Sebaceous carcinoma of the eyelid: anatomoclinical data

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Abstract
Sebaceous gland carcinoma of the eyelid is a rare slow-growing tumor and is one of the most aggressive malignancies of the eyelid. Diagnosis is often delayed because it can be confused with other periorbital lesions. We report the case of a 78-year-old female who presented for the anesthetic aspect of a nodular tumor on the right upper eyelid occurring one year earlier. The patient was treated for three months for recurrent chalazion. Ophthalmologic examination revealed a nodular ulcerated tumor of 1 cm in size adherent to adjacent tissues. Surgical excision was performed with a safety margin of 4 mm. The diagnosis of moderately differentiated sebaceous carcinoma was made by routine morphological methods and immunohistochemical reactions (EMA and Ki-67). Being a rare tumor with considerable morbidity and mortality, early diagnosis and proper treatment are essential for a favorable prognosis and preservation of visual function.

Keywords: sebaceous carcinoma of the eyelid, chalazion, immunohistochemistry.

\section*{Introduction}
Sebaceous carcinoma is an uncommon malignancy that is most often found in the periorbital area, especially the eyelids. The tumor is locally aggressive and can metastasize to regional lymph nodes and distant organs [1–3]. The tumor is also called adenocarcinoma of sebaceous gland, meibomian gland carcinoma, or Zeis gland carcinoma. The incidence of sebaceous carcinoma varies in different series, in the United States is about 0.5 per million in the white population and is more common in Caucasians than in African-Americans [1]. The incidence of sebaceous carcinoma among all eyelid tumors is 2% to 7% and among eyelid malignancies, 1% to 5.5% [4]. Sebaceous carcinoma more frequently involves women than men [1–4]. Among the large studies, between 57\% and 77\% of afflicted patients were women [2, 4]. Patients are usually between 50 and 90-year-old [1, 4]. In most cases, the etiology of sebaceous carcinoma is unknown, but a minority has a history of radiation exposure after retinoblastoma [1, 2, 4].

Clinically, sebaceous carcinoma is characterized by the “masquerade syndrome” of some benign and malignant tumors, resulting in the delay of correct and early diagnosis. For these reasons, ophthalmologists, dermatologists and other specialists should be familiar with the clinical features and appropriate treatment of these tumors [1, 4]. Shields JA et al. (2005) [5] state that although ophthalmologists are familiar with the various clinical features of sebaceous carcinoma, the diagnosis of this tumor is still seriously delayed. Correct and early diagnosis of eyelid sebaceous carcinoma favors a less aggressive treatment, and prevents local recurrence and metastasis [1–3].

\section*{Patient and Methods}
A 78-year-old female patient presented in 2013 to the II\textsuperscript{nd} Ophthalmology Clinic, Iassy, Romania, for the anesthetic aspect of a tumor mass on her right upper eyelid (Figure 1).

Figure 1 – Sebaceous carcinoma of the right upper eyelid. Firm, yellow tumor nodule with central ulceration.

She had the tumor for one year, and during the last six months, it had rapidly increased in size. The patient reported that she received topical and subsequently surgical treatment for recurrent chalazion on the right upper eyelid.

The tumor was surgically excised with safety margins of 4 mm. The specimens were fixed in 4\% formaldehyde, paraffin embedded, and stained with Hematoxylin–Eosin. Immunohistochemical reactions were performed using the EnVision method. Two monoclonal mouse antibodies produced by Dako Company, Copenhagen, Denmark: anti-
human epithelial membrane antigen, clone E29 (EMA) and anti-human Ki-67 antigen were used. Immunostaining for epithelial membrane antigen and Ki-67 was performed using the EnVision detection system (Dako, Denmark), 3,3'-diaminobenzidine as chromogen and Mayer’s Hematoxylin for nuclear counterstaining against nuclear staining. Antigen retrieval was done with sodium citrate buffer, pH 6, in water bath at 95°C. The reaction was considered positive only when a brown cellular membrane coloration in the case of EMA immunostain and brown stained nuclei in the case of Ki-67 immunostain were obtained. Mean Ki-67 labeling index was determined by counting both positive and negative nuclei in 10 different microscope fields using a 40× objective. The percentage of positive cells in each field was calculated and then the mean Ki-67 labeling index was determined by the arithmetic mean of the 10 previously recorded values.

**Results**

Ophthalmologic examination: moderately reduced visual acuity (corrected visual acuity – right eye 1/2, left eye 1/3), with ocular motility in both eyes. Examination of eye adnexa showed a firm, yellow, ulcerating nodule of approximately 1cm in size, deep-seated, and located in the middle 1/3 of the right upper eyelid. Macroscopically, the 1/0.5 cm tumor was nodular; yellow, of higher consistency, and with central ulceration.

The surgically excised mass was composed of tumor lobules surrounded by a vascular-connective stroma infiltrating the dermis and presenting central cores of necrosis having a comedocarcinoma-like pattern (Figure 2). In some lobules, tumor cells showed varying degrees of sebaceous differentiation, with foamy cytoplasm and fine vacuoles. The centrally located nuclei were hyperchromatic, pleomorphic, with conspicuous nucleoli and presented atypical mitosis (Figure 3). The neoplastic lobules showed basaloid differentiation (Figure 4) and squamous differentiation with keratinization and forming of corneous globes (Figure 5).

Thirty-three percent of tumor cells were positive for Ki-67, consistent with a high-proliferative activity of tumor cells (Figure 6). Immunohistochemical staining for EMA was intensely positive in most tumor cells (Figure 7). Given the degree of sebaceous differentiation, this tumor was classified as sebaceous carcinomas with basaloid and squamous areas.

![Figure 2 – Sebaceous carcinoma with lobules infiltrating the dermis, composed of tumor cells with basaloid differentiation, and comedocarcinoma-like pattern (HE stain, ×40).](image)

![Figure 3 – Sebaceous carcinoma composed of tumor cells showing sebaceous differentiation (HE stain, ×200).](image)

![Figure 4 – Sebaceous carcinoma with basaloid differentiation (HE stain, ×200).](image)

![Figure 5 – Sebaceous carcinoma with squamous differentiation and forming of corneous globes (HE stain, ×200).](image)
Figure 6 – Sebaceous carcinoma. The tumor has significantly increased levels of index Ki-67 (IHC stain, ×200).

Figure 7 – Sebaceous carcinoma. Tumor cells showed intense immunohistochemical staining positive for EMA (IHC stain, ×200).

Discussion

The first case of periorbital sebaceous carcinoma was published by Allaire, in 1891 (quoted by [6]). Sebaceous carcinomas of the eyelid are rare tumors originating in the meibomian glands, Zeis glands, or both when of multicentric origin. In some cases, the tumor origin cannot be determined [7–9]. The occurrence rate of these carcinomas varies with ethnicity of the population. The tumor is rare in the Caucasian population, with a frequency of less than 1% to 5.5% of all malignant eyelid tumors [4, 10]. On the other hand, in the Chinese and Japanese population sebaceous carcinoma is the second most common malignant eyelid tumor, accounting for 39% and 37.5%, respectively, of all malignant eyelid tumors [11, 12]. Similar studies in India and Singapore reported that sebaceous carcinoma accounts for 31.2% and 10.2%, respectively, of malignant eyelid tumors [9, 13]. The increased frequencies in the Asian populations may have genetic or racial causes. The absolute incidence in the non-Caucasian population is not known [10]. Sebaceous carcinoma of the eyelid occurs in people aged 50 to 90 years but it can also be seen in young people [4, 6–8]. Some studies suggest a female preponderance, while others show no gender preference [1, 4, 5, 8].

Clinically, the tumor is most commonly a small, firm, yellow nodule adherent to the adjacent tissues and resembling a chalazion. The tumor may have a papillomatous appearance or that of a diffuse plaque-like thickening of the tarsus with lid eversion [5, 14]. Sebaceous carcinoma of the eyelid is known for masquerading as a benign or malignant condition (“masquerade syndrome”) often causing a delay before correct diagnosis. The misleading clinical manifestations may suggest an inflammation, including unilateral conjunctivitis, blepharitis, tarsitis, blepharocconjunctivitis and keratoconjunctivitis [8, 15]. In our patient, the tumor manifested clinically as a chalazion, and was treated with topical medications for three months. Later, the mass was incised and drained in a medical unit. The tumor most commonly affects the upper eyelid, and to a lesser extent the lower eyelid or both eyelids [5, 8, 15]. Tumor size has a significant prognostic role in sebaceous carcinoma. In the casuistry of Rao NA et al. (1982) [1], including 104 patients, none of the patients with tumors less than 6 mm died. With tumors 6 mm to 10 mm, mortality was 18%, reaching 60% when the tumor was between 11 mm and 20 mm. In our patient, the tumor was less than 20 mm.

Microscopically, sebaceous carcinomas are composed of tumor cells with foamy cytoplasm and fine vacuoles signifying sebaceous differentiation. Tumor cell nuclei are hyperchromatic, pleomorphic with conspicuous nucleoli and atypical mitosis. Sebaceous carcinomas are classified into three groups according to their degree of sebaceous differentiation: well differentiated, moderately differentiated, and poorly differentiated. Sebaceous carcinomas present three histological patterns: lobular, comedocarcinoma-like, and mixed. The lobular pattern is characterized by basaloid tumor cells, which in poorly differentiated tumors may be confused with basal cell carcinoma. In the comedocarcinoma-like pattern, the large lobules have a central necrotic core. Other sebaceous carcinomas have squamous appearance with areas of keratinization and therefore can be mistaken for squamous carcinoma [1, 16–18]. Microscopically, the tumor diagnosed by us had the appearance of a moderately differentiated sebaceous carcinoma with basaloid and squamous areas. Studies reveal erroneous diagnosis in 23–77% of the poorly differentiated sebaceous carcinomas [15]. In about 18% of cases, sebaceous carcinoma may be mistaken for squamous cell carcinoma [15].

Sinard JH (1999) [19] used immunohistochemistry to differentiate sebaceous carcinoma from basal and squamous cell carcinomas. He found that sebaceous carcinoma generally expressed EMA, Cam5.2 and BRST-1. Basal cell carcinoma expressed neither EMA or BRST-1 whereas squamous cell carcinoma expressed EMA but not Cam5.2. In our case, most tumor cells showed intense immunohistochemical staining positive for EMA. The tumor showed a high-proliferative activity, confirmed by a high Ki-67 proliferative index, which was positive in 33% of tumor cells.

Intraepithelial invasion to conjunctiva, cornea and eyelid skin is common in sebaceous carcinomas. There are two types of intraepithelial invasion, pagetoid and
carcinoma “in situ-like” [1, 2, 16]. In the study by Rao NA et al. [1], the mortality rate in the patients with pagetoid invasion was 50%, while in those without pagetoid invasion it was 11%. Moderately- and poorly-differentiated eyelid sebaceous carcinomas have and infiltrative growth with lymphatic and blood vessel invasion [1, 16].

Rao NA et al. [1] present four histological features of poor prognosis: multicentric origin of the tumor, moderate or low sebaceous differentiation, highly infiltrative pattern, and intraepithelial carcinomatous changes that induce pagetoid invasion and presence of intraepithelial carcinoma. Other morphological features are the presence of lymphatic and vascular invasion. Clinically, Rao et al. [1] concluded that the upper eyelid location of the tumor, a tumor 10 mm or more in size, and a duration of symptoms longer than five months indicate a poor prognosis.

Our patient was classified as stage T2aN0M0 and had a favorable clinical course. Data in the literature indicate that sebaceous carcinomas have a 30–40% risk for recurrence, 20–25% for metastases, and 20% for tumor-related mortality [3, 10]. Our case showed no recurrence or metastasis to the regional lymph nodes or distant metastases five months following surgery. Local excision of the tumor, orbital exenteration, radiation therapy and chemotherapy are the methods used in the management of patients with sebaceous carcinoma of the eyelid in different clinical stages [9, 20].

Conclusions

Sebaceous gland carcinoma is a rare tumor of the eyelid that can mimic many inflammatory lesions. The correct diagnosis by light microscopy and immunohistochemistry requires an adequate management, based on using advanced surgical methods and adjuvant therapy for a good tumor control, aimed at reducing morbidity and mortality in these patients.

References


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