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Sebaceous Cell Carcinoma: A Persistent Challenge in Clinical and Histopathological Diagnosis

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Abstract

Sebaceous cell carcinoma continues to defy clinicians and pathologists in terms of early diagnosis. The tumor may be mistaken as benign lesions such as chalazion and blepharitis, and also as malignant neoplasms, mainly basal cell carcinoma and squamous cell carcinoma. Despite advances in immunohistochemical analysis and treatment options during the last decades, morbidity and metastasis rates remain high. Prognosis is strongly related to the length of time between diagnosis and initiation of treatment, which reinforces the importance of early recognition of this condition. This article reviews key features of sebaceous cell carcinoma, from epidemiology to treatment, and new strategies to improve outcome.

Introduction

Sebaceous cell carcinoma (SC) is an uncommon malignant tumor; however increasing incidence rates have been reported in the past decades, with 1,349 cases registered between 1973 and 2003 by the National Cancer Institute's Surveillance, Epidemiology, and End Results database [1]. It accounts for up to 34.9% of cutaneous appendageal carcinomas [2], and is predominantly observed at the periocular region due to its origin in sebaceous glands [3]. In the eyelids, it is the second most common neoplasm after basal cell carcinoma (BCC), and is more prevalent in this region than squamous cell carcinoma (SCC) [4,5]. Extra-ocular SC are usually located on the head and neck area [2,6], and corresponds to 25% of all reported lesions [7].

Epidemiology

SC affects patients between the sixth and eighth decades of life; it is rarely seen in younger individuals, except for those under immunosuppression or radiotherapy [8]. Children with hereditary retinoblastoma treated with radiation have an increased risk for development of SC at a median age of 13.3 years; such lesions may also emerge without association with prior radiation therapy and outside the radiation field [9]. Among all secondary primary tumors occurring in association with retinoblastoma, SC corresponds to 3.3% of neoplasms inside and to 1.0% of carcinomas outside the radiation field [10].

Skin photo type and Muir-Torre syndrome are also risk factors for SC. Caucasians have a higher incidence of SC [11]; some reports claim an elevated incidence in Asians, but this might be attributed to the rarity of other tumours in the eyelid skin in this population, thus increasing the proportion of SC [12,13].

Pathogenesis

SC pathogenesis remains unknown. In sporadic cases, Human Papilloma Virus infection, dysregulated cytokine secretion and mutations in tumour suppressor genes such as p53 might contribute to SC development [14,15].

It has been postulated that the hair follicle bulge region and the suprabasilar layer contain stem cells able to express multiple embryonic markers. They possess the ability to form a complete pilosebaceous unit, and according to environmental stimuli, may originate different cutaneous tumors including SC [16]. As for extra-cutaneous sites, SC may arise in parotid and submandibular glands, hypopharynx and lungs [17-19].

SC has usually a de novo origin, but it may also arise from previous lesions, such as nevus sebaceous of Jadassohn [20]. Twenty-four cases of SC predominantly on the scalp of female elderly patients, arising from nevus sebaceous have been reported, [20-27]. This hamartomatous lesion is usually observed in the perinatal period on the scalp, and presents as a waxy yellowish plaque with underdeveloped hair [28]. After puberty, the nevus becomes verrucous, as a result of epidermal and sebaceous gland hyperplasia combined with dilated sweat glands. In elderly patients, SC may develop from either benign or malignant epidermal/adnexal neoplasms, such as syringocystadenoma papilliferum, trichoblastoma, sebaceoma, and BCC [20,24].

Muir-Torre syndrome (MTS)

Muir-Torre syndrome (MTS) is an autosomal dominant disorder with no gender predominance that comprises cutaneous and internal malignancies, mainly colorectal and genitourinary carcinomas. Among skin tumors, sebaceous adenomas are more frequently associated with MTS, followed by SC and sebaceous epithelioma [29].

MTS and DNA Mismatch Repair Mutations

As opposed to sporadic neoplasms, MTS tumors exhibit a less aggressive course, and tend to appear in extra-facial sites. Their occurrence is attributed to a combination of germline and somatic mutations in mismatch repair proteins that are responsible for elimination of DNA replication errors [29]. Mutations in both alleles of DNA mismatch repair (MMR) genes MSH-2, MLH-1 or MSH-6 cause an accumulation of replication errors known as microsatellite instability (MSI). The presence of germline MMR mutations may be assessed using PCR in DNA samples. Another valuable screening method for MMR mutations consists in MSI detection in tumor tissue through immunohistochemistry, using antibodies against MSH-2 and MLH-1 proteins [30]. Patients with sporadic SC exhibit normal mismatch repair genes [31].

Sebaceous carcinoma and immunosuppression

In immunocompromised patients, SC develops at an earlier age, with increased number of lesions and more aggressive behavior in comparison to immunocompetent individuals [32-34]. Such differences are attributed to changes in DNA stability in immunocompromised patients, similar to Muir-Torre syndrome, such as the emergence of replication errors due to mutations in DNA repair genes, or the modification in DNA repair proteins induced by immunosuppressant's [35].

Figure 1: Sebaceous cell carcinoma. Clinical pictures. A - sebaceous cell carcinoma of the superior eyelid; B - same lesion disclosure on A (everted eyelid); C - advanced sebaceous cell carcinoma exhibiting conjunctival invasion; D - benign-looking lesion on the lower eyelid.
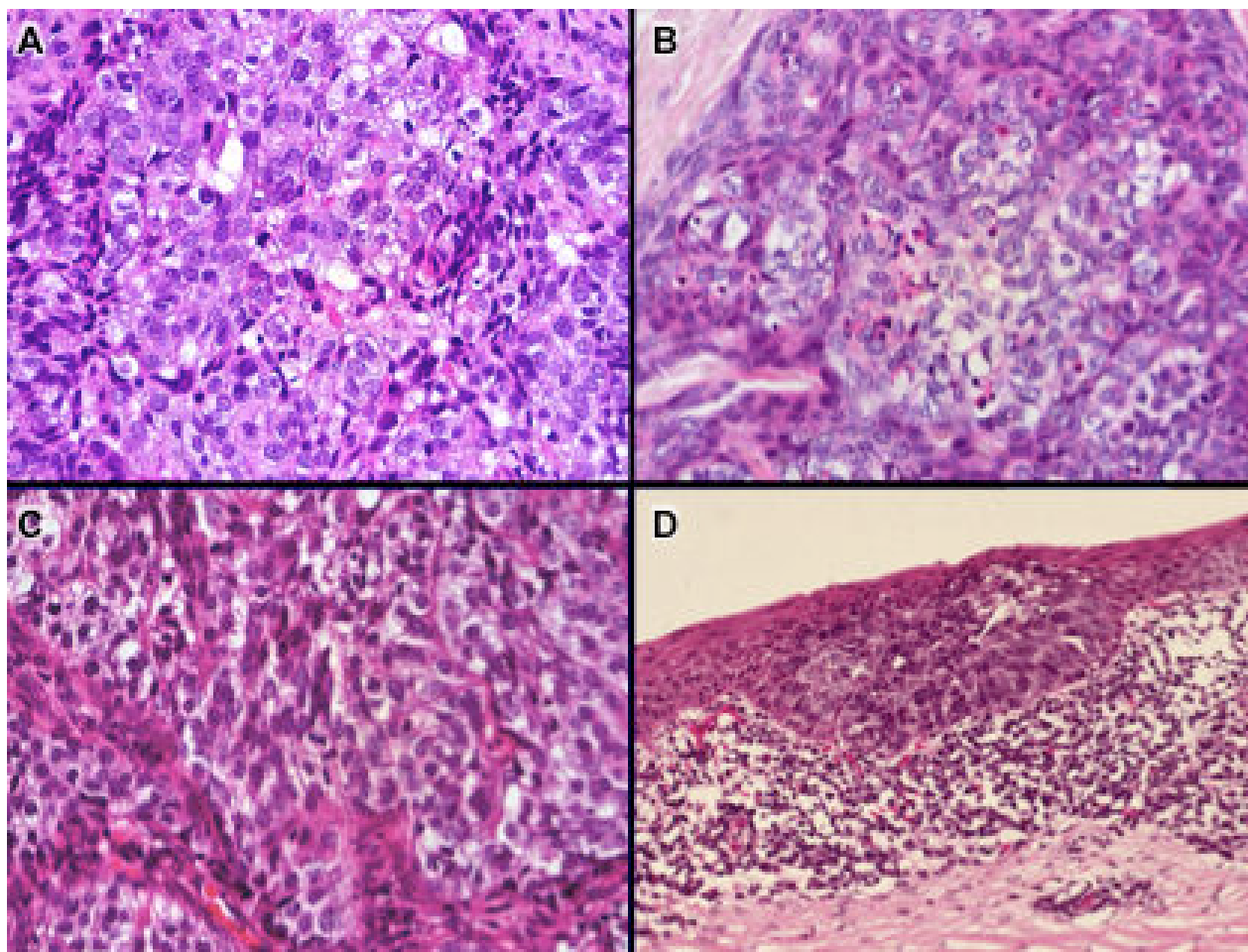
Figure 2: Sebaceous cell carcinoma. Histopathology. A - foam cells with vacuolated cytoplasm between basophilic cells; B - lobular growth pattern; C - well differentiated lesion; D - intraepithelial invasion in a sebaceous cell carcinoma with pagetoid spread.

Clinical features

SC presents a diverse clinical and histopathological presentation that may be mistaken for other inflammatory and neoplastic conditions [4,36]. Misdiagnosis continues to be an important issue concerning SC, with rates ranging between 18.6% and 37.5%.

SC manifests as a subcutaneous yellowish painless nodule, mainly located on the tarsus, caruncle and lid areas (Figures 1A and 1B), making it difficult to differentiate from chalazion, BCC or SCC. Özdal et al. retrospectively analyzed the histopathology of 1,060 lesions clinically diagnosed as chalazion; among them, 12 (1.1%) corresponded to SC [37].

Another possible clinical presentation is as a diffuse eyelid thickening, expanding into the conjunctiva or corneal epithelium, similar to blepharitis or keratoconjunctivitis, but usually of unilateral nature, recurrent and unresponsive to clinical treatment (Figures 1C and 1D) [38]. Ulceration, ectropion and loss of cilia may be observed in advanced cases [3]. While BCC and SCC usually involve the lower lid and medial canthus because of their correlation to ultraviolet radiation exposure, SC are more common on the upper eyelid, where the Meibomian and Zeis glands are found [11-13].

Extra-ocular SC may arise on any other hair-bearing area, especially on the head and neck region, where sebaceous glands are more numerous. It usually presents as a painless round yellowish friable nodule, with variable size (6 mm to 20 cm) [3,38].

Dermoscopic features of sebaceous cell carcinomas

Dermoscopic evaluation of suspected SC lesions might help differentiating them from benign sebaceous proliferations: while benign tumors have homogenous background with yellow ovoid structures, and regularly distributed crown vessels around a central crater [39], SC neoplasms exhibit heterogeneous yellowish background with irregular and polymorphous vessels, with areas of ulceration [40,41].

Histopathology

SC features were described in a retrospective analysis by Pereira et al. that included 31 cases from the Henry C. Witelson Ophthalmic Pathology Registry (Canada) and 13 cases from Hospital Luis S. Bulnes Pathology Registry (Mexico) [4]. Since its publication in 2005, 28 additional patients were diagnosed as SC at the Henry C. Witelson

Ophthalmic Pathology. Among 59 clinically suspected SC from 1996 to 2012, twenty-eight were histopathologically confirmed (Table 1). BCC (20.3%), SCC (16.9%) and chalazion (3.4%) were the most frequent clinical diagnosis after SC (44.1%).

In accordance to previously published data, the diagnosis of SC was set between the seventh and eighth decades of life (29 to 93 years).

There was a male predominance (54.2%) and the eyelid was the most frequent affected site (80.0%). Two patients had multicentric tumors: one had a lesion on the right upper lid and orbit, and the other had both right upper and lower lid involvement, reinforcing that SC may arise concomitantly in different sites [3,36].

Age (years)	Range	29-93
	Average	68
	Median	68
Gender	Male	32 (54.2%)
	Female	27 (45.8%)
	Male : Female	1.2:1
Location	Left lower lid	13 (21.7%)
	Right lower lid	11 (18.3%)
	Right upper lid	10 (16.7%)
	Left upper lid	6 (10.0%)
	Eyelid (unspecified)	8 (13.3%)
	Eye	5 (8.3%)
	Conjunctiva	4 (6.7%)
	Other	2 (3.3%)
	Caruncle	1 (1.7%)
Clinical diagnosis	Sebaceous cell carcinoma	26 (44.1%)
	Basal cell carcinoma	12 (20.3%)
	Squamous cell carcinoma	10 (16.9%)
	Non specified	6 (10.2%)
	Chalazion	2 (3.4%)
	Clear cell carcinoma	1 (1.7%)
	Granuloma	1 (1.7%)
	Pinguecula	1 (1.7%)

Table 1: Main features of sebaceous cell carcinoma cases at the Henry C. Witelson Ocular Pathology Laboratory (1996-2012).

From 1996 to 2012, only six sebaceous adenomas were diagnosed at the Henry C. Witelson Ocular Pathology Laboratory, when compared to 38 SC. According to our registry, unlike SC, sebaceous adenomas were diagnosed in younger patients, with an average age of 54.3 years,

and exhibited a female predominance (66.7%). Three lesions were located on the eyelid (50%), while others were found on the caruncle, eyebrow, and forehead (Table 2).

Age (years)	Range	49-72
	Average	54.3
	Median	53
Gender	Male	2 (33.3%)

	Female	4 (66.7%)
	Male : Female	01:02
Location	Forehead	1 (16.7%)
	Right lower lid	1 (16.7%)
	Right upper lid	1 (16.7%)
	Left lower lid	1 (16.7%)
	Eyebrow	1 (16.7%)
	Caruncle	1 (16.7%)
Clinical diagnosis	Basal cell carcinoma	1 (16.7%)
	Sebaceous cyst	2 (33.3%)
	Inclusion cyst	1 (16.7%)
	Sebaceous adenoma	1 (16.7%)
	Hemangioma	1 (16.7%)

Table 2: Clinical features of sebaceous adenoma cases at the Henry C. Witelson Ocular Pathology Laboratory (1996-2012).

As for histopathology analysis, SC may exhibit multiple features [4], which also contributes to the delay in diagnosis. Doxanas et al. reported 22.5% accurate diagnosis among 40 SC. BCC was the prevailing initial misdiagnosis (27.5%), followed by SCC (25%) [42]. Late diagnostic confirmation retards initiation of appropriate treatment, and significantly increases mortality rates [36].

Lobular growth is the prevailing pattern, characterized by aggregates of basophilic undifferentiated cells with hyper chromatic nuclei surrounding lipid-rich vacuolated cells. Comedocarcinoma features, as a result of central necrosis may also be observed. Papillary protrusions of neoplastic cells with areas of sebaceous differentiation were described in the papillary pattern. The tumour is considered mixed when it contains a combination of the three previously described patterns [3,4,12,38,43].

Lesions are also classified according to the degree of differentiation (Figure 2C). Poorly differentiated tumours usually present cytomorphological features resembling SCC, such as cells with eosinophilic scanty cytoplasm and prominent nucleoli. Similarities to BCC, with basophilic cells with scarce cytoplasm distributed as a palisade have also been described, contributing to misdiagnosis. Presence of foamy cells with lipid-rich vacuolated cytoplasm helps to distinguish SC from other tumours in well-differentiated lesions [3,36].

Pagetoid spread is observed in up to 76.9% tumors, and defined as intraepithelial invasion of neoplastic cells to the epidermis, conjunctiva or cornea adjacent to the dermal tumor (Figure 2D). It must be distinguished from Bowenoid disease, and amelanotic melanoma [3].

Immunohistochemistry

Immunohistochemistry analysis may help in differentiating SC from SCC, and BCC. SC expresses epithelial membrane antigen (EMA), CAM5.2 (low molecular-weight keratin), BRST-1 (breast carcinoma marker) (Figure 3), CA15-3, adipophilin (ADP) and androgen receptors (AR); Ber-EP4 staining is negative. SCC stain positive for EMA, and are negative for carcinoembryonic antigen (CEA), CA19-9,

Ber-EP4, ADP, AR and CAM5.2. BCC are Ber-EP4 positive, and EMA, BRST-1, CA15-3 and ADP negative [4,12,44-46].
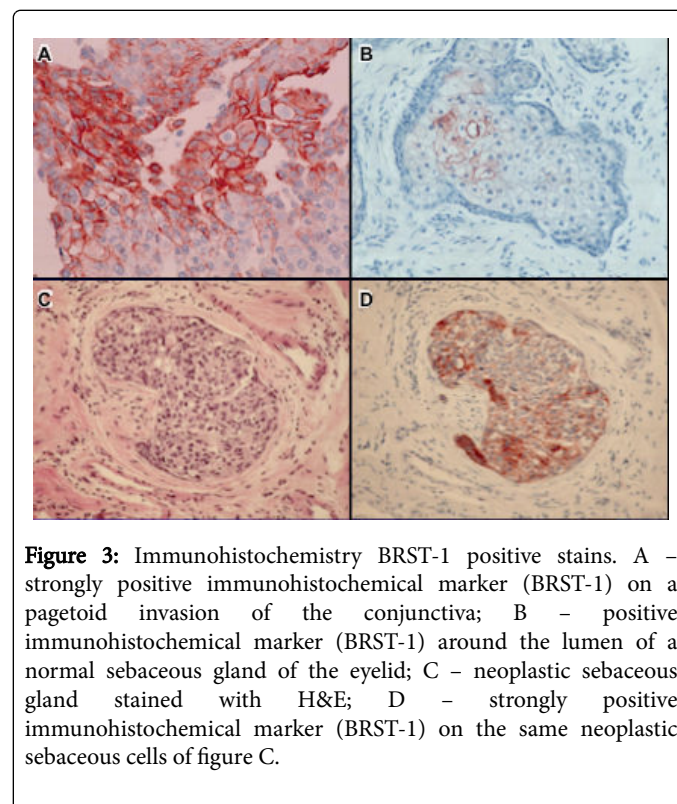

Figure 3: Immunohistochemistry BRST-1 positive stains. A – strongly positive immunohistochemical marker (BRST-1) on a pagetoid invasion of the conjunctiva; B – positive immunohistochemical marker (BRST-1) around the lumen of a normal sebaceous gland of the eyelid; C – neoplastic sebaceous gland stained with H&E; D – strongly positive immunohistochemical marker (BRST-1) on the same neoplastic sebaceous cells of figure C.

Prognosis

The age of diagnosis, degree of differentiation, type of infiltration, presence of pagetoid spread, angiolymphatic invasion, simultaneous involvement of upper and lower eyelid, multicentric presentation, and

tumor size influence the prognosis in SC [3,36]. Multivariate analysis demonstrated the main factors that determine 5-year disease specific survival: age at diagnosis ≥ 80 years, histologic degree of differentiation, and distant metastasis [47].

Eyelid SC tend not only to be less differentiated and invasive, but also present a higher incidence of lymphatic metastasis (4.4%) in comparison to extra-ocular tumours (0.9%) [48]. For these reasons, sentinel lymph node biopsy has been suggested for staging of eyelid SC [49].

Metastasis

Ocular SC invasiveness beyond the primary site may present as local spread, regional or distant metastasis. SC can extend to adjacent epithelia, orbital soft tissues, and the lacrimal system. Lymphatic metastasis occurs in 30% of the cases, and the dissemination correlates with tumor location: lower eyelid SC disseminates to submandibular and cervical nodes, while upper eyelid SC affects preauricular and parotid nodes. Distant metastasis frequently affects the lungs, liver, bones, and brain [50].

A retrospective study analyzed the correlation between T category of the American Joint Committee on Cancer and lymph node metastasis for SC: tumors classified as T2b or ≥ 10mm exhibited increased risk of regional lymph node metastasis [51]. Lymphatic invasion to regional lymph nodes is observed in 18-30% of cases. Fine-needle aspiration biopsy of suspected metastatic lymph nodes may confirm the diagnosis, and support lymph node dissection [52].

Evaluation of sentinel lymph node biopsy (SNLB) as a predictor of nodal micrometastasis revealed that among 16 patients with SC who were submitted to SNLB, 3 (13%) had positive findings. In all 3 patients tumors were >10mm in size and had been staged T2b [53,54]. However, only 1 patient had positive SNLB at the first analysis; the other 2 patients had an initial false-negative SNLB, and after the development of lymph node metastasis, revision of sentinel lymph node resulted positive in both patients [53].

As SNLB may yield false-negative results, new biomarkers emerged as potential predictors of metastasis. Kim et al. demonstrated increased sonic hedgehog (Shh) and Wnt expression in SC cells. Both pathways become inactive after embryogenesis, but reactivation occurs in SC, more frequently in patients with metastatic disease [55]. Other proteins overexpressed in SC, such as epidermal growth factor receptor, vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor alpha and beta, cyclooxygenase 1 and 2, may become potential targets for adjuvant therapy and prevention of recurrence and metastasis [56].

Recently, Kim et al. first described the presence of cancer stem cells markers in SC. These cells participate in carcinogenesis, and also contribute to recurrence and metastasis in solid tumors, such as breast and colon cancer. In SC, positive ALDH1 correlates with metastasis in comparison to ALDH1 negative tumours, and might serve as a prognostic factor [57].

Larger lesions are usually poorly differentiated and, therefore, associated with poorer outcomes. Mortality rates are higher in the presence of pagetoid invasion (50%) vs. absence of pagetoid spread (11%). Delay in diagnosis also affects prognosis: 14% mortality rate when tumor excision occurs 1 to 6 months after arising vs 38% if treatment is performed after 6 months [36]. Meanwhile, high clinical suspicion and early histopathological confirmation and treatment significantly decreases mortality rates up to 3% [58].

Map biopsies

As SC may exhibit different growth patterns, pagetoid invasion, and multicentric origin, map biopsies of the palpebral and bulbar conjunctiva are recommended to properly delineate tumor for precise staging. Ten to sixteen samples are intraoperatively collected for small well-defined tumors, or preoperatively, for large ill-defined lesions; samples are preferably paraffin-embedded to better evaluate tumor extension and to plan definitive treatment [12,59,60].

Treatment

Mainstay of treatment is surgical excision with 5 to 6 mm margins checked with either frozen sections or permanent sections, except when orbital invasion occurs. In such cases, exenteration is recommended [14]. For incompletely excised or recurrent tumors, and lesions located on cosmetically sensitive areas, Mohs' micrographic surgery is the treatment of choice [3,12,38]. While recurrence rate after conventional surgery is near 32% [61], Mohs' technique has reduced the recurrence of SC to 11.1% [62].

Other therapeutic modalities are usually recommended for neoadjuvant or palliative purposes. Cryotherapy is an option to treat conjunctival pagetoid spread, thus avoiding exenteration [63]. Radiotherapy is recommended in metastatic SC, or for patients who refuse exenteration [12,64], due to increased recurrence rates and mortality in comparison to surgical treatment [14]. There are few case reports regarding systemic chemotherapy platinum-based and with 5-fluorouracil. Topical chemotherapy with mitomycin C was described for pagetoid invasion of conjunctiva also as an alternative to exenteration [65], or in tumours exhibiting high-risk features associated with worse prognosis [66].

Conclusion

SC continues to defy clinicians, surgeons, and pathologists in terms of early suspicion, diagnosis confirmation, and treatment. Despite recent advances in diagnostic tools and therapeutic options, early recognition remains decisive for prognosis and mortality. Overcoming this challenge relies on acknowledging SC as a differential diagnosis of common benign and malignant lesions, enabling its prompt recognition.

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