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CLINICAL STUDY

Sebaceous gland carcinoma of the eyelid: clinico-pathological features and outcome in Asian Indians

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Abstract

Purpose **To study the clinical and histopathological features of eyelid sebaceous gland carcinoma (SGC) and to evaluate the prognosis in the Asian-Indian population.**
Methods **This is a retrospective study of 191 patients with SGC.**
Results **The mean age at presentation of eyelid SGC was 57 years (median, 56 years). The tumor epicenter was most commonly located in the upper eyelid ($n=125$, 65%). The mean tumor basal diameter was 15 mm (median, 10 mm). There was evidence of tumor extension into the orbit ($n=30$, 16%), paranasal sinuses ($n=3$, 2%), and brain ($n=1$, 1%). Wide excision biopsy ($n=146$, 78%) was the most common treatment modality. Tumor recurrence was noted in 42 (24%) patients over a mean follow-up period of 29 months (median, 20 months). On the basis of the Kaplan–Meier estimate, lymph node metastasis occurred in 18%, systemic metastasis was detected in 10%, and death occurred in 2% of patients at 10 years. On multivariate analysis, the factors predicting locoregional lymph node and systemic metastasis were medial canthal involvement ($P=0.004$; $P=0.013$), lateral canthal involvement ($P=0.013$; $P=0.025$), tumor basal diameter >10 mm ($P=0.002$; $P=0.002$), and perivascular invasion ($P=0.043$; $P<0.001$), respectively. The factors predicting death due to metastasis on multivariate analysis were medial canthal involvement ($P=0.012$) and tumor basal diameter >10 mm ($P=0.001$).**
Conclusion **Advanced eyelid SGC is a tumor associated with poor prognosis. In this study, canthal involvement, larger tumor diameter, and perivascular invasion were poor prognostic factors.**

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Introduction

Sebaceous gland carcinoma (SGC) is more frequent in the head and neck region, with eyelid being the most common site. In a retrospective study of 1349 patients with SGC from the Surveillance, Epidemiology, and End Results database from 1973 through 2004 in the US population, eyelid was the most common site including 522 (39%) cases.[1] Eyelid SGC is relatively uncommon accounting for 1–5% cases of malignant eyelid tumors in the USA.[2] In the United Kingdom, the estimated annual incidence is 0.41 cases per million population.[3] In the Asian-Indian population, eyelid SGC is a relatively common eyelid malignancy accounting for 28–60% cases of all eyelid malignancies.[2,4,5]

Eyelid SGC is an aggressive tumor causing metastasis-related mortality in 3–41%.[6–13] On the basis of published literature, the clinical features predictive of poor prognosis are duration of symptoms >6 months, tumor diameter exceeding 10 mm, involvement of both upper and lower eyelids, and orbital invasion.[10] The pathologic features predictive of poor prognosis are multicentric origin, poor differentiation, high infiltrative pattern, vascular invasion, lymphatic invasion, and pagetoid invasion by the tumor.[9,10] Herein, in this study, we evaluate the factors predicting locoregional lymph node metastasis, systemic metastasis, and death in 191 Asian-Indian patients.

Materials and methods

A computerized database search was conducted for the diagnosis of 'Eyelid SGC' at the Institute for Eye Cancer, L V Prasad Eye Institute, Hyderabad, India from April 1995 to May 2013.

All patients with confirmation of diagnosis of SGC on histopathology were included in this study. This is a retrospective interventional case series. Institutional Review Board approval was obtained for the study.

The data were retrieved from the medical records. The data included age at diagnosis (years), gender, referral diagnosis, prior intervention, laterality, presenting complaints, duration of symptoms (months), and associated ocular/systemic disease. The status of eyelid margin, tumor epicenter, extent of tissue involvement by the tumor, largest tumor dimension (mm), lesion morphology, and associated features (intrinsic vascularity, overlying skin, and underlying conjunctival changes) were noted. The gland of tumor origin was determined on the basis of tumor location (meibomian gland, Glands of Zeis, sebaceous glands of caruncle, ectopic). Tumors located at the eyelid margin were classified as tumors arising from glands of Zeis, tumors at tarsal plate and/or larger tumors with tarsal plate as epicenter as tumors arising from the meibomian glands, and tumors at caruncle as tumors arising from the meibomian glands of the caruncle. All findings were documented by large drawings and external photography. Computed tomography of the orbit was performed in those cases with no visualization of the posterior extent of tumor. Locoregional lymph node examination was performed in all cases. In those cases with palpable lymph nodes, fine needle aspiration cytology was performed to rule out locoregional metastatic spread of tumor. Systemic metastatic workup was done with chest X-ray, ultrasound abdomen, and liver function tests.

The details of primary treatment were recorded. In cases that received secondary and/or adjuvant treatment, the indication of treatment and treatment details were noted. Any event of tumor recurrence and the time interval between primary treatment and tumor recurrence (months) were recorded. Histopathology features were noted. The final outcome at last follow-up (alive and well, alive with locoregional/systemic metastasis, dead owing to metastasis/unrelated cause) was recorded. The date and interval to locoregional lymph node/systemic metastasis were recorded. If the patient was deceased, the date and interval to metastasis-related death as indicated by the family was recorded.

Statistical analysis

The Kaplan–Meier analysis was performed to estimate the cumulative probability of locoregional lymph node metastasis, systemic metastasis, and death due to metastasis at 1, 3, 5, 10, and 20 years of follow-up. The factors predictive of locoregional lymph node metastasis, systemic metastasis, and death were analyzed using multivariate Cox-regression model with stepwise elimination using Akaike information criteria. The factors significant at the 0.05 level on multivariate analysis were reported.

Results

A total of 191 patients with eyelid SGC were included in this study. The demographic details are listed in Table 1. The mean age at presentation was 57 years (median, 56 years; range, 21–100 years). There were 78 (41%) males and 113 (59%) females. The mean duration of symptoms was 21 months (median, 13 months; range, 1–260 months). Two patients had a history of retinoblastoma, among whom one patient had undergone prior orbital external beam radiotherapy for retinoblastoma.

Table 1 Sebaceous gland carcinoma of the eyelid in 191 cases: demographics and clinical features

Features	n *(%)*
Age (years), mean (median; range)	57 (56; 21–100)
Gender (n = *191)*	
Male	78 (41)
Female	113 (59)
Laterality (n = *191)*	
Unilateral	191 (100)
Bilateral	0 (0)
Referral diagnosis (n = *131)*	
Sebaceous gland carcinoma	60 (49)
Squamous cell carcinoma	23 (18)
Basal cell carcinoma	10 (8)
Chalazion	11 (8)
Blepharoconjunctivitis	1 (<1)
Eyelid mass	26 (20)
Prior intervention before referral	97 (51)
Duration of symptoms (months), mean (median; range)	21 (13; 1–260)
Tumor epicenter (n = *191)*	
Upper eyelid	125 (65)
Lower eyelid	57 (30)
Caruncle	4 (2)
Conjunctiva	5 (3)
Tumor basal dimension (mm), mean (median, range)	15 (10; 1–80)
Tumor origin (n = *191)*	
Meibomian gland	161 (84)
Zeiss gland	21 (11)
Sebaceous glands of caruncle	4 (2)
Ectopic (conjunctiva)	5 (3)
Extent of tumor involvement (n = *191)*	
Orbital extension	30 (16)
Paranasal sinus involvement	3 (2)
Intracranial extension	1 (1)

The clinical features are listed in Table 1. The tumor epicenter was located in the upper eyelid ($n=125$, 65%), lower eyelid ($n=57$, 30%), caruncle ($n=4$, 2%), or conjunctiva ($n=5$, 3%). The mean tumor basal diameter was 15 mm (median, 10 mm; range, 1–80 mm). Eyelid SGC originated from tarsal meibomian glands ($n=161$, 84%), glands of Zeis ($n=21$, 11%), sebaceous glands of caruncle ($n=4$, 2%), or had an ectopic origin in the conjunctiva ($n=5$, 3%). Tumor extended into the orbit ($n=30$, 16%), paranasal sinuses ($n=3$, 2%), and/or cranium ($n=1$, 1%).

The treatment details are listed in Table 2. The most common primary treatment for periocular SGC was wide excision biopsy under frozen section control followed with eyelid reconstruction ($n=146$, 78%). Tumor recurrence was noted in 42 (24%) cases who subsequently underwent secondary treatment. Orbital exenteration was performed in 37 (20%) cases either as primary or secondary treatment. Over a mean follow-up period of 29 months (median, 20 months; range, <1–208 months), locoregional lymph node metastasis was noted in 41 (23%) patients, systemic metastasis in 26 (14%) patients, and death due to metastasis in 19 (10%) patients. The histopathology features are listed in Table 3.

Ten and 20-year Kaplan–Meier estimates of locoregional lymph node metastasis were 18 and 21%, systemic metastasis were 10 and 17%, and metastasis-related death were 2 and 8%, respectively (Table 4). The factors predictive of prognosis are listed in Table 5. The factors predicting locoregional lymph node and systemic metastasis were medial canthal involvement ($P=0.004$; $P=0.013$), lateral canthal involvement ($P=0.013$; $P=0.025$), tumor basal diameter >10 mm ($P=0.002$; $P=0.002$), and perivascular invasion ($P=0.043$; $P<0.001$, respectively). The factors predicting death due to metastasis were medial canthal involvement ($P=0.012$) and tumor basal diameter >10 mm ($P=0.001$).

Table 2 Sebaceous gland carcinoma of the eyelid in 191 cases: treatment and outcome

Features	*All patients* (n = *191*)
Primary treatment (n = *186*)	
Topical mitomycin-C	2 (1)
Wide excision biopsy	146 (78)
Orbital exenteration	22 (12)
Neoadjuvant systemic chemotherapy	16 (9)
Secondary treatment (n = *175*)	
Topical mitomycin-C	3 (2)
Cryotherapy	6 (3)
Wide excision biopsy	31 (18)
Orbital exenteration	10 (6)
Adjuvant treatment (n = *175*)	
Systemic chemotherapy	9 (5)
External beam radiotherapy	31 (18)
Radical neck dissection	13 (7)
Primary/secondary orbital exenteration ($n=186$)	37 (20)
Tumor recurrence ($n=175$)	42 (24)
Time interval between primary treatment and tumor recurrence (months), mean (median, range)	19 (13; <1–125)
Follow-up duration (months), mean (median, range)	29 (20; <1–208)
Final outcome at last follow-up (n = *181*)	
Alive and well	136 (75)
Regional lymph node metastasis	41 (23)
Systemic metastasis	26 (14)
Death due to systemic metastasis	19 (10)
Death due to unrelated cause	4 (2)

Discussion

Eyelid SGC is a relatively common eyelid malignancy in the Indian subcontinent, as compared with the West. Eyelid SGC is commonly seen in older individuals with a mean age at diagnosis ranging from 57 to 72 years.[2,8,9,12,14–16] In our series, the mean age at diagnosis was 57 years. Eyelid SGC is more common in female individuals.[2,12,14,15] In our series, there was a female preponderance with male to female ratio at 1 : 1.4.

An association between retinoblastoma and SGC has been reported.[17–21] In patients with a history of irradiation for hereditary retinoblastoma, SGC occurs within the

Table 3 Sebaceous gland carcinoma of the eyelid in 191 cases: histopathology features

Features	*All patients* (n = *191*)
Tumor differentiation (n = *173*)	
Well differentiated	30 (17)
Moderately differentiated	113 (59)
Poorly differentiated	30 (17)
Tumor growth pattern (n = *161*)	
Lobular	86 (53)
Comedo	21 (13)
Papillary	15 (9)
Mixed	39 (24)
Mitotic activity (n = *170*)	
High	114 (67)
Moderate	48 (28)
Low	8 (5)
Pagetoid involvement of the conjunctiva ($n=180$)	92 (51)
Pagetoid involvement of the conjunctiva detected by map biopsy ($n=129$)	21 (16)
Perivascular invasion ($n=180$)	15 (8)
Perineural invasion ($n=180$)	10 (5)

Table 4 Sebaceous gland carcinoma of the eyelid in 191 patients: outcome based on KM estimates

Features	*KM estimate (years)*				
	1 year (%)	*3 years (%)*	*5 years (%)*	*10 years (%)*	*20 years (%)*
Regional lymph node metastasis	14	17	17	18	21
Systemic metastasis	8	9	10	10	17
Death due to metastasis	1	2	2	2	8

Abbreviation: KM, Kaplan–Meier.

Table 5 Sebaceous gland carcinoma of the eyelid in 191 cases: multivariate analysis to predict outcome

Features	*Regional lymph node metastasis*		*Systemic metastasis*		*Death due to metastasis*	
	Hazard ratio (95% CI)	P-*value*	*Hazard ratio (95% CI)*	P-*value*	*Hazard ratio (95% CI)*	P-*value*
Medial canthus involvement	0.35 (0.17–0.72)	0.004	0.33 (0.14–0.79)	0.013	0.27 (0.1–0.75)	0.012
Lateral canthus involvement	0.42 (0.21–0.83)	0.013	0.38 (0.16–0.89)	0.025	—	—
Tumor basal diameter >10 mm	1.03 (1.01–1.06)	0.002	1.05 (1.02–1.08)	0.002	1.06 (1.02–1.1)	0.001
Perivascular invasion	0.42 (0.18–0.97)	0.043	0.19 (0.07–0.5)	<0.001	—	—

Abbreviation: CI, confidence interval.

irradiated field usually after a delay of 5 to 15 years.[17–21] SGC can also occur in these patients with retinoblastoma without any history of prior radiation.[19,21] In our series, there were two patients (1%) with a history of bilateral retinoblastoma. One patient had undergone external beam radiotherapy at the age of 5 months and developed eyelid SGC in the irradiated field at the age of 21 years. The second patient had no history of radiation but had a family history of retinoblastoma and developed eyelid SGC at the age of 46 years. This patient died 5 years later owing to urinary bladder carcinoma. Eyelid SGC and urinary bladder carcinoma could represent second cancers in this patient with hereditary retinoblastoma. However, some authors believe that patients with SGC are at risk for second cancers, and inactivation of the retinoblastoma gene might be a feature of SGC.[19,22]

The rate of clinical and histopathological misdiagnosis is high with eyelid SGC. They typically masquerade as a recurrent chalazion, chronic blepharitis, and chronic blepharoconjunctivitis causing a clinical misdiagnosis.[2,12,14,15] Histopathology misdiagnosis is reported in 40–75% of cases when the sections are interpreted by an inexperienced pathologist.[2,8,12] In our series, the referral clinical diagnosis was SGC in only 42% cases (60/142), and referral histopathology diagnosis was SGC in 49% cases (27/55). Most cases were referred with a clinical diagnosis of chalazion (8%), squamous cell carcinoma (18%), or basal cell carcinoma (8%). The histopathology diagnosis included chalazion (4%), squamous cell carcinoma (25%), or basal cell carcinoma (7%). The most common clinical and histopathology misdiagnosis was squamous cell carcinoma. Clinical misdiagnosis can be avoided by careful examination of the eyelid margin, conjunctiva, and the tumor. Histopathology misdiagnosis can be avoided by examination of the sections by an experienced ocular pathologist, and with the aid of special stains such as oil red O and Adipophilin stains.[23,24]

SGC most commonly arises from the meibomian glands of the tarsus (80–85%) followed by glands of Zeis (10%).[2,8–10,12] On the basis of the literature, SGC rarely arises from the caruncle (5–10%) or the conjunctiva.[8,10,12,25,26] In our series, 84% tumors arose from the meibomian glands, whereas 11% lesions were at the eyelid margin involving the glands of Zeis, 2% arose from the meibomian glands of the caruncle, and 3% had only intraepithelial SGC of the conjunctiva without involvement of the tarsus, eyelid margin, or caruncle.

The recommended management of eyelid SGC is wide excision biopsy under frozen section or Moh's micrographic surgery control followed by eyelid reconstruction.[2,15] Topical chemotherapy and cryotherapy are beneficial in cases with localized pagetoid involvement.[27,28] Systemic chemotherapy is useful in cases with diffuse eyelid SGC.[29] Orbital exenteration is the recommended treatment in cases with very advanced tumors with diffuse orbital and/or pagetoid involvement.[30] In our study, wide excision biopsy was done in 79% cases, and orbital exenteration was required in 20% of cases. Map biopsy from 17 sites (four clock hours of limbus, three each from upper and lower bulbar conjunctiva, three each from upper and lower forniceal conjunctiva, three each from upper and lower tarsal conjunctiva, and one from caruncle) is recommended

in cases with suspicion of diffuse conjunctival, caruncle, and eyelid involvement.[2,31] In our study, pagetoid involvement was identified in 51% cases in the conjunctiva adjacent to the main tumor. On map biopsy from 17 sites in 129 patients, 16% of the cases were positive for pagetoid involvement distant from the main tumor.

Regional lymph node metastasis can occur in 20–30% of cases, systemic metastasis in 8–67%, and disease-related mortality in 3–41%.[9–12,19,20,32] The factors predictive of metastasis and death include duration of symptoms >6 months, tumor diameter exceeding 10 mm, involvement of both upper and lower eyelids, and orbital invasion, multicentric origin, poor differentiation, high infiltrative pattern, vascular invasion, lymphatic invasion, and pagetoid invasion of the tumor.[10] In our series, the overall 5-year KM estimate was 17% for regional lymph node metastasis, 10% for systemic metastasis, and 2% for metastasis-related death. The factors predictive of locoregional lymph node and systemic metastasis were medial canthal involvement, lateral canthal involvement, tumor basal diameter >10 mm, and perivascular invasion. The factors predictive of death due to metastasis were medial canthal involvement and tumor basal diameter >10 mm.

In summary, eyelid SGC is a tumor associated with poor prognosis. In the present study, lymph node metastasis occurred in 18%, systemic metastasis was detected in 10%, and death occurred in 2% patients at 10 years. Canthal involvement, larger tumor, and perivascular invasion were poor prognostic factors. Patients with these features require close monitoring for early detection and treatment of locoregional and systemic metastasis.

Summary

What was known before

- The clinical features and prognosis of SGC in Caucasians.

What this study adds

- No large series has been published from India.
- With this study, we elaborate the clinical features and prognosis of SGC in Asian Indians.

Conflict of interest

The authors declare no conflict of interest.

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