

Sebaceous Cell Carcinoma: Wide Histological Spectrum and Correlation to Prognosis. A Case Report and Review of the Literature

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Received date: Oct 05, 2015; Accepted date: Oct 23, 2015; Published date: Oct 27, 2015

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Abstract

Sebaceous cell carcinoma (SCC) is the second most common eyelid malignancy among Caucasians, next to Basal cell carcinoma (BCC). It is an uncommon malignant neoplasm, and there are several reports describing the multiple clinical and histopathological presentations of SCC. Given its rarity, diagnosing SCC remains a challenge for ophthalmologists and pathologists, especially when conducting incisional biopsies. A 66-year-old male presented with a recurrent right upper eyelid mass for 4 years. The lesion recurred 4 times, and a biopsy was performed twice. In the first biopsy, a mild cell atypia was observed; the second biopsy was negative for atypia or cancerous cells. The patient was followed-up closely and in the 4th recurrence, a full thickness biopsy was performed. Histopathologically, areas of well-differentiated SCC were observed, as well areas of poorly differentiated SCC resembling BCC, squamous cell carcinoma in situ, and mucoepidermoid carcinoma. We highly recommend clinical and pathological suspicion of SCC in clinical cases of recurrent chalazion, treatment-resistant blepharoconjunctivitis, and undifferentiated malignant tumors of the eyelid present late in life.

Keywords: Sebaceous cell carcinoma; Eyelid tumors; Sebaceous glands; Meibomian glands

Introduction

Sebaceous cell carcinoma (SCC) of the eyelid is an uncommon eyelid tumor, accounting for 1% to 5% of eyelid malignancies [1]. However, next to Basal cell carcinoma (BCC) it is the second most common eyelid malignancy among Caucasians [2,3]. It is a challenging tumor to diagnose, as it tends to masquerade itself as either benign or other malignant conditions [4-7].

Case History

A 66 year old male presented with a right conjunctival/eyelid lesion (Figure 1a). His history included a recurrent small upper right eyelid mass diagnosed as recurrent chalazion. A biopsy performed 2 years ago in one of the recurrences tested negative for malignancy; however, a previous biopsy performed in the first lesion 4 years ago indicated cells with mild atypia. After the 4th recurrence, he was referred to our hospital. On examination, the patient's vision was 20/30 bilaterally and his intraocular pressure was 12 and 15 in his right and left eye, respectively. He presented with entropion, madarosis, and an ill-defined mass on his right upper eyelid. His right lower eyelid showed mild induration, erythema, and white plaques. The rest of the ophthalmic examination was within normal limits and there was no evidence of lymphadenopathy.

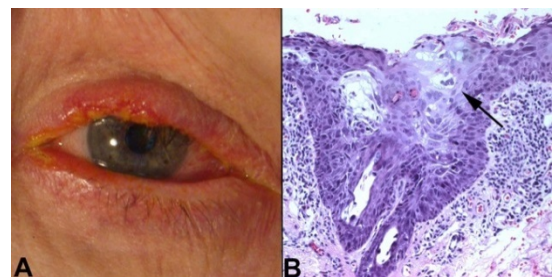


Figure 1: (a) Clinical picture showing an ulcerated lesion located in the upper eyelid. The lesion extended to the palpebral conjunctiva. Madarosis and entropion were also observed. (b) Histopathological picture of the incisional biopsy showing an intraepithelial proliferation of neoplastic cells with high-grade nuclear atypia and focal areas showing cells with vacuolated cytoplasm. Periodic-Schiff acid and alcian blue stains were negative (Hematoxylin-Eosin (H&E), 400X).

A full thickness biopsy of the right upper and lower lid lesions was done. The histopathological exam showed cells with atypical nuclei and vacuolated cytoplasm (Figure 1b) with extension to the conjunctiva. Differential diagnosis included squamous cell carcinoma (SqCC), mucoepidermoid carcinoma (MEC), and SCC invading the

conjunctiva. The periodic acid-Schiff (PAS) and alcian blue stains were negative. Right eye exenteration was performed. Systemic work-up ruled out distant metastasis.

Histopathologically, the tumor displayed different morphological patterns. The main component showed areas of neoplastic cells with sebaceous differentiation, where cells had foamy vacuolated cytoplasm, prominent nuclei together with multiple mitotic figures (Figure 2a). In other areas, the tumor exhibited a poorly differentiated component with anaplastic large cells with scanty cytoplasm (Figure 2b). Other areas displayed solid structures and lobulated mass made of cells with large nuclei and abundant eosinophilic cytoplasm, dyskeratosis, resembling a SqCC. Some follicles were invaded by the neoplastic cells (Figure 2c). Also, tumor necrosis resembling comedocarcinoma as seen in breast carcinoma in situ was observed. Furthermore, there was an extensive area of intraepithelial atypia diffusely infiltrating the palpebral conjunctiva, mimicking SqCC in situ. These areas were observed in both superior and inferior palpebral conjunctiva. Another histological variant was observed, which was formed by small basophilic cytoplasm with a peripheral ill-defined palisade-like configuration that might resemble BCC.

Immunohistochemistry was performed using a panel of BRST-, EMA, and CAM5.2. The tumor was positive for all the 3 markers. BRST-1 was positive predominantly within the well-differentiated sebaceous areas of the tumor (Figure 2d).

Interestingly, a granulomatous inflammatory reaction consistent with that observed in chalazion lesions was found within the neoplastic lesion, mainly in the superficial subepithelial zones, suggesting that this tumor may have formed on top of this chalazion.

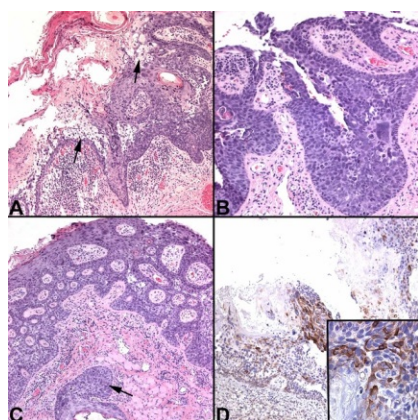


Figure 2: (a) Photomicrograph of the enucleation specimen showing an area of extensive intraepithelial proliferation of cells with nuclear atypia and vacuolated cytoplasm (arrows) (H and E, 100X). (b) Some areas presented cells with high-grade nuclear atypia with scanty cytoplasm, simulating SqCC in situ (H and E, 400X). (c) Extension to the hair follicle was observed (arrow), explaining the madarosis of the patient (H and E, 200X). (d) Immunohistochemistry for BRST-1 showing positive stain on the neoplastic cells, especially in those well-differentiated sebaceous cells with vacuolated cytoplasm (BRST-1 100X). Inset, a closer view of the positive cells for BRST-1 (BRST-, 400X).

Discussion

Eyelid tumors are the most common neoplasm in daily ophthalmology practice and encompass a wide variety of benign and malignant tumors [8]. SCC of the eyelid is the second most common eyelid malignancy after BCC among Caucasians [2]. This tumor usually arises from the meibomian glands and glands of Zeis, and contains neoplastic cells which are characterized by the presence of “foamy” cytoplasm [9]. The initial likelihood of recognition or correct diagnosis is only 18.6% among physicians in general and 50% among ophthalmologists [10]. This is demonstrated by the fact that the average interval between presentation and diagnosis ranges from one year to three years [6,1,12]. For these reasons, SCC is a challenging tumor as it tends to masquerade as other common malignant tumors and benign conditions such as blepharitis, chalazion, or conjunctivitis [4-7]. SCC commonly presents itself or is misdiagnosed as blepharoconjunctivitis [13] as it tends to occur in the upper eyelid [6]. In general, SCC is found more frequently in women than in men, and it often affects an older population [6]. If present among younger individuals (<30 y/o), there is usually a history of radiation to the ocular area [6]. Interestingly, the clinical presentations vary from nodular mass resembling chalazion to diffuse eyelid thickening [1,14] resulting in frequent misdiagnoses of this particular pathology. Inflammatory changes simulate diffuse blepharoconjunctivitis, which results from the intraepithelial spread or “Pagetoid spread” of tumor cells (Masquerade syndrome) in 30% to 50% [1,14].

A previous study by PC Ozdal et al. was conducted examining a total of 1060 patients with clinical diagnoses of chalazion. In this series, pathology examinations were conducted and it was discovered that 68 cases (6.4%) of chalazion were misdiagnosed, while 15 cases (1.4%) were found to be malignant. SCC was the most commonly missed malignancy (12 cases, 1.1%) followed by BCC (3 cases, 0.3%) [15].

To complicate results even further, SCC may also present itself as Muir-Torre syndrome, which includes the association of sebaceous gland tumors or keratoacanthomas. Muir-Torre syndrome frequently presents itself with the development of coexistent distant primary malignancies, most commonly colon carcinoma (47%) followed by genitourinary malignancies (21%) [16,17]. Moreover, distant malignancies can metastasize to both regional and distant lymph nodes [18].

SCC may also mimic other lesions histopathologically. SCC may have focal areas of squamous differentiation and is therefore commonly mistaken for SqCC [19]. BCC on the other hand can have areas of sebaceous differentiation, resulting in increased difficulty in distinguishing SCC from BCC [19]. In a study of 40 cases of SCC, correct diagnosis was given for only 22.5% of tumors on initial pathologic examination, with most common misdiagnoses being BCC (11 cases) and SqCC (10 cases) [20]. Pereira et al. studied 44 cases of SCC, with 75% of them having features of SqCC and 7% have showing features of BCC [21]. In sum, all these studies predict high frequency of clinical and pathological misdiagnosis of SCC. The analysis of the literature correlates with our clinical case and histopathological findings. Indeed, our patient presented recurrent chalazion, which finally received a correct diagnosis of malignant SCC. Moreover, the diverse histological patterns found with SCC tumors proves to be a confounding factor for general pathologists to arrive at a correct diagnoses, rendering this an interesting case from both clinical and pathological points of view.

Immunohistochemistry remains an important tool to distinguish ocular SCC from both BCC and SqCC. Epithelial membrane antigen (EMA) staining can effectively distinguish sebaceous carcinoma from BCC. However, most SqCC examined with EMA were also positive. CAM 5.2 reactivity on the other hand was seen in most sebaceous carcinomas but not in SqCC. Therefore, CAM 5.2 can be a useful marker for distinguishing between SCC and SqCC. In addition, at least focal BRST-1 reactivity was also seen in most sebaceous carcinomas but not in basal cell carcinomas [19]. In our experience, BRST-1 is positive mainly on the well-differentiated sebaceous areas of the tumor, as exemplified in this case.

Histopathologic findings remain one of the important prognostic factors in SCC. According to a highly reliable study conducted by Rao et al. [22], it was described that the clinicopathologic features that yielded a bad prognosis of SCC were commonly vascular, lymphatic, and orbital invasion; involvement of both upper and lower eyelids; poor histological differentiation; multicentric origin prior to diagnosis; duration of symptoms greater than 6 months; tumor diameter exceeding 10 mm; a highly infiltrative pattern; and pagetoid invasion of the overlying epithelia of the eyelids. The case reported here presented several of these features, including involvement of both upper and lower eyelids, poor histopathological differentiation, duration of symptoms greater than 6 months, and pagetoid invasion. These findings reflected the necessity of performing an extensive surgery like exenteration to excise the tumor from the eyelid. In sum, given the complex nature of correctly diagnosing an SCC tumor, it is critical to perform the appropriate and most reliable histopathological tests to ensure a timely diagnosis and hopefully an improved prognosis for patients who are affected by this malignancy.

Conclusion

Our case is aligned with the literature highlighting high frequency of clinical and pathological misdiagnoses associated with SCC. Given the masquerading clinical and pathological features of SCC, these eye tumors are frequently misdiagnosed SqCC, BCC, as well as MEC. Also, it is extremely important to maintain a high clinical and pathological suspicion in cases of recurrent chalazion and/or treatment-resistant blepharconjunctivitis. By being aware of the alternatives in clinical presentation and diagnoses of other eye tumors, physicians and pathologists can exercise caution in diagnosing SCC in order to determine the proper course of treatment that can subsequently improve patient outcomes.

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