Eyelid sebaceous gland carcinoma: Varied presentations and reconstruction outcome

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Abstract:

PURPOSE: To analyze varying clinical presentations, histopathological features, and management outcome of sebaceous gland carcinoma (SGC) of the eyelid.

MATERIALS AND METHODS: We retrospectively reviewed medical records of 30 patients with histologically proven cases of SGC of eyelid treated at tertiary care hospital.

RESULTS: Patients were in the age group of 28–80 years, among which 18 (60%) were females and 12 (40%) were males. Mean follow-up period was 29.83 ± 8.14 months. Six out of 30 cases were lost to follow-up; hence, only 24 cases were analyzed for reconstruction techniques and management outcome. Initial anatomic sites involved were upper eyelid (10 cases [33.33%]), lower eyelid (5 cases [16.66%]), both upper and lower eyelid (10 cases [33.33%]), and medial canthus (1 case [3.33%]). Orbital extension at presentation was present in 4 cases (13.33%) while metastasis to preauricular lymph nodes was seen in 1 case (3.33%). T2 was the most common category according to TNM staging (14, 58.33%). Reconstruction techniques included direct closure with or without cantholysis in 5 (20.83%), closure with Tenzel’s semicircular flap in 2 (8.33%), Cutler Beard repair in 5 (20.83%), and Hughes’s flap with either cheek advancement flap or full-thickness skin graft in 3 (12.5%). Both upper eyelid and lower eyelid repair were done in three (12.5%) cases and medial canthal repair in one (4.16%) case. Five (20.83%) cases underwent exenteration. On histopathological examination, 23 (95.83%) patients had localized tumors while only 1 (4.16%) patient had pagetoid invasion. Recurrence was observed in three (12.5%) cases. One (4.16%) case died subsequent to brain metastasis.

CONCLUSION: SGC of eyelid may have varied presentations, but early diagnosis and consequent surgical therapy has good outcome and higher survival rate.

Keywords: Eyelid, reconstruction, sebaceous gland carcinoma, varied presentations

Introduction

Sebaceous carcinoma, sebaceous gland carcinoma (SGC), sebaceous cell carcinoma, and meibomian gland carcinoma are all terms used in the literature to describe a malignant neoplasm of the eyelid and ocular adnexa which is of sebaceous origin. The tumor is notorious for not only mimicking various benign and malignant clinical entities but also for aggressive local behavior and the potential for distant metastasis. The first series on eyelid sebaceous carcinoma was presented by Straatsma in 1956 which consisted of 16 patients. Thereafter, lots of series have been published worldwide. Although quite a few studies have been published from India on eyelid malignancies, there is still a paucity of literature on SGC from India. The present study describes the demographics, clinical presentations, management, and outcome of a series of cases of SGC from Northern India.

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Materials and Methods

The institutional review board approved the study and we strictly adhered to the tenets of Declaration of Helsinki. Consent for publication of the study was taken from patients or their kin and was archived. Medical records of 30 patients with histopathologically proven SGC of the eyelid between January 2009 and December 2015 were reviewed and analyzed retrospectively. All patients were staged according to the seventh edition of American Joint Committee on Cancer (AJCC) staging system for eyelid carcinoma. Demographics, duration of symptoms, clinical presentation, treatment methods, follow-up, recurrences, management of recurrences, and mortality were thoroughly reviewed and recorded. Any previously available histopathological diagnosis was also noted and compared. Imaging in the form of magnetic resonance imaging and computed tomography was done in all cases of suspicious orbital involvement and positron imaging tomography scan in all cases of nodal metastases and suspicious distant metastases. Small- to medium-sized tumors were excised with a clinical margin of 5 mm under frozen section and reconstructed at the same sitting. An incisional biopsy was done to confirm the diagnosis before performing any mutilating procedure (exenteration, extended enucleation). Map biopsy was performed in all cases wherever a pagetoid spread was suspected. Lymphadenectomy was done in cases with nodal metastasis. Postoperative radiotherapy was advised for all cases of deep orbital involvement after exenteration. Patients were initially followed up at monthly intervals for 3 months and then subsequently at 6 months and 1 year periods. Patients with nodal metastases were followed up more closely.

Results

A total of 30 patients were included in the study. The demographics are shown in Table 1. Duration of symptoms ranged from 6 to 24 months. Patients presented with myriad presentations [Figure 1]. The most common clinical presentation was a nodular mass lesion [Table 2]. The tumor was localized to upper eyelid in 10 (33.33%) cases, to lower eyelid in 5 (16.66%) cases, and to both eyelids in 10 (33.33%) cases. Four (13.33%) cases showed orbital extension and 1 (3.33%) case involved medial canthus. None of the patients had any prior history of radiotherapy. There was no evidence of any other malignancies in any of the patients. A total of 24 patients underwent surgical excision of the mass and were followed up. Six patients either refused further treatment after incisional biopsy or were lost to follow-up.

Staging: Most of the patients fell in Stage 1B (T2AN0M0) category (9, 37.5%). Five patients (20.83%) were staged as Stage 1C (T2BN0M0), four (16.66%) as Stage 2 (T3AN0M0), three (12.5%) as Stage 3A (T3BN0M0), two (8.33%) as Stage 1A (T1N0M0), and one (4.16%) as Stage 3B (T3BN1M0). Overall, T2 was the most common category (14, 58.33%), [Table 3].

The primary treatment modality was wide surgical excision under frozen section with a margin of 5 mm. Reconstruction was carried out at the same sitting after obtaining a margin clearance [Figure 2]. Reconstruction techniques included direct closure with or without cantholysis in 5 (20.83%), closure with Tenzel’s semicircular flap in 2 (8.33%), Cutler Beard repair in 5 (20.83%), and Hughes’s flap with either cheek advancement flap or full-thickness skin graft in 3 (12, 5%). Both upper and lower eyelid repair were done in 3 (12.5%) cases and medial canthal repair in 1 (4.16%) case. Five (20.83%) cases underwent exenteration. Radical lymph node dissection was done in 1 (4.16%) case [Table 4].

On histopathology, 23 (95.83%) patients had localized tumors without any pagetoid invasion.

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Table 1: Patient demographics

| n     | Age          |
|-------|--------------|
|       | Mean±SD      |
| 58.96±14.41 |               |
| Median | 64.5         |
| Range  | 28-80        |

| Sex     | n     |
|---------|-------|
| Male    | 12    |
| Female  | 18    |

| Affected eye | n     |
|--------------|-------|
| Right        | 18    |
| Left         | 12    |

| Affected site                | n     |
|------------------------------|-------|
| Upper eyelid                 | 10    |
| Lower eyelid                 | 5     |
| Both eyelids                 | 10    |
| Eyelids and surrounding facial/orbital structures | 4 |
| Medial canthus               | 1     |
| Prior irradiation            | 0     |

Table 2: Initial clinical presentation and duration of symptoms

| Mode of Presentation                                                   | Number of Cases |
|------------------------------------------------------------------------|-----------------|
| Initial clinical presentation                                          |                 |
| Localized nodular mass including medial canthus                        | 15              |
| Diffuse eyelid involvement                                             | 10              |
| Orbital mass                                                           | 4               |
| Orbital mass infected with maggots                                     | 1               |
| Duration of symptoms before presenting (months)                        |                 |
| Mean                                                                    | 10.26±4.22      |
| Range                                                                   | 6-24            |
| Follow-up period (months)                                              |                 |
| Mean                                                                    | 29.83±8.14      |
| Range                                                                   | 8-44            |
Seventeen (73.91%) cases had well-differentiated tumors while 6 (26.08%) cases had poorly differentiated sebaceous carcinomas. Only 1 (4.16%) patient had pagetoid invasion of the tumor [Figure 3a-d].

Three (12.5%) cases had recurrences. One of these cases had undergone Cutler Beard repair for the upper eyelid SGC and had a recurrence on the same site 8 months after the procedure. She was an extremely old debilitated female who refused further surgery. She was then advised radiotherapy and was lost to follow-up thereafter. The second case had undergone excision of the mass from the
lower eyelid but came back with an orbital recurrence after 5 months. The third case had undergone excision of a well-defined orbital mass (SGC on histopathology) presented with orbital recurrence 6 months after the surgery. These two cases underwent orbital exenteration. The mean duration of recurrence was 6.3 months. All patients were negative on metastatic workup. All recurrences were in the T3 category, and the Fisher's exact test was statistically significant when compared with T category better than this ($P = 0.027$).

Follow-up period ranged from 8 to 44 (29.83 ± 8.14) months. Only 1 (4.16%) case died because of brain metastasis. Rests of the 23 (95.83%) patients were alive at their last follow-up.

Discussion

SGC is a rare eyelid malignancy among the western population accounting for <1%–5.5% of all malignancies.[7,8] On the contrary, the tumor is much more common in the Asian population (31%–39%).[4,9,10] Till date, the largest published series from the Indian subcontinent on eyelid SGC is by Kaliki et al.[5] They published a case series of 191 cases managed over a period of 18 years (1995–2013). The number of cases in the present study (30) is also quite high for a 7-year period when compared to previous western studies.[5,8] A clinically similar study published by Song et al. reports a number of 31 cases over a 22-year period (1984–2006) which is quite less as compared to the present study.[11]

This points to a predisposition for developing SGC in the Asian population.[12] Surprisingly, there is a paucity of literature on eyelid SGC from India and its surrounding countries.

Previous studies have shown that the tumor is more common in older age group and among females.[8,11] Our study corroborates with the findings of the previous studies.

SGC notoriously masquerades as several benign conditions such as chalazion, sebaceous cyst and blepharoconjunctivitis, and other eyelid tumors such as basal cell and squamous cell carcinoma.[11,13] This often leads to a delay in diagnosis. In our series, the average duration of complaint was 10.26 months. This delay in diagnosis contributes to the extension of tumor both locally and to distant organs. The mean duration of symptoms reported by Kaliki et al. was 21 months[5] and that by Shields et al. was 23 months.[13] Duration of presentation of >6 months has been considered as a factor predictive of metastasis and death.[14]

Sebaceous cell carcinoma is much more common in the upper eyelid due to the larger number of meibomian glands being present there, followed by the lower lid. Many of the previous studies suggest a similar occurrence.[11,13,14] SGC was present in upper eyelid in 33.33% of cases. SGC involving both upper and lower eyelids has been attributed to its multicentric origin.[8] About 33.33% of the cases in the present series too had involvement of both the eyelids. SGC arising from glands of Zeis has a better prognosis as compared to that arising from meibomian glands.[19] Although Kaliki et al. reported 81% of the tumors to arise from meibomian glands and 21% from glands of Zeis, the findings are purely clinical and it is very difficult to determine the exact site of origin.[13] Four out of 191 cases (2%) in the series reported by Kaliki et al. and one out of 60 cases reported by Shields et al. were caruncular in origin.[9,13] We did not have any case arising from the caruncle, but we did have one case arising from the medial canthal skin adjacent to caruncle. Tumors arising from caruncle and medial canthus have a greater chance of locoregional and distant metastasis as compared to other sites.[9] Hence, all such patients require a more close follow-up.

Eyelid sebaceous cell carcinoma has a peculiar diffuse intraepithelial growth pattern. The neoplasm invades the surface epithelium and replaces it in a pagetoid fashion. This peculiar pagetoid growth pattern predisposes this tumor to be frequently misdiagnosed as blepharoconjunctivitis and poses a diagnostic and therapeutic challenge. Only 1 (4.16%) of our cases had pagetoid growth pattern on histopathology. The reported incidence of pagetoid pattern was 47% and 36.6% by Shields et al. and Song et al., respectively.[11,13] Although Kaliki et al. have reported that 51% of their cases had
pagetoid changes in the conjunctiva surrounding the tumor, only 16% cases had histopathologically proven intraepithelial pagetoid spread in all cases who underwent map biopsy. It is interesting to note that our series had a surprisingly lower incidence of pagetoid spread as compared to studies from the west.\cite{11,13}

SGC most commonly metastasizes to regional lymph nodes.\cite{14,16} Role of clinical examination to rule out regional lymph node involvement in every case cannot be overemphasized. In the series reported by Kaliki et al., 41 (23%) cases had nodal metastasis and only 13 (7%) cases underwent radical neck dissection. Shields et al. reported 5 cases of lymph node metastasis in their series. Out of these 5 cases, 3 died because of widespread metastasis after 39, 29, and 15 months of developing lymph node metastasis, respectively. One patient was alive till the last follow-up while once case died of unrelated cause 47 months later.\cite{13} Song et al. reported 3 cases of lymph node metastasis, out of which two underwent parotidectomy along with lymph node and neck dissection.\cite{11} In a study by Deo et al. which studied lymph node metastasis in advanced SGC of the eyelid, 10 cases had histopathologically proven lymph node involvement and 100% of these cases had parotid involvement.\cite{6} Two of these patients had Level IIb cervical lymph node involvement as well. Seven of these patients had recurrence and seven cases received postoperative radiotherapy. In our series, only one patient had cervical lymph node involvement and underwent radical neck dissection. Recently, role of sentinel lymph node biopsy has been described to rule out any occult lymph node involvement.\cite{17,18}

Distant organs commonly involved are lung, liver, brain, and bone, but it is fortunately rare.\cite{19} Kaliki et al. reported 26 (14%) cases of metastasis and 19 (10%) metastasis-related death over a mean follow-up period of 29 months. Ten- and 20-year Kaplan–Meier estimates of systemic metastasis were 10% and 17%, respectively, while that for metastasis-related death were 2% and 8%, respectively.\cite{23} The rate of metastasis and metastasis-related death in the series reported by Shields et al. was 8% and 6%, respectively.\cite{13} Only one patient (4.16%) in our series had a distant metastasis to brain and eventually succumbed to it. The patient had presented to us quite late with an infiltrative mass infected with maggots. He underwent exenteration and adjuvant radiotherapy but developed metastasis during the course of treatment.

Complete surgical excision with surgical margin control under frozen section is the most widely accepted method of treatment for nodular localized eyelid SGCs. Margins of 4 mm can be used\cite{20} although recurrences have been reported even with 5–6 mm of surgical margins.\cite{21}

Margin clearance should be confirmed on permanent sections. For larger well-circumscribed lesions where complex eyelid repair techniques are anticipated, it is advisable to attempt removing the lesion along with conjunctival map biopsies. Definitive surgery should be planned based on the result of these biopsies.\cite{13}

For ill-defined diffuse lesions without any nodular component, map biopsies are submitted, and definitive surgery is planned only after permanent section results.\cite{11,13,22} It is advisable to apply cryotherapy to bulbar conjunctiva in the same sitting while taking map biopsies.\cite{23} Topical chemotherapy with Mitomycin C can be used in cases of residual bulbar conjunctiva involvement.\cite{24}

However, we followed a complete surgical removal under frozen section clearance with 5 mm surgical margins. Eyelid repair was done in the same sitting after communicating with the pathologist. Map biopsy was performed wherever diffuse conjunctival involvement was suspected. It was not done for well-localized nodular cases. Any destructive procedure like exenteration was carried out only after permanent section diagnosis.

Final diagnosis was confirmed on permanent section results. The traditional approach to diagnosis is using oil red O stains for examining the fresh tissues and demonstrating intracytoplasmic lipid vacuoles.\cite{25} The same technique was used at our center [Figure 3a]. The tumor cells are generally arranged in the form of lobules or sheets sometimes with central comedo necrosis. Individual tumor cells have distinct cell membranes, clear to vacuolated cytoplasm, and vesicular nuclei with prominent nucleoli, numerous mitosis, and apoptotic cells.\cite{12} The tumor can have squamous or basal differentiation which incurs an aggressive behavior.\cite{26}

Well-differentiated tumors have a better prognostic outcome as compared to poorly differentiated tumors [Figure 3b and c]. Pagetoid spread is also associated with a poorer prognosis [Figure 3d]. None of the tumors in our series had any squamous or basal differentiation. One case however had apocrine differentiation.

Tumor recurrence in cases of eyelid SGC poses a major problem. The recurrence can be at the same site or at a different location. It is difficult to say whether it is a true recurrence or a new tumor altogether because of the multicentric nature of SGC.\cite{13,27} Kaliki et al. had a recurrence rate of 24% and the mean duration of recurrence after primary treatment was 19 months. Shields et al. have very extensively studied the pattern of recurrences in their cases. The reported recurrence rate in their series was 18% after a mean duration of 21 months from the primary treatment. Six cases in their series had single recurrence, 4 recurred twice while one case had 4 recurrences. About 73% of the recurrences in their series occurred at the primary site while 23% occurred at a new
Three (12.33%) cases in our series experienced recurrence. Two cases had recurrence at the same site while the third case (where a mass was excised from the lower eyelid) had a recurrence in the orbit. Mean duration of recurrence was 6.3 months. One case was advised radiotherapy because of advanced age while rest two underwent exenteration.

The reported mortality for SGC in the past ranged from 3% to 41%. The mortality rate and prognosis have improved considerably over the past decade. This is mainly attributed to early diagnosis and extensive surgical measures. The reported mortality resulting from eyelid SGC was 6% and 10% by Shields et al. and Kaliki et al., respectively. Our series reports a mortality rate of 4.16%. This was mainly because majority of patients had well-defined nodular lesions and were well differentiated on histopathology. Very few patients had diffuse and pagetoid involvement and only one patient had lymph node involvement.

In studies by Esmaeli et al., Kaliki et al., and Watanabe et al., the T2 category was found to be most common based on the seventh edition of AJCC staging system. Esmaeli et al. noted that the T category of T2b or worse correlated with lymph node metastasis and T category of T3a or worse correlated with distant metastasis and death as a result of disease. However, no association was found between T category and recurrence. In our series too, T2 category was the most common. One patient each had lymph node and systemic metastasis and both of them had T3a or worse disease. However, we noted a statistically significant correlation between recurrence and T3 category ($P = 0.027$). The findings clearly suggest that SGC with higher T category has greater chances of lymph node and systemic metastasis and recurrences.

Neoadjuvant chemotherapy is a recently introduced concept in the management of chemotherapy which not only offers organ preservation but also downstages the disease and provides excellent locoregional control. Kaliki et al. studied the role of cisplatin/carboplatin and 5-fluorouracil as neoadjuvant chemotherapeutic agents in 10 cases of advance SGC of the eyelid and reported excellent results. They recorded 74% reduction in the mean basal tumor diameter without any serious adverse effects. In their series of 10 cases, 6 cases were suitable for excision biopsy and 4 for eyelid-sparing orbital exenteration; however, postchemotherapy, only 5 underwent excision biopsy and 2 underwent eyelid-sparing orbital exenteration. External beam radiotherapy was given in 7 cases for possible microscopic tumor residue in the orbit and regional lymph nodes. No recurrence was noted at a mean follow-up of 18 months.

It is one of the very few larger series on eyelid SGC from India which describes in detail the various clinical patterns, histopathology, management methodology, and outcome. As compared to western population, SGC is far more common among the Asians. We also noted that our series had very few cases of pagetoid spread as compared to series from the west. This also points toward a difference in the behavior of tumor growth pattern at least in the Indian subcontinent leading to an overall better prognosis. The advent of modern surgical techniques and neoadjuvant chemotherapy will further obviate the need of exenterations and a better prognostic outcome.

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Conflicts of interest
There are no conflicts of interest.

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