Ocular Oncology Update

Periocular sebaceous gland carcinoma: A comprehensive review

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Abstract

Sebaceous gland carcinoma (SGC) is a rare tumour occurring at periocular and extra-ocular sites. SGC can be a challenging diagnosis for both clinicians and pathologists. High recurrence rates and a tendency for intra-epithelial spread, locoregional and distant metastases make it important for SGC to be suspected and be included in the differential diagnosis of an eyelid lesion. Early diagnosis, that may sometimes need ancillary testing, and prompt management using a multimodal approach can help reduce morbidity and mortality in patients with SGC.

Keywords: Periocular, Sebaceous gland, Carcinoma

Introduction

The sebaceous glands are microscopic glands in the skin that secrete sebum. In humans, they are found abundantly in the face and scalp although they are distributed throughout all skin sites except palms and soles. Sebaceous glands are associated with the hair follicle, arising at the junction of the inferior portion of the follicle infundibulum and the isthmus. \(^1\) Sebaceous gland proliferations include senile sebaceous gland hyperplasia, sebaceoma, sebaceous adenoma and sebaceous gland carcinoma. \(^2\) First described by Allaire in 1891, sebaceous gland carcinoma (SGC) accounts for less than 1% of all cutaneous malignancies. \(^3,4\) SGC can masquerade as other inflammatory lesions, and benign and malignant tumours thus delaying diagnosis possibly leading to inappropriate management and an increase in morbidity and/or mortality.

The purpose of this review is to summarize in a multifaceted manner the data available in the literature regarding the epidemiology, aetiology, clinicopathological features, molecular advancements, differential diagnosis, management and prognosis of patients with periocular SGC.

Surgical anatomy

The eyelid can be divided into anterior and posterior lamellae. The skin, orbicularis muscle, eyelashes, and their follicles are present in the anterior lamella while the posterior lamella contains the mucocutaneous junction, meibomian gland orifices, and tarsal plate. Sebaceous glands are found in the tarsal plate (upper and lower), caruncle and eye brow. The glands of Zeis open into the hair follicles at the base of eyelashes.

Epidemiology

SGC can occur in either the periocular location or at extra-ocular sites with the periocular sites accounting for 75% of all...
SGC.5,6 Periocular SGC usually arise from the meibomian glands, the glands of Zeis and the sebaceous glands of the eyelid skin, with the former being most frequent. SGC arise two to three times more frequently in the upper eyelid than its lower counterpart due to the presence of more meibomian glands in the upper eyelid compared to the lower eyelid.7 Other periocular sites include the eye-brow, caruncle, lacrimal gland and conjunctiva.24–26 The rate of SGC varies according to the ethnicity of the population. In Caucasians, SGC are rare accounting for less than 1–5.5% of eyelid malignancies.11,12 On the contrary, in the Chinese and Japanese population, SGC is the second most common eyelid malignancy with the highest reported rates being 39% and 37.5% respectively.13,14 Similar studies in the Indian population and in Singapore report rates of 31.2% and 10.2% respectively.15,16 The reason for higher rates of SGC in the Asian population could be genetic or racial in nature. Alternatively, the rates of SGC could be higher due to the lower incidence of other eyelid malignancies. The absolute incidence in non-Caucasians is unknown. SGC is considered to be a tumour of the eyelid malignancies. The absolute incidence in non-Caucasians is unknown. SGC is considered to be a tumour of the older age group, mostly arising between the sixth and eighth decades of life, although it can occur in younger age groups as well.1,15 Some reports suggest a female preponderance while others report no gender predilection.6,7,17,18

Aetiology

The aetiology of SGC is largely unknown. Several risk factors have been associated with this tumour. Asian race is reported to be significantly associated with SGC.19–21 However, recent reports suggest a contradictory observation of the tumour being more common in whites thus suggesting the role of sunlight exposure.17 Muir–Torre syndrome (MTS), a rare genodermatologic disorder characterized by autosomal dominant non-polyposis colorectal carcinoma, sebaceous gland tumours and visceral malignancies is a risk factor for SGC.22,23 Other reported associations include Rb and p53 mutations, HIV and HPV.24–27

Clinical features

The upper lid is more frequently involved by SGC than the lower lid.1 It masquerades not only as various inflammatory conditions such as blepharocconjunctivitis or chalazion but also as premalignant lesions and other benign or malignant tumours.28–31 The nodular form of SGC presents as a discrete, hard, immobile nodule commonly located in the upper tarsal plate having a yellowish appearance (Fig. 1A). The pagetoid variety of SGC occurs with intraepithelial infiltration of the lid margin and/or conjunctiva causing diffuse thickening and loss of eyelashes resembling chronic blepharocconjunctivitis (Fig. 1B).32,33

Diagnosis, microscopy and immunostaining

It is important to include SGC in the differential diagnosis of all eyelid lesions, particularly in populations with a higher reported frequency. Microscopic examination is the gold standard in diagnosis and confirmation of SGC. Most patients have a moderately differentiated tumour.34 The tumour cells are arranged in the form of sheets or lobules, sometimes with central comedo necrosis (Fig. 1C). Individual tumour cells have distinct cell membranes, clear to vacuolated cytoplasm and vesicular nuclei with prominent nucleoli, numerous mitoses and apoptotic cells (Fig. 1D). The demonstration of intracytoplasmic lipid vacuoles by Oil red O or Sudan IV stains, performed on frozen sections of fresh or formalin-fixed tissues is reported to aid in the diagnosis of SGC, but is rarely necessary and has largely been superseded by adipophilin (see below).35 Studies have reported a missed diagnosis on light microscopy in 23–77% cases of poorly differentiated SGC.36–38 Sometimes, the tissues are extremely small or SGC may not be suspected before light microscopic examination. In such situations, immunohistochemical staining helps in the diagnosis. A recent study reported that more than 75% SGC stained positively for anti-CKS and anti CK-15 and were negative with anti-CK1, CK10, CK15, CK17, CK18 and CK20 antibodies.39 Antibodies to phosphoinothrin-N-acetyl transferase (PAT) or periplin family have been used to demonstrate proteins associated with lipid droplets (Fig. 1E).39 Adipophilin (ADP) had a lower specificity (77%) but higher sensitivity (88.5%) as compared to perilipin (specificity 100%, sensitivity 45.5%) and tail-interacting protein of 47 kDa (TIP47, specificity 100%, sensitivity 8.3%).39 This study also suggested that ADP was a more sensitive marker of lipid droplets in SGC than Oil red O.39 However, a similar staining pattern for ADP is also seen in xanthomatous lesions and metastatic renal cell carcinoma.40 SGC are immunoreactive for epithelial membrane antigen (EMA) with staining being restricted to the centre of cell nests.39 BRST-1 antibody stains most SGC, either focally or diffusely. It is negative in basal cell carcinoma (BCC) but can be focally positive in squamous cell carcinoma (SCC).34 Cam 5.2, an anti-low molecular weight keratin antibody, is positive in most cases of SGC.34,41 It can be positive in BCC but is negative in SCC.34 Immunostaining for androgen receptor (AR) in SGC has been extensively described in the recent literature suggesting AR to be a reliable marker of sebaceous differentiation (Fig. 1F).42–46 A panel of antibodies comprising carcinoembryonic antigen (CEA), EMA, AR, Ber-EP4, ADP, CA15-3 and CA19-9 has been suggested to differentiate SGC from SCC and BCC (Table 1).47 Intra-epithelial spread, a common cause of misdiagnosis, is a characteristic feature of SGC seen in up to 39% patients.31 Intra-epithelial spread can have a Bowenoid, pagetoid or mixed pattern. Reports in the literature describe the Bowenoid and pagetoid patterns in up to 35% and 47% of SGC respectively.36,48

Molecular pathology

Muir-Torre syndrome and mismatch repair genes

Several studies have investigated the relationship between MTS and SGC.1,22,23,49 A subset of patients with clinical or phenotypic MTS have a defect in the DNA mismatch repair (MMR) genes and are at a risk for developing a future malignancy.49 An MMR defect results in the accumulation of replication errors or unstable microsatellite sequences.50 In MTS, germline mutation in one of the MMR-genes is complemented by a second somatic molecular alteration in a neoplasm. A sebaceous lesion is present either before or concurrent with the first visceral malignancy in 63% patients with MMR-deficient MTS.51 Diagnosis of SGC or a benign sebaceous neoplasm should prompt the clinician to carry
out a thorough history and physical examination to rule out a visceral malignancy. It should also prompt the laboratory to perform immunostaining for the commonly absent MMR proteins (MSH2, MLH1, PMS1 and PMS2). One-third of patients with clinical MTS demonstrate failure to express normal MMR proteins. Mutations in MSH2 and MLH1 are more frequent than those in MSH6, MSH3, MLH3, PMS2 and PMS1.1

Many cell signalling pathways have been shown to be dysregulated in SGC (Table 2 and Fig. 2).

**Wnt/β-catenin pathway**

The Wnt/β-Catenin pathway regulates stem cell pluripotency and cell fate decisions during development. In the absence of Wnt, glycogen synthase kinase 3 (GSK-3) constitutively phosphorylates the β-catenin protein. Overexpression of β-catenin has been demonstrated in SGC thus suggesting a possible dysregulation of the Wnt/β-catenin pathway.52-54 Further, it was also shown that reduced membranous expression of β-catenin correlated with invasion and metastasis, especially at the site of invasion.54

**Table 1. Antibody panel that may be helpful in the differential diagnosis of sebaceous gland carcinoma, basal cell carcinoma and squamous cell carcinoma.**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Sebaceous gland carcinoma</th>
<th>Basal cell carcinoma</th>
<th>Squamous cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA46</td>
<td>±</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>ADP39,40,43,46-48</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>AR46,46</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>EMA46,47</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Ber-EP446</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>CA19-946</td>
<td>±</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>BRST134</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CAM5.234,47</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

CEA, carcinoembryonic antigen; ADP, adipophilin; AR, androgen receptor; EMA, epithelial membrane antigen.

**Figure 1.** Clinicopathological features of sebaceous gland carcinoma. Nodular form of sebaceous carcinoma involving both fornices (Fig. 1A) and pagetoid variety presenting as diffuse thickening of the eyelid (Fig. 1B). Lobules of tumour cells with central comedo necrosis (Fig. 1C, haematoxylin and eosin ×40). Tumour cells with vacuolated cytoplasm and vesicular nuclei having prominent nucleoli (Fig. 1D, haematoxylin and eosin ×400). Tumour cells showing cytoplasmic staining for adipophilin (Fig. 1E, ×400) and nuclear staining for androgen receptor (Fig. 1F, ×400).

TP53

p53 Mutations in SGC, as demonstrated by overexpression, suggest a possible role of UV radiation and subsequent signal alterations.25
Table 2. Signalling pathways and proteins involved in periocular sebaceous gland carcinoma.

<table>
<thead>
<tr>
<th>Study group</th>
<th>Protein involved</th>
<th>Protein function</th>
<th>Signal pathway</th>
<th>Expression change</th>
<th>Prognostic significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jayaraj et al.51</td>
<td>β-catenin</td>
<td>Co-ordination of cell–cell adhesion and gene transcription</td>
<td>Wnt/b-catenin</td>
<td>Overexpression</td>
<td>Correlated with tumour size &gt;2 cm Invasion and metastasis</td>
</tr>
<tr>
<td>Jayaraj et al.53</td>
<td>p53</td>
<td>Apoptosis tumour suppressor inhibits angiogenesis DNA repair</td>
<td>p53</td>
<td>Overexpression</td>
<td>Correlates with tumour type and tumour location</td>
</tr>
<tr>
<td>McBride et al.54</td>
<td>p21WAF1</td>
<td>Cyclin-dependent kinase inhibitor</td>
<td>p53/p21</td>
<td>Loss of compartmentalization</td>
<td>Preserved in benign and normal sebaceous glands</td>
</tr>
<tr>
<td>Kiyosaki et al.55</td>
<td>p53</td>
<td>Cell-cycle regulation Prevents cell proliferation</td>
<td>p53/p21</td>
<td>Down regulation</td>
<td>Lymph node metastasis</td>
</tr>
<tr>
<td>Kim et al.52</td>
<td>Shh ABCG2</td>
<td>Maintenance of stem cells in adult tissues</td>
<td>Sonic hedgehog</td>
<td>Overexpression</td>
<td>Metastatic disease Aggressiveness</td>
</tr>
<tr>
<td>Rokhin et al.59,</td>
<td>Androgen receptor</td>
<td>Regulation of gene expression</td>
<td>NA</td>
<td>Increased activity</td>
<td>Inhibits p53 expression and p53 activity.</td>
</tr>
<tr>
<td>Nantermet et al.60</td>
<td>E-cadherin</td>
<td>Suppressor of invasion and growth of epithelial cancers. Cell–cell adhesion</td>
<td>Wnt/β-catenin/TCF</td>
<td>Lower expression</td>
<td>Poor tumour differentiation and high proliferation rate Reduced disease-free survival, size &gt;2 cm, lymph node metastases, poor differentiation</td>
</tr>
<tr>
<td>Jayaraj et al.53</td>
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</table>

Figure 2. Sonic hedgehog and Wnt/β-catenin signalling pathways in sebaceous gland carcinoma.78

p21/WAF1

p21/WAF1, a cyclin-dependent kinase inhibitor, regulates G1-S transition and mediates G1 cell cycle arrest. It can be transcriptionally upregulated by p53 but may be activated independently. Compartmentalization of p21/WAF1 in the differentiated component of the gland, seen in normal sebaceous glands and benign sebaceous lesions, is lost in SGC.55 A recent study associated downregulation of p21 with lymph node metastasis in SGC.56

Sonic hedgehog pathway

The sonic hedgehog (Shh) signalling pathway is also altered in SGC with Shh and ABCG2 proteins being overexpressed in patients with a metastatic disease.53 This study thus suggested that activation of Wnt and Shh signalling pathways is associated with higher cumulative incidences of lymph node and distant metastasis in SGC.53

Androgen receptor

AR has been identified as a MYC target gene in mouse epidermis.57 p53 can inhibit AR gene expression by direct association with AR promoter58 and by inhibiting AR protein activity.59 On the other hand, strong AR activity can inhibit p53 expression60 and p53 activity.61 Thus, the expressions of AR and p53 are inversely related to each other in SGC.62

E-cadherin

E-cadherin promoter hypermethylation has been associated with poor clinical outcome.54,63

Treatment

As discussed earlier, SGC may be a difficult clinical diagnosis to make due to its masquerading nature and thus, might delay diagnosis and appropriate management. Local
Excision, orbital exenteration, radiotherapy and chemotherapy are various methods used to manage patients with SGC based on tumour stage at presentation. Wide excision with at least 4 mm margin and radical neck dissection is necessary in patients with locoregional metastases. However, 32% cases recur even with a margin clearance of 5–6 mm. Frozen section and Mohs' micrographic surgery are now used in specialized centres. Definitive margin excision and minimal loss of surrounding normal tissue are advantages of Mohs' surgery. A recent study suggested the use of 'slow' Mohs' surgery which uses paraffin embedded sections to identify pagetoid spread that is otherwise difficult or impossible to identify on frozen sections. A recurrence rate of 11.1% has been reported after Mohs' surgery. Exenteration is the treatment of choice for patients with extensive or multifocal tumour or extensive pagetoid spread. Radical neck dissection is indicated in patients of SGC with regional nodal metastases. The role of radiotherapy in SGC has been extensively studied and found to have variable results. Radiation of 50–66.6 Gy administered with a curative intent has been effective in achieving a prolonged survival and good tumour control in addition to facilitating functional and cosmetic preservation of the eyelid. Radiotherapy given post-operatively following orbital exenteration provides a better disease control as compared to treatment by exenteration only. Radiation is best avoided due to the various complications associated with it such as blepharocconjunctivitis, lid atrophy, dry eye, ectropion, epiphora, cataract and keratopathy. Cryotherapy may be used as a coadjuvant. The role of Mitomycin C, a non-cell cycle specific alkylating agent, is controversial. It has been used in patients with SGC and pagetoid spread to reduce the need for further invasive management. More recently, neoadjuvant chemotherapy using carboplatin and 5-fluorouracil has been shown to reduce morbidity in a patient with metastatic nodal disease. Recent studies on expression of oestrogen receptor (ER), progesterone receptor (PR) and androgen receptor (AR) suggest a potential role of hormonal therapy in patients with SGC.

**References**


**Conflict of interest**

The authors declared that there is no conflict of interest.

**Acknowledgment**

We would like to acknowledge Mr. C. Jangaiah for his help with photography.

**Prognosis**

Various clinicopathological factors are reported to indicate a poor prognosis in SGC and include lymphovascular and orbital invasion, involvement of both upper and lower eyelids, poor differentiation, multicentric origin, long duration of symptoms, large tumour size, an infiltrative pattern and orbital invasion, involvement of both upper and lower lids and recurrence are seen in 6–29% cases. The overall mortality rate in SGC is 5–10%. Locoregional metastases and recurrence are seen in 6–29% cases. 14–25% patients develop metastases, either in the form of lymphatic spread to the lymph nodes and/or haematogenous spread to the liver, lungs, brain, and bones.


