prognosis.[29,50]Bladen JC et al have identified aberrant miRNAs and their gene targets in sebaceous gland carcinoma. He demonstrated overexpression of has-miR-205 and down regulation of has-miR-199a in invasive pagetoid variants of SGC.[51]

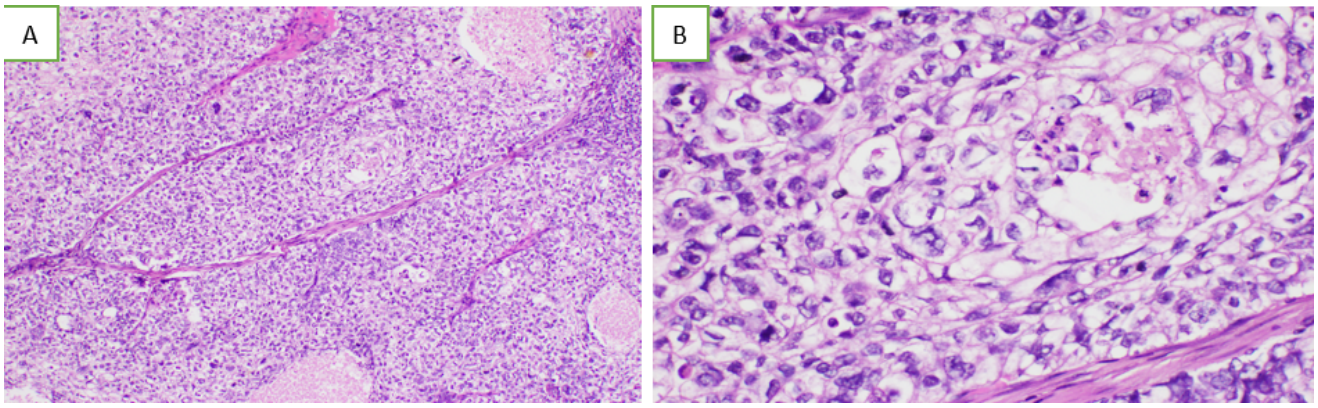

Fig. 9: Lobular growth pattern of sebaceous gland carcinoma of eyelid showing cytoplasmic vacuoles and mitotic activity (**A.** Hematoxylin-eosin X 4 & **B.** Hematoxylin-eosin X 100).

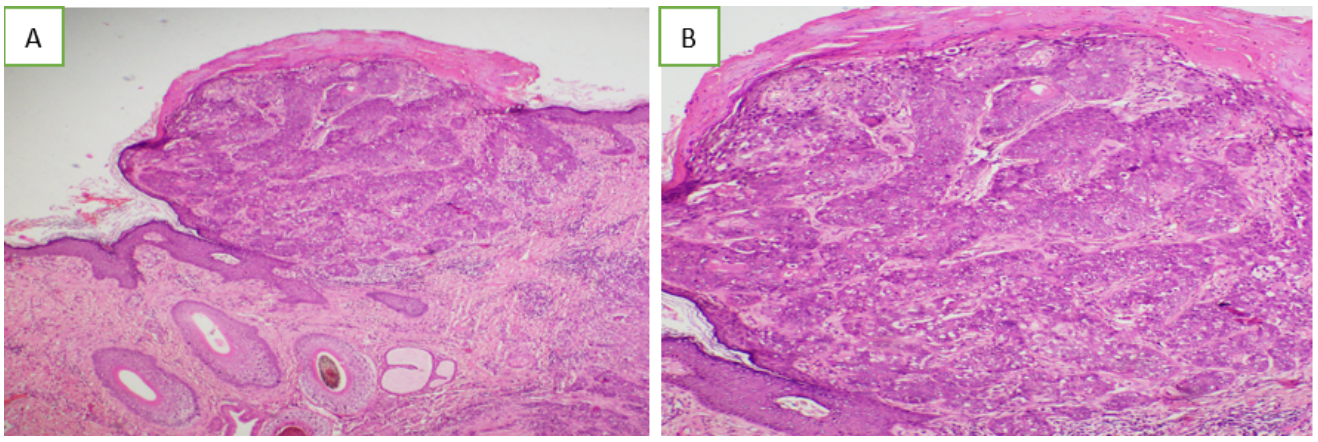

Fig. 10: Localized sebaceous gland carcinoma near the eyelid margin arising from the gland of Zeis (Hematoxylin-eosin X 4 & 10X)

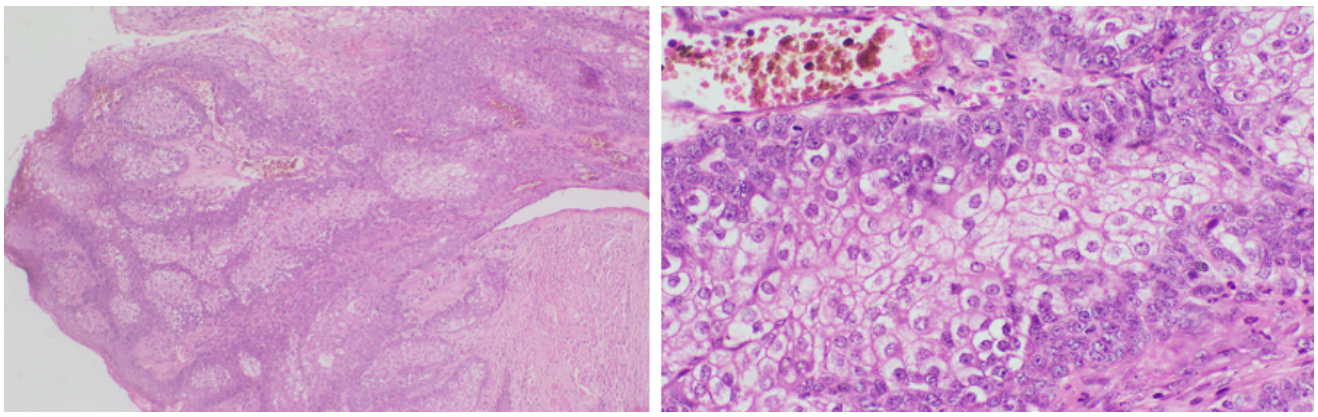

Fig. 11: High grade lobular sebaceous gland carcinoma of the eyelid showing malignant lobules. (Hematoxylin-eosin X 5 & 10X)

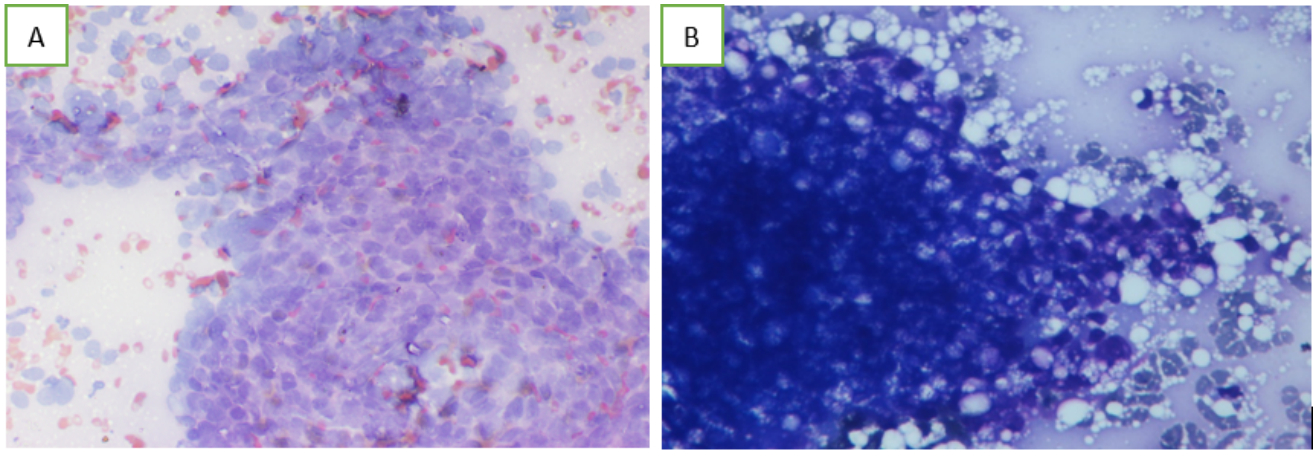

Fig. 12: High power photomicrograph **A.** Imprint cytology & **B.** Fine needle aspiration cytology of cervical lymph node of a patient of advanced staged sebaceous gland carcinoma of the eyelid. (Hematoxylin-eosin X 50)

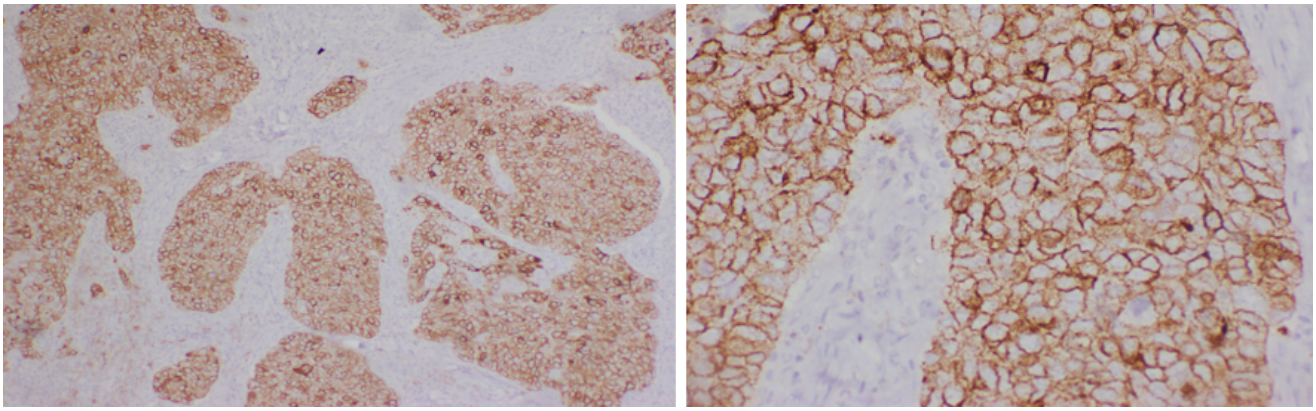

Fig. 13: Tumour cell showing strong immune reactivity to Anti-epithelial membrane antigen (EMA) in sebaceous gland carcinoma of eyelid. (EMA 10X & 40X)

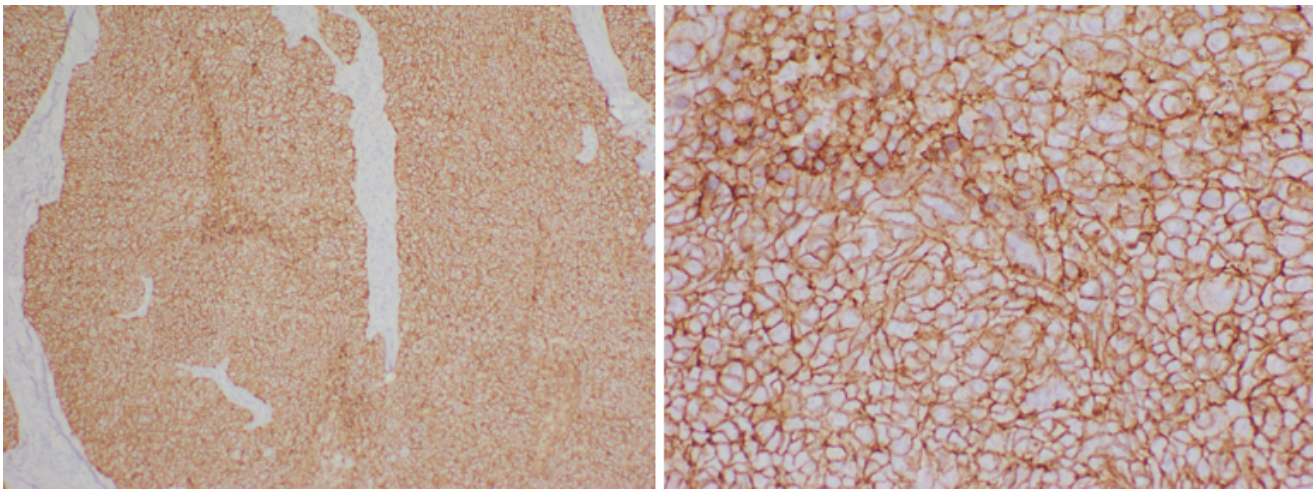

Fig. 14: Tumor cell showing strong immune-reactivity to Anti-epithelial antigen (Ber-EP4) high-grade lobular sebaceous gland carcinoma of the eyelid showing malignant lobules. (Ber-EP4 10X& 40X)

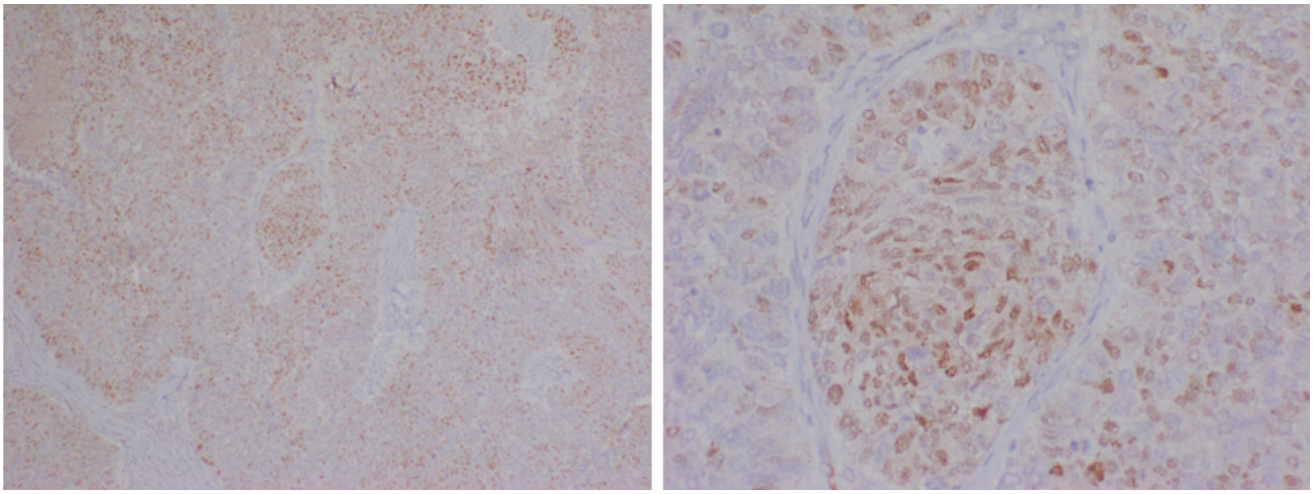

Fig. 15: Tumor cell showing immune-reactivity to Androgen receptor antibody high gradelobular sebaceous gland carcinoma of the eyelid showing malignant lobules. (AR10X& 40X).

6. Management

6.1. Wide local excision (WLE)

Full-thickness excision (with posterior lamellar) of the eyelid tumor with intraoperative margin control by frozen section or chemosurgery is the gold standard treatment for localized / circumscribed SGC. Wide local with ≥ 5mm normal appearing tissue is recommended where a frozen section biopsy facility is not available.[1,2,52,53] For the SGC with suspected pagetoid spread, scheduled map biopsies at the time of WLE should be done. Dogru M reported 36% recurrence when 1-3 mm margins were taken and no recurrence if margins were ≥ 5mm.[54] Local recurrence and metastasis after wide excision have been reported in SGC having the involvement of both eyelids, diffuse growth pattern, multicentric origin, large tumor (T3a) and non-tubular histopathological patterns.[1,3,7,52,55,56]

To get good functional and aesthetic outcomes appropriate eyelid reconstruction is to be performed after WLE. Reconstructive techniques may be two-staged e.g. Cutler Beard or single-staged procedures like Tanzel's rotational flap or Mastarde's cheek rotational flap etc.

6.2. Mohs micrographic surgery (MMS

Mohs micrographic surgery consists of removal and extemporaneous analysis of every skin stratum until the identification of disease-free margins With the advent of MMS, ophthalmologists can intraoperatively assess the surgical margins while ensuring maximal preservation of healthy tissue.[53] MMS is the appropriate choice for SGC in all locations, except the inner and outer canthus and cases with orbital involvement. A series of retrospective studies from 2001 to 2017 summarizes that MMS is associated with lower local recurrence rates (6.4%–11%) than wide local excision (11%–36%).[3,11,55,57] Overall, MMS has very good outcomes for tumor control and should be considered for all patients with ocular SGC.[58] The rarity of this tumor precludes large-scale comparative studies, but the existing studies may have provided some clues. Circumstances might be different in the UK, where MMS is not frequently considered in ophthalmic/oculoplastic services.

6.3. Topical Chemotherapy

Topical and systemic chemotherapy can be useful in SGC for the reduction of tumor size and prevention of micrometastasis. Tumuluri et al recommended topical mitomycin-C 0.02% four times a day for two weeks followed by two weeks interval therapy as adjuvant therapy after surgical excision of SGC with pagetoid spread.[59] In a pilot study conducted by Shield et al. mitomycin 0.04 % four times a day for one week followed by 1week interval found complete clearance of intraepithelial pagetoid invasion.[60] Larger studies with longer follow-up are necessary to establish the efficacy of topical mitomycin –C.

6.4. Neoadjuvant systemic chemotherapy

Recently systemic Chemotherapy has been recommended for patients with metastatic or locally advanced periocular SGC. Combination chemotherapy can be used in different ways in eyelid carcinomas. Neoadjuvant chemotherapy is given before to surgery to reduce the tumor bulk hence allowing less extensive surgery, eradicates micro-metastasis and improve disease free survival. Adjuvant chemotherapy given for localized tumour after primary surgery to "mop-up" the micro surgical residual tumour thus reducing loco-regional relapse. Palliative systemic chemotherapy is given in recurrent cases or advanced SGC with systemic

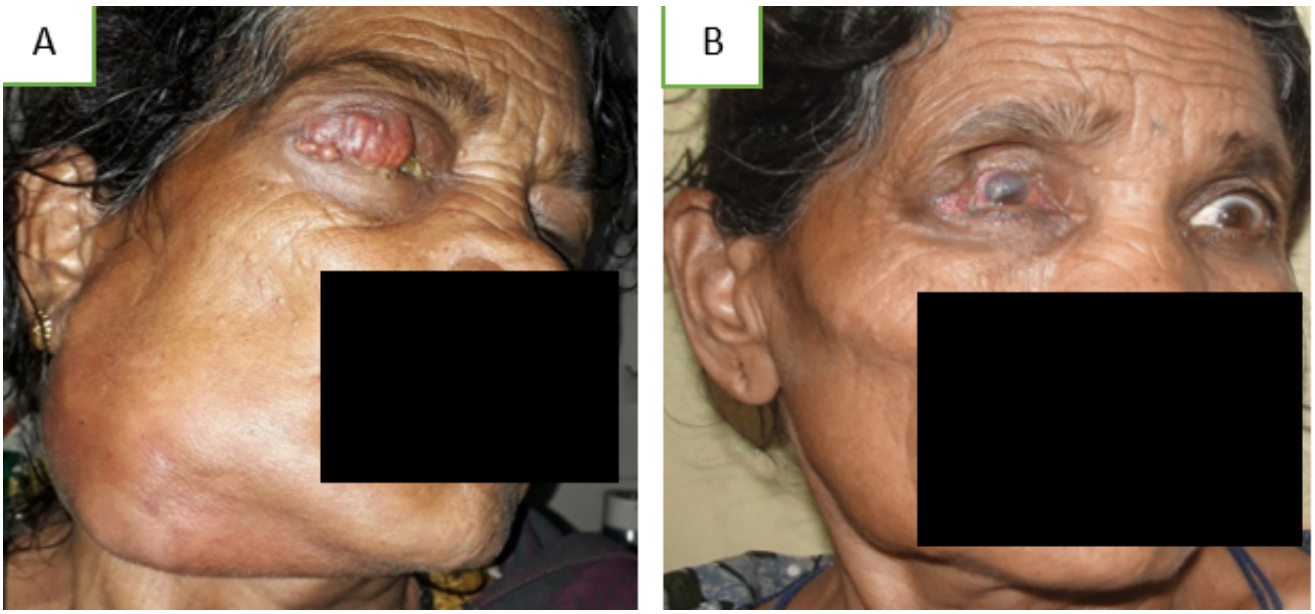

Fig. 16: A. Advanced stage sebaceous gland carcinoma of the right upper eyelid with Lymph node metastasis. **B**. Photograph after 4 cycle of systemic chemotherapy showing marked reduction of tumor and lymph node size.

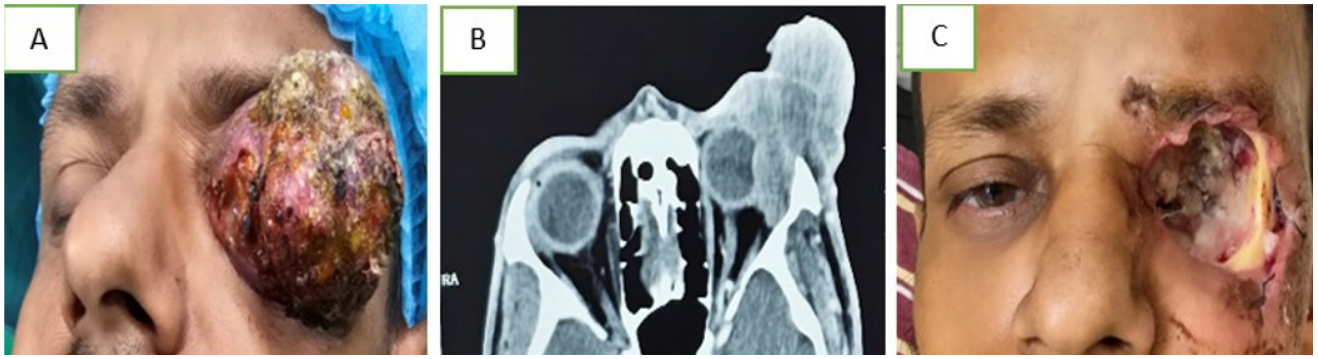

Fig. 17: A. Extensive sebaceous gland carcinoma arising from left upper eyelid **B.** CT Scan Axial view showing orbital extension of carcinoma. **C**. Post- Exenteration Photograph

metastasis (Figure 16). The chemotherapeutic regimen used for eyelid and periocular SGC are:

1. cis-platin 100 mg/m^2 on day 1 and
2. 5 FU 1000 mg/m^2 on day 1-5. Repeated every 21 days cycle. Kaliki et al used cisplatin and 5 FU combination neoadjuvant chemotherapy in 10 cases of advanced stage SGC of eyelid and observed 74% reduction in tumor basal diameter.[61]

6.5. Radiotherapy

Radiation therapy, especially brachytherapy, has been proven as an efficient treatment of ocular SGC. It facilitates functional and cosmetic preservation of the eyelid with good local control and acceptable levels of toxicity. However, the tumor is generally regarded as resistant to radiation therapy, and higher recurrence rates have been reported.[17,18,62,63] Radiation is only employed as adjuvant therapy for locally advanced (stage T3a or higher) or high-risk (pagetoid spread) periorbital SGC,[58,64,65] perineural invasion, nodal metastasis, or palliative treatment.[24,65] Till date, numerous case series and case reports have demonstrated a good response to radiation therapy in patients who were either poor surgical candidates or who refused surgical treatment. In a study of 13 patients with T3 SGC, the local recurrence rate was lower in the patients who received adjuvant radiotherapy (28%) than among those who did not (83.3%).[22] Complications from radiotherapy can be quite extensive and it includes chronic dry eye, conjunctival keratinization, blepharitis, trichiasis, exposure keratopathy, cataract, optic neuropathy, retinopathy, and even permanent loss of visual acuity.[58,65] The risk should be minimized with

appropriate shielding and balancing against the obvious morbidity of orbital exenteration.

6.6. Cryotherapy

Cryotherapy has a certain effect on ocular SGC with pagetoid spread to the conjunctiva or cornea.[23] For elderly patients where conservative approaches are preferred, these seem to be the feasible choices. In a retrospective case series identifying predictors of ocular surface squamous neoplasm recurrence after surgical resection, the addition of cryotherapy to the margins and the scleral bed have shown to cause a dramatic reduction in recurrence rates,[66] which may be significant in ocular SGC. The side effects of cryotherapy include permanent loss of visual acuity, corneal ulceration, and chronic dry eye. The use of this method is somewhat controversial and is largely surgeon dependent at this point.[58]

6.7. Targeted therapy

In recent years, targeted therapy is having an emerging role in the treatment of refractory tumors such as advanced melanoma[44] It is very efficacious in preventing disease progression in patients with metastatic or locally advanced BCC or SCC as in these cases targeted therapy against the Hedgehog pathway or epidermal growth factor receptor is used.[45,67] In a series of current studies, overexpression of HER2 is observed in SGC,[68,69] which suggests the possibility of targeted therapy with monoclonal antibodies trastuzumab and cetuximab.[67] Frequent PI3K signaling pathway activation provides a strong rationale for the application of target rapamycin inhibitors in targeted therapy of ocular SGC.[70,71]

6.8. Orbital Exenteration

This is a psychologically and anatomically disfiguring procedure. It is usually reserved for the treatment of extensive SGC or those tumours that have invaded the orbital soft tissue and are relentlessly progressive despite other treatments (Figure 17). Recently, as an alternative to exenteration, surgeons employed several variations of complete posterior lamellar removal of the eyelids followed by reconstruction using tarsal graft (usually from buccal mucosa) or amniotic membrane graft.[72] This procedure has been done primarily in older patients who had minimal residual disease and good vision in the affected eye. The above technique was employed with the tumor involving only the conjunctiva and eyelid tissue and was not used if there was any clinical or radiologic involvement of deeper orbital soft tissue.[72] However, a few patients still required exenteration because their tumors were extensive or had invaded the orbital soft tissue.

7. Prognosis

The prognosis of periocular SGC depends on duration, extent, type of tumor and its histological characteristics. Well differentiated tumors, localized tumors, originating from glands of Zies have better prognosis. Reported poor prognostic indicators of periocular SGC are delayed diagnosis (symptoms > 6 months duration), tumour larger than 10 mm, involvement of both eyelids, presence of metastasis.[22,73] In addition, other histological biomarkers of poor prognosis included poor differentiation, multicentric origin, pagetoid spread, highly infiltrative growth patterns, orbital extension and vascular, lymphatic and perineural invasion.[74] The hyperexpression of tumor suppresser gene p53 is one of the important molecular genetic factor associated with recurrence, metastasis and poor prognosis.[50]

8. Ethical Clearance

Obtained from Institute Ethical Committee.

9. Source of Funding

None.

10. Conflict of Interest

None.

References

1. Kaliki S, Ayyar A, Dave TV, Mishra DK, Naik MN. Sebaceous cell carcinomas of the eyelid: clinicopathological features and outcome in Asian Indians. *Eye (Lond)*. 2015;29(7):958–63. doi:10.1038/eye.2015.79.
2. Thomas WW, Fritsch VA, Lentsch EJ. Population- based analysis of prognostic indicators in sebaceous carcinoma of the head and neck. *Laryngoscope*. 2013;123(9):2165–9. doi:10.1002/lary.24042.
3. Shields JA, Demirci H, Marr BP, Eagle RC, Shields CL. Sebaceous carcinoma of the ocular region: a review. *Surv Ophthalmol*. 2005;50(2):103–22.
4. Abdi U, Tyagi N, Maheshwari V, Gogi R, Tyagi SP. Tumors of eyelid: a clinic-pathological study. *J Indian Med Assoc*. 1996;94(11):405–9.
5. Sihota R, Tondon K, Betharia SM. Malignant eyelid tumors in an Indian population. *Arch Ophthalmol*. 1996;114(1):108–9. doi:10.1001/archopht.1996.01100130104031.
6. Maurya RP, Singh VP, Singh MK, Srivastava T, Dwivedi M. Ocular sebaceous gland carcinoma in northern India: Clinico-pathological features and treatment outcome. *IP Int J Ocul Oncol Oculoplasty*. 2016;2(3):168–74.
7. Maurya RP, Bhatia RP, Thakur V, Maurya OPS, Kumar M. A clinic-pathological study of meibomian gland carcinoma. *Ann Ophthalmol*. 1997;29(1):27–30.
8. Ni C, Searl SS, Kuo PK. 8.Ni C , Searl SS, Kuo PK,et al .Sebaceous cell carcinoma of the ocular adnexa. In Ni C , Albert DM (eds) Tumors of the eyelid and orbit : A Chinese-American Collaborative Study,vol 22. Boston Littl Brown & Co 1982,pp23-61. *Int Ophthalmol Clin*. 1982;22(1):23–61. doi:10.1097/00004397-198202210-00006.
9. Shields JA, Shields JA, White D, Augsburger JJ. Types and frequency of lesions of the caruncle. *Am J Ophthalmol*. 1986;102(6):771–8. doi:10.1016/0002-9394(86)90407-1.
10. Awan KJ. Sebaceous carcinoma of the eyelid. *Ann Ophthalmol*. 1977;9(5):608–10.

11. Brauninger GE, Hood CI, Worthen DM. Sebaceous carcinoma of lid margin masquerading as cutaneous horn. *Arch Ophthalmol*. 1973;90(5):380–1. doi:10.1001/archopht.1973.01000050382009.
12. Shields CL, Shields JA. Tumors of the conjunctiva and cornea. *Surv Ophthalmol*. 2004;49(1):3–24. doi:10.1016/j.survophthal.2003.10.008.
13. Lee SC, Roth LM. Sebaceous carcinoma of the eyelid with Pagetoid involvement of the bulbar and palpebral conjunctiva. *J Cutan Pathol*. 1977;4(3):134–45. doi:10.1111/j.1600-0560.1977.tb00899.x.
14. Foster CS, Allansmith MR. Chronic unilateral blepharoconjunctivitis caused by sebaceous carcinoma. *Am J Ophthalmol*. 1978;86(2):218–20. doi:10.1016/s0002-9394(14)76815-1.
15. Shields JA, Shields CL. Sebaceous carcinoma of the glands of Zeis. *Ophthal Plast Reconstr Surg*. 1988;4(1):11–4. doi:10.1097/00002341-198801130-00002.
16. Jakobiec FA, To K. Sebaceous tumor of the ocular adnexa. In: Albert D, Jakobiec F, editors. Principle and Practice of Ophthalmology. vol. 4. Philadelphia, PA, WB Saunders Co; 2000. p. 3400–1.
17. Harvey PA, Parsons MA, Rennie IG. Primary sebaceous carcinoma of lacrimal gland: a previously unreported primary neoplasm. *Eye*. 1994;8(Pt 5):592–5.
18. Esmaeli B, Dutton JJ, Graue GF. Eyelid carcinoma. In: Edge S, Greene FL, Byrd D, editors. Carcinoma of the eyelid. AJCC cancer staging manual, 8th edn. New York: Springer; 2017. p. 779–85.
19. Snow SN, Larson PO, Lucarelli MJ. Sebaceous carcinoma of the eyelids treated by Mohs microscopic surgery report of nine cases with review of the literature. *Dermatol Surg*. 2002;28(7):623–31. doi:10.1046/j.1524-4725.2002.01306.x.
20. Khan JA. Sebaceous and meibomian carcinomas of the eyelid. Recognition, diagnosis and management. *Ophthal Plast Reconstr Surg*. 1991;7(1):61–6. doi:10.1097/00002341-199103000-00008.
21. Mandreker S, Pinto RW, Usgaonkar U. Sebaceous carc noma of the eyelid with metastasis to the parotid region:" diagnosis by fine needle aspiration cytology. *Acta Cytol*. 1997;41(5):1636–7.
22. Rao NA, Hidayat AA, Mclean IW. Sebaceous carcinomas of the ocular adnexa: A clinicopathologic study of 104 cases, with five-year follow-up data. *Hum Pathol*. 1982;13(2):113–22. doi:10.1016/s0046-8177(82)80115-9.
23. Shields JA, Demirci H, Marr BOP. Sebaceous carcinoma of the eyelids: personal experience with 60 cases. *Ophthalmology*. 2004;111(12):2151–7. doi:10.1016/j.ophtha.2004.07.031.
24. Font RL. Sebaceous gland tumors. In: Spencer W, editor. Ophthalmic Pathology. An Atlas and Textbook. vol. 4. Phila delphia, PA. WB Saunders; 1996. p. 2278–97.
25. Rao NA, Mclean IW, Zimmerman LE. Sebaceous carcinoma of 48. the eyelids and caruncle: Correlation of histopathologic features with prognosis. In: Jakobiec F, editor. Ocular and Adnexal Tumors. Birmingham, AL, Aesculapius; 1978. p. 461–76.
26. Cavanagh HD, Green WR, Goldberg HK. Multicentric sebaceous adenocarcinoma of the meibomian gland. *Am J Ophthalmol*. 1974;77(3):326–32. doi:10.1016/0002-9394(74)90738-7.
27. Muqit MM, Foot B, Walters SJ, Mudhar HS, Roberts F, Rennie IG, et al. Observational prospective cohort study of patients with newly- diagnosed ocular sebaceous carcinoma. *Br J Ophthalmol*. 2013;97(1):47–51.
28. Song A, Carter KD, Syed NA. Sebaceous cell carcinoma of the ocular adnexa: clinical presentations, histopathology, and outcomes. *Ophthalmic Plast Reconstr Surg*. 2008;24(3):194–200. doi:10.1097/IOP.0b013e31816d925f.
29. Sinard JH. Immunohistochemical distinction of ocular sebaceous carcinoma from basal cell and squamous cell carcinoma. *Arch Ophthalmol*. 1999;117(6):776–83. doi:10.1001/archopht.117.6.776.
30. Muthusamy K, Halbert G, Roberts F. Immunohistochemical staining for adipophilin, perilipin and TIP47. *J Clin Pathol*. 2006;59(11):1166–70. doi:10.1136/jcp.2005.033381.
31. Cabral ES, Auerbach A, Killian JK, Barrett TI, Cassarino DS. Distine tion of benign sebaceous proliferations from sebaceous carcinomas by immunohistochemistry. *Am J Dermatopathol*. 2006;28(6):465–71.
32. Alhumaidi A. Practical immunohistochemistry of epithelial skin tumor. *Indian J Dermatol Venereol Leprol*. 2012;78(6):698–708.
33. Asadi-Amoli F, Khoshnevis F, Haeri H, Jahanzad I, Pazira R, Shahsiah R, et al. Comparative examination of androgen receptor reactivity for differential diagnosis of sebaceous carcinoma from squamous cell and basal cell carcinoma. *Am J Clin Pathol*. 2010;134(1):22–6. doi:10.1309/AJCP89LYTPNVOBAP.
34. Bayer-Garner IB, Givens V, Smoller B. Immunohistochemical staining for androgen receptors: a sensitive marker of sebaceous differentiation. *Am J Dermatopathol*. 1999;21(5):426–31.
35. Sinard JH. Immunohistochemical distinction of ocular sebaceous carcinoma from basal cell and squamous cell carcinoma. *Arch Ophthalmol*. 1999;117(6):776–83. doi:10.1001/archopht.117.6.776.
36. Ansai S, Hozumi Y, Kondo S. An immunohistochemical study of BCA-225 in various skin cancers. *J Dermatol*. 1994;21(1):20–4. doi:10.1111/j.1346-8138.1994.tb01404.x.
37. Esmaeli B, Nasser QJ, Cruz H, Fellman M, Warneke CL, Ivan D, et al. American Joint Committee on Cancer T category for eyelid sebaceous carcinoma correlates with nodal metastasis and survival. *Ophthalmology*. 2012;119(5):1078–82.
38. Sawyer AR, Mcgoldrick RB, Mackey S. Should extraocular sebaceous carcinoma be investigated using sentinel node biopsy? *Dermatol Surg*. 2009;35(4):704–8.
39. Epstein GA, Putterman AM. Sebaceous adenocarcinoma of the eyelid. *Ophthalmic Surg*. 1983;14(11):935–40.
40. Putterman AM. Conjunctival map biopsy to determine pagetoid spread. *Am J Ophthalmol*. 1986;102(1):87–90. doi:10.1016/0002-9394(86)90214-x.
41. Shields JA, Demirci H, Marr B, Eagle R, Shields CL. Sebaceous Carcinoma of the Eyelids: Personal Experience with 60 Cases. *Ophthalmology*. 2005;111(12):2151–7.
42. Shields CL, Naseripour M, Shields JA, Eagle RC. Topical mitomycin-C for pagetoid invasion of the conjunctiva by eyelid sebaceous gland carcinoma. *Ophthalmology*. 2002;109(11):2129–33.
43. Shield JA, Shields CL. Sebaceous gland tumours. In: Atlas of eyelid and conjunctival Tumours. Pheladelphia. PA, Lippincott Williams and Wilkins; 1999. p. 39–40.
44. Kruse R, Lamberti C, Wang Y, Ruelfs C, Bruns A, Esche C, et al. Is the mismatch repair deficient type of Muir-Torre syndrome confined to mutations in the hMSH2 gene. *Hum Genet*. 1996;98(6):747–50. doi:10.1007/s004390050298.
45. Ponti G, Longo C. Microsatellite instability and mismatch repair protein expression in sebaceous tumors, keratocanthoma, and basal cell carcinomas with sebaceous differentiation in Muir-Torre syndrome. *J Am Acad Dermatol*. 2013;68(3):509–10. doi:10.1016/j.jaad.2012.09.054.
46. Mulay K, Aggarwal E, White VA. Periocular sebaceous gland carcinoma : A comprehensive review. *Saudi J Ophthalmol*. 2013;27(3):159–65. doi:10.1016/j.sjopt.2013.05.002.
47. Kim N, Kim JE, Choung HK. Expression of Shh and Wnt signaling pathway proteins in eyelid sebaceous gland carcinoma: clinicopathologic study. *Invest Ophthalmol Vis Sci*. 2013;54(1):370–7.
48. Bladen JC, Mariya M, Tracey-White D, Beaconsfield M, O'Toole EA, Philpott MP. Analysis of hedgehog signalling in periocular sebaceous carcinoma. Graefe's Archive for. *Graefes Arch Clin Exp Ophthalmol*. 2018;256(4):853–60. doi:10.1007/s00417-018-3900-5.
49. Shalin SC, Sakharpe A, Lyle S, Lev D, Calonje E, Lazar AJ, et al. AJ. p53 staining correlates with tumor type and location in sebaceous neoplasms. *Am J Dermatopathol*. 2007;34(2):129–35. doi:10.1097/DAD.0b013e3181ed39f9.
50. Gonzalez-Fernandez F, Kaltreider SA, Patnaik BD, Retief JD, Bao Y, Newman S, et al. Sebaceous carcinoma. Tumor progression through mutational inactivation of p53. *Ophthalmology*. 1998;105(3):497–506.
51. Bladen JC, Wang J, Sangaralingam A, Moosajee M, Fitchett C, Chelala C, et al. MicroRNA and transcriptome analysis in periocular sebaceous gland carcinoma. *Sci Rep*. 2018;8:7531. doi:10.1038/s41598-018-25900-z.
52. Cook BE, Bartley GB. Treatment options and future prospects for the management of eyelid malignancies: an evidence-based

update. *Ophthalmology*. 2001;108(11):2088–98. doi:10.1016/s0161-6420(01)00796-5.
53. Nerad JA, Whitaker DC. Periocular basal cell carcinoma in adults 35 years of age and younger. *Am J Ophthalmol*. 1988;106(6):723–9. doi:10.1016/0002-9394(88)90708-8.
54. Dogru M, Matsuo H, Inoue M. Management of eyelid sebaceous carcinomas. *Ophthalmologica*. 1997;211(1):40–3. doi:10.1159/000310872.
55. Mehta M, Fay A. Squamous cell carcinoma of the eyelid and conjunctiva. *Int Ophthalmol Clin*. 2009;49(1):111–132.
56. Margo C, Mulla ZD. Malignant tumor of eyelid: a population based study of non-basal cell and non-squamous cell malignant neoplasm. *Arch Ophthalmol*. 1998;116(2):195–8. doi:10.1001/archopht.116.2.195.
57. Shields CL, Shields JA. Tumors of the conjunctiva and cornea. *Surv Ophthalmol*. 2004;49(1):3–24. doi:10.1016/j.survophthal.2003.10.008.
58. Lee SC, Roth LM. Sebaceous carcinoma of the eyelid with Pagetoid involvement of the bulbar and palpebral conjunctiva. *J Cutan Pathol*. 1977;4(3):134–45. doi:10.1111/j.1600-0560.1977.tb00899.x.
59. Tumuluri K, Kourt G, Martin P. Mitomycin C in sebaceous gland carcinoma with pagetoid spread. *Br J Ophthalmol*. 2004;88(5):718–9. doi:10.1136/bjo.2003.034215.
60. Shields CL, Naseripour M, Shields JA, Eagle RC. Topical mitomycin-C for pagetoid invasion of the conjunctiva by eyelid seba- ceous gland carcinoma. *Ophthalmology*. 2002;109(11):2129–33.
61. Kaliki S, Ayyar A, Nair AG, Mishra DK, Reddy VA, Naik MN, et al. Neoadjuvant systemic chemotherapy in the management of extensive eyelid sebaceous gland carcinoma: A study of 10 cases. *Ophthal Plast Reconstr Surg*. 2016;32(1):35–9. doi:10.1097/IOP.0000000000000398.
62. Harvey PA, Parsons MA, Rennie IG. Primary sebaceous carcinoma of lacrimal gland: a previously unreported primary neoplasm. *Eye*. 1994;8(Pt 5):592–5.
63. Akpek EK, Polcharoen W, Chan R. Ocular surface neoplasia masquerading as chronic blepharoconjunctivitis. *Cornea*. 1999;18(3):282–8. doi:10.1097/00003226-199905000-00007.
64. Brownstein S, Codere F, Jackson WB. Masquerade syndrome. *Ophthalmology*. 1980;87(3):259–62. doi:10.1016/s0161-6420(80)35245-7.
65. Bounik M, Zimmerman LE. Sebaceous carcinoma of the eyelid, eyebrow, caruncle and orbit. *Trans Am Acad Ophthalmol Otolaryngol*. 1968;72(4):619–42.
66. Jakobiec FA, Zimmerman LE, La PF, Hornblass A, Breffeilh RA, Lackey JK. Unusual eyelid tumors with sebaceous differentiation in the Muir-Torre syndrome. Rapid clinical regrowth and frank squamous transformation after biopsy. *Ophthalmology*. 1988;95(11):1543–8.
67. Rahman AWM, Mecklin JP, Peltomaki P. The genetics of HNPCC: application to diagnosis and screening. *Crit Rev Oncol Hematol*. 2006;58(3):208–20. doi:10.1016/j.critrevonc.2005.11.001.
68. Shalin SC, Sakharpe A, Lyle S, Lev D, Calonje E, Lazar AJ, et al. p53 staining correlates with tumor type and location in sebaceous neoplasms. *Am J Dermatopathol*. 2012;34(2):129–35. doi:10.1097/DAD.0b013e3181ed39f9.
69. Niemann C, Owens DM, Hulsken J, Birchmeier W, Watt FM. Expression of Delta N Lef1 in mouse epidermis results in differentiation of hair follicles into squamous epidermal cysts and formation of skin tumours. *Development*. 2002;129(1):95–104. doi:10.1242/dev.129.1.95.
70. Niemann C, Unden AB, Lyle S, Zouboulis CHC, Toftgård R, Watt FM, et al. Indian hedgehog and beta-catenin signaling: role in the sebaceous lineage of normal and neoplastic mammalian epidermis. *Proc Natl Acad Sci*. 2003;1(Suppl 1):11873–80. doi:10.1073/pnas.1834202100.
71. Tetzlaff MT, Singh RR, Seviour EG. Next generation sequencing identifies high frequency of mutations in potentially clinically actionable genes in sebaceous carcinoma. *J Pathol*. 2016;240(1):84–95.
72. Soysal HG. Orbital exenteration: a 10-year experience of a general oncology hospital. *Orbit*. 2010;29(3):136–9. doi:10.3109/01676830903342252.
73. Tryggvason G, Bayon R, Pagedar NA. Epidemiology of sebaceous carcinoma of the head and neck: implications for Rlymph node management. *Head Neck*. 2012;34(12):1765–8.
74. Takahashi Y, Takahashi E, Nakakura S, Kitaguchi Y, Mupas-Uy J, Kakizaki H. Risk factors for local recurrence or metastasis of eyelid sebaceous gland carcinoma after wide excision with paraffin section control. *Am J Ophthalmol*. 2016;171:67–74. doi:10.1016/j.ajo.2016.08.028.

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