

Sebaceous Carcinoma and its Biomarkers: Outline

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Introduction

- Sebaceous carcinoma (SC) is a malignant neoplasm that arises from the sebaceous glands, most commonly in the periocular areas. Clinical manifestations are often mistaken for benign conditions and thus proper diagnosis and management is delayed. Metastasis to regional lymph nodes and other sites are common in these situations.
- Pathologists must be aware of the varied clinical manifestations, histopathological morphology and its multiple biomarkers for an accurate diagnosis. Herein we provide an overview of the most important factors in ocular and periocular sebaceous carcinomas and its biomarkers.

Definitions

- Sebaceous carcinoma, sebaceous gland carcinoma, sebaceous cell carcinoma all implicate the same disease, a malignant neoplasm that arises from the cells that form the sebaceous glands.
- These are most commonly found on the eyelid (tarsus) and periocular area. The most common glands in these areas are named: Meibomian glands (eyelid) and Zeis glands (cilia). The caruncle and brow also contain these glands and thus these regions can develop this carcinoma.

Historical aspects

- Kass and Hornblass provided an in depth report on the historical aspects of sebaceous carcinoma in 1989.
- First case was reported by Thiersh in 1865. Allaire is credited with reporting the first well documented case in 1891.
- The largest understanding of the behavior of this carcinoma is due to the case series by Straatsma in 1956.

Extraorbital primary locations

- Approximately 25% of the sebaceous carcinomas arise from an extraocular region. Of this 25%, 70% arises in the head and neck region with the parotid gland being the most common location. These tumors arise from two possible cells: pluripotent cells with capacity for sebaceous differentiation or from ectopic sebaceous cells that developed during embryogenesis.
- Other reported locations include: submandibular glands, extremities, toes, penis, chest, sole of foot, external auditory canal and anterior neck region. The varied origin of this neoplasm highlights the importance of considering sebaceous carcinoma regardless of anatomical location.

Incidence

- Periocular skin neoplasms account for 5-10% of all skin malignancies. Basal cell carcinoma is the most common with 90% of all malignant eyelid tumors, sebaceous 5% of eyelid tumors, squamous cell 4% of eyelid tumors and melanoma and others for 1% in the United States.
- The differential diagnosis of eyelid skin lesions includes all of the aforementioned neoplasms and distinction between these are of the utmost importance as prognosis and management vary widely.

Incidence

- In the United States the reported incidence is 0.5 per million in the white population older than 20 years old. Reports from China and India account for far higher incidence rate of sebaceous carcinoma.
- The incidence has risen over the last years, possible explanations include: longer lifetime of individuals (sebaceous carcinoma tends to be a neoplasm that affects older individuals), increased awareness of the disease by pathologist, dermatologist, ophthalmologist or the fact that the United States contains a more varied population mainly from Asia.

Demographics and Risk Factors

- Age: Mean age at diagnosis in the reported series has ranged from 57 years to 72 years. It is possible to arise in older children and younger adults due to previous irradiation.
- Sex: Most commonly in females, with reports of 70% of the sebaceous carcinomas occurring in females.
- Race: In the United States, Sebaceous carcinoma is most common in whites. The incidence in Asians from India is well known, with sebaceous carcinoma accounting for 40-60% of malignant eyelid tumors from India.

Demographics and Risk Factors

- Irradiation: Several reports of patients with prior history of irradiation due to hereditary retinoblastoma treatment. Various reports have also revealed sebaceous carcinomas development after irradiation due to other causes such as: acne, cutaneous hemangioma and eczema.
- Muir-Torre Syndrome: Autosomal dominant condition that predisposes to development of cutaneous sebaceous adenomas, keratoacanthomas and internal malignancies. Some patients with this syndrome may develop periocular sebaceous carcinomas.

Demographics and Risk Factors

- Diuretics: Reports have described the use of certain diuretics with sebaceous but no firm evidence of a relation between diuretics and sebaceous carcinomas exists.
- Immunosuppression: Multiple reports of patients with HIV developing sebaceous carcinoma earlier in life.

Ocular origins

- Sebaceous glands: Associated with hair follicles and thus abundant wherever hair is present. Functions by holocrine secretion in which the entire cell is desquamated into the lumen and secreted through a duct to the skin surface.

Ocular origins

- Meibomian glands: Most sebaceous carcinomas arise from these glands within the tarsus. Kass and Hornblass found that 63% arise in the upper lid, 27% in the lower lid and 5% in both lids.
- Zeis glands: Glands associated with cilia that have been reported to be the origin of 10% of SC of the eyelid.
- Caruncle: Abundant sebaceous glands, 5-10% of all SC arise in the caruncle.
- Brow: Underrepresented in the literature.
- Conjunctiva: There have been reports of SC of the conjunctiva with no involvement of the nearby skin structures.

Clinical Features

- Commonly can masquerade as a benign condition (“masquerade syndrome”), often resulting in a delay in diagnosis. This in turn can increase the chance of local recurrence, metastasis, and death. Pathologist must be familiar with the clinical features.

Clinical Features

- Solitary eyelid nodule: Most common clinical manifestation, it presents as a painless, firm, sessile to round, subcutaneous nodule in the eyelid. It assumes a yellow color due to the presence of lipid in the mass. Eventually causes loss of cilia, a feature present in other tumors.
- Diffuse pseudoinflammatory pattern: The second most common manifestation. Diffuse unilateral thickening of the eyelid. This presentation is more likely to extend to the epithelium of nearby structures such as the cornea and conjunctiva. The lack of a nodule, causes the clinician to suspect an inflammatory condition. SC must be ruled out in unilateral blepharitis in an older patient that does not respond to standard treatment, and thus biopsy is indicated.

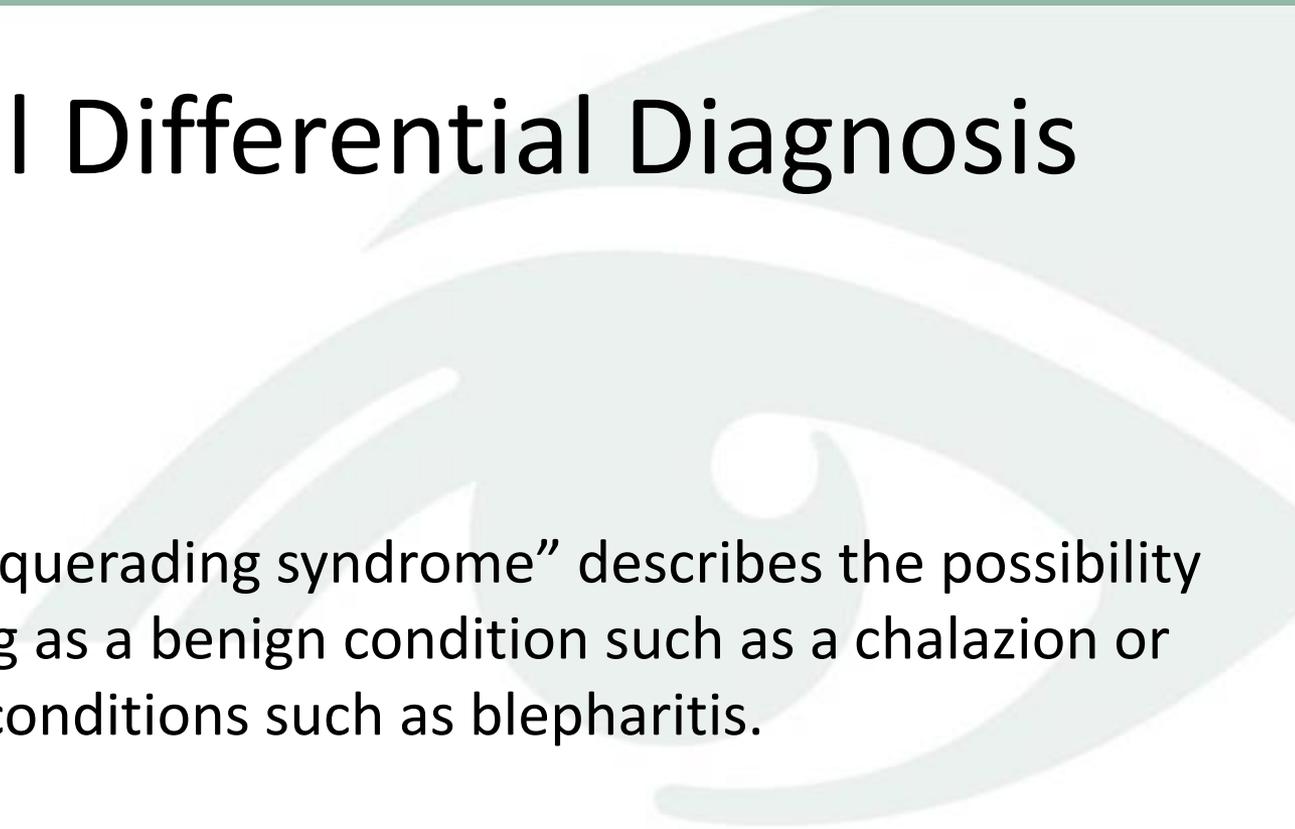
Clinical Features

- Pedunculated lesion: SC may sometimes grow outward and become pedunculated with keratinization and possess a cutaneous horn appearance. Most commonly occur in the eyelid margin, from the gland of Zeis. Less commonly, SC may ulcerate and have basal cell carcinoma appearance.
- Caruncular mass: Irregular, yellow mass in the medial canthal lesion. May replace the entire eyelid and involve the orbit.

Clinical Features

- Eyebrow mass: Has appearance of a deep cutaneous mass that may be difficult from the epidermal inclusion cyst.
- Lacrimal gland mass: Progressive enlargement of the lacrimal gland, very rare instances. History reveals chronic unilateral blepharoconjunctivitis that was previously unrecognized or treated as an inflammatory condition.
- Extensive Invasion: May present as diffuse involvement of the lids, conjunctiva, cornea and anterior orbital tissue.

Clinical Differential Diagnosis



- The term “masquerading syndrome” describes the possibility of SC appearing as a benign condition such as a chalazion or inflammatory conditions such as blepharitis.

Clinical Differential Diagnosis

- Chalazion: Painful, tender, circumscribed nodule, without diffuse involvement that has similar appearance to SC. Occurs in younger individuals. Any patient with recurrent chalazia, especially in older individuals must undergo biopsy to rule out SC.
- Blepharitis: Common diffuse involvement of the eyelids, and thus often SC is misdiagnosed as blepharitis. Does not cause loss of cilia. Seborrheic blepharitis is bilateral, making its distinction simpler.

Clinical Differential Diagnosis

- Conjunctivitis: Diffuse SC involvement of the palpebral, forniceal and bulbar conjunctiva can appear as a conjunctivitis. Bilateral conjunctivitis is less likely to be SC.
- Keratoconjunctivitis: As SC progresses it may involve the corneal epithelium. It causes reactive inflammation around the neoplasms. Other manifestations include peripheral ulcerative keratitis around the SC.
- Other inflammatory conditions: Due to the diverse clinical manifestations of SC, almost all inflammatory conditions must be included in the differential diagnosis. Unilateral papillary conjunctivitis, cicatricial pemphigoid, granuloma, sarcoidosis and allergic conjunctivitis associated with Churg-Strauss syndrome are all included in the differential diagnosis.

Clinical Differential Diagnosis:

Other tumors:

- Basal cell carcinoma: Nodular or noduloulcerative form of BC presents as a solitary nodule, most common in the lower eyelid. Generally white, with vascular elevated margins with likely ulceration. The diffuse sclerosing or morpheiform forms of BC most closely resembles SC, with unlikely involvement of the conjunctiva.
- Squamous cell carcinoma: Most common in upper lid, but it is more superficial and lacks yellow color. Associated with actinic keratosis. Conjunctival intraepithelial neoplasia (CIN) can be similar to diffuse epithelial invasion of SC.

Clinical Differential Diagnosis:

Other tumors:

- Melanoma: Nodular or diffuse growth pattern. Generally pigmented with black or brown appearance, rather than the characteristic SC yellow. Amelanotic melanoma may resemble SC.
- Merkel cell carcinoma: Solitary subcutaneous nodule in the upper eyelid of older individuals, with red or red-blue color.
- Lymphoma: More common than SC. In the eyelid area, it is usually deep to the epidermis and the skin moves freely over the lesion. Conjunctival lymphoma has characteristic “salmon patch” with no inflammatory signs that are present in SC.

Clinical Differential Diagnosis:

Other tumors:

- Sweat gland neoplasms: Benign adenomas and malignant adenocarcinomas of eccrine and apocrine sweat glands are rare tumors that can be mistaken for SC. Moll gland tumors are deep to the intact epidermis and may be confused with chalazion.
- Other tumors: Metastatic carcinomas, papillomas, hereditary benign intraepithelial dyskeratosis are other considerations in the differential of SC.

Methods of Spread

- One of the most important characteristics of SC is its ability to extend beyond its original site and affect nearby and distant structures by direct local extension, regional metastasis or distant metastasis.

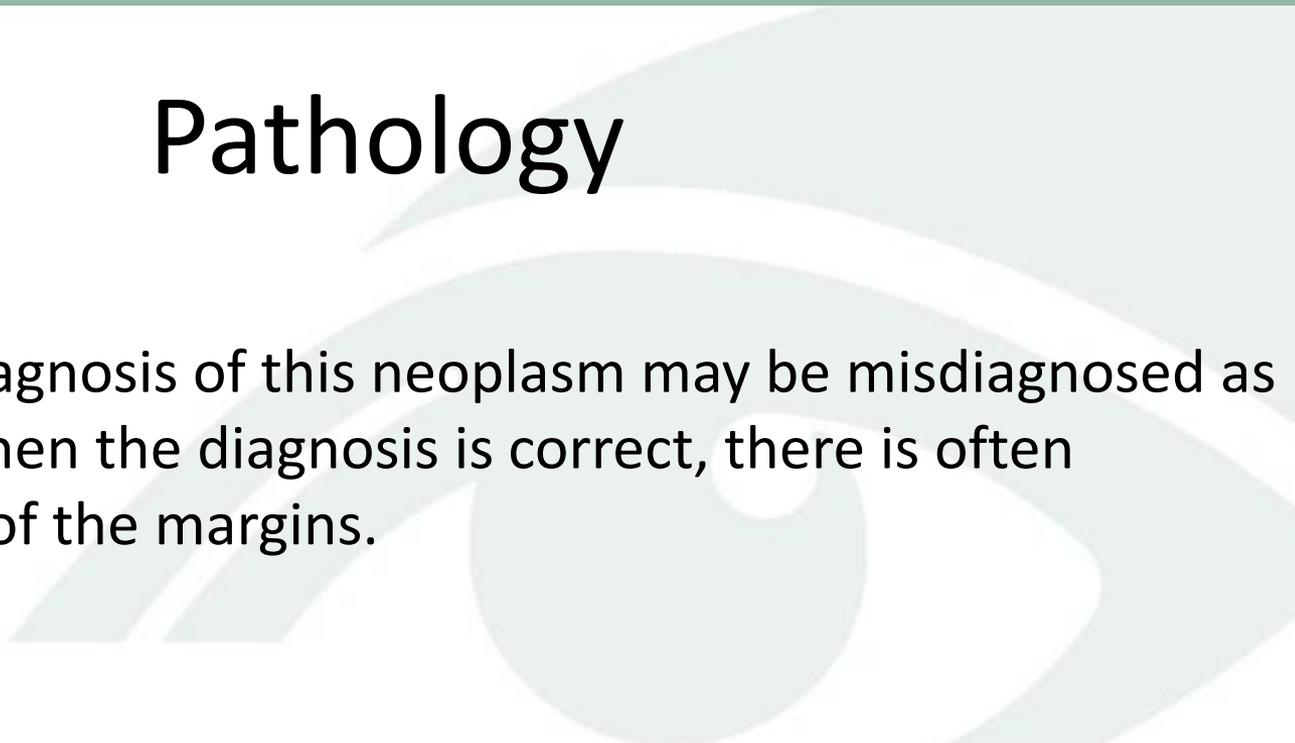
Methods of Spread

- Local extension: SC can invade adjacent epithelia, orbital soft tissue, lacrimal system or in advanced cases the cranial cavity.
- Epithelial involvement: SC has been shown to exhibit flat, superficial involvement of the eyelid or conjunctival epithelium. This is referred as pagetoid growth because of the morphological similarity of pagetoid spread of some breast tumors.
- Orbital soft tissue: Advanced cases can involve the orbital cavity.

Methods of Spread

- Lacrimal secretory system: SC can involve the lacrimal gland. This can occur as direct epithelial extension from the conjunctiva or from dissemination of tumor cells through the lacrimal gland ducts that open into the conjunctival fornix.
- Regional metastasis: Most common route of metastasis is via lymphatic channels to regional lymph nodes. SC of the upper eyelid tends to invade the preauricular and parotid nodes. SC of the lower eyelids tend to metastasize to the submandibular and cervical nodes.
- Distant metastasis: Organs most commonly involved are lung, liver, bone, and brain.

Pathology



- Histopathologic diagnosis of this neoplasm may be misdiagnosed as BC or SCC. Even when the diagnosis is correct, there is often misinterpretation of the margins.
- Gross pathology: No specific gross characteristics. Neoplasms have yellow color due to the lipid deposition. Specimens may show origin in the tarsal plate.

Microscopic Pathology

- Several patterns are recognized: lobular, comedocarcinoma, papillary and mixed. It can also be classified as well-differentiated, moderately-differentiated and poorly differentiated. A characteristic feature of SC is its ability to exhibit intraepithelial spread into conjunctival, eyelid and corneal epithelium, this occurs in 44-80% of the cases. The individual cells have finely vacuolated, frothy cytoplasm. Lipid deposition may induce a foreign body granulomatous reaction that may resemble a chalazion clinically. Pleomorphism and high nuclear mitotic rate are frequent features.
- A useful stain for SC is oil-red O stain which highlights the lipid deposition in the glandular cells, along with morphology establish the diagnosis.

Microscopic Pathology

- Lobular pattern: Occurs more frequently and looks like a normal sebaceous gland with undifferentiated cells in the periphery, and well-differentiated lipid producing cells centrally.
- Comedocarcinoma: Lobules show large necrotic central core with peripheral viable cells.
- Papillary: occurs in conjunctiva SC, with papillary projections and sebaceous differentiation.
- Mixed pattern: Can present in a combination of all three previous patterns.

Immunohistochemistry

- A large variation of biomarkers exists with questionable utility. Experienced pathologist can usually confirm the diagnosis using morphology and immunohistochemistry is not necessary.

Immunohistochemistry

- EMA (Epithelial membrane antigen) - Large cell surface mucin glycoprotein expressed by most glandular and ductal epithelial cells and some hematopoietic cells. Highly expressed by most adenocarcinomas, associated with poor prognosis.
- CK7 (Cytokeratin 7): Type II keratin of simple nonkeratinizing epithelia found in simple glandular epithelia, and in transitional epithelium. Epithelial cells of the lung and breast both contain keratin-7, but some other glandular epithelia, such as those of the colon and prostate, do not.

Immunohistochemistry

- Ber-EP4: Antibody to cell membrane glycoproteins expressed on healthy epithelia and in various carcinomas. Membranous staining.
- Factor 13A: Fibrohistiocytic marker and marker of dermal dendrocytes.
- Androgen receptor: Member of the superfamily of ligand responsive transcription regulators. The androgen receptor functions in the nucleus where it is believed to act as a transcriptional regulator mediating the action of male sex hormones (androgens).

Immunohistochemistry

- P53: Tumor suppressor gene at 17p13, p53 ensures that cells repair any damaged DNA before cell division by inducing cell cycle arrest to allow time.
- Adipophilin: Adipophilin is involved in the development and maintenance of adipose tissue. Adipophilin, previously believed to be specific to adipocytes, is a major constituent of the globule surface and is present in a detergent-insoluble complex that contains stoichiometric amounts of butyrophilin and xanthine oxidase.

Immunohistochemistry

- PGRMC1: Protein which co-purifies with progesterone binding proteins in the liver and ovary. The PGRMC1 protein is encoded by the *PGRMC1* gene. The Sigma-2 receptor was recently identified as a protein that binds the PGRMC1 protein. PGRMC1 is highly expressed in the liver and kidney in humans with lower expression in the brain, lung, heart, skeletal muscle and pancreas. PGRMC1 also promotes survival in human cancer cells after treatment with chemotherapy. In contrast, PGRMC1 promotes cell death in cancer cells after oxidative damage.

Immunohistochemistry

- Squalene synthase (SQS) or farnesyl-diphosphate: farnesyl-diphosphate farnesyl transferase: Enzyme localized to the membrane of the endoplasmic reticulum. SQS participates in the isoprenoid biosynthetic pathway, catalyzing a two-step reaction in which two identical molecules of farnesyl pyrophosphate (FPP) are converted into squalene, with the consumption of NADPH. Catalysis by SQS is the first committed step in sterol synthesis.

Immunohistochemistry

- Alpha/beta hydrolase domain-containing protein 5 (ABHDC5): The protein encoded by this gene belongs to a large family of proteins defined by an alpha/beta hydrolase fold, and contains three sequence motifs that correspond to a catalytic triad found in the esterase/lipase/thioesterase subfamily.
- Perforin: a protein, released by killer cells of the immune system, that destroys targeted cells by creating lesions like pores in their membranes.

Pathogenesis

- Most SC arise de novo, and not from previous sebaceous adenomas, hyperplasia or nevus. Reports from Japan have showed a relation between SC and HPV. Overexpression of p53 is involved in the carcinogenesis of this tumor.

Management

- The first step is to establish the diagnosis and determine the extent of the disease, carefully evaluating nearby skin, conjunctiva, cornea, caruncle and periocular tissue. Palpation of head and neck nodes is advisable. Ancillary studies to determine distant metastasis are usually not performed.
- Management options include: surgical excision, surgical excision combined with cryotherapy, topical chemotherapy, radiotherapy, amniotic membrane grafting and other techniques.

Management

- Primary excisional biopsy: It is generally preferred to perform a complete surgical excision of the lesion when the diagnosis is suspected. Cosmetic appearance is an issue to consider if the diagnosis is unclear, clinicians may prefer a biopsy to confirm and then perform the excisional biopsy.
- Full-thickness, pentagonal, eyelid resection is favorable. The recommended margins are 5.0 mm on the nasal and temporal sides. One study revealed a recurrence rate of 36% if 1.0-3.0 mm of resection margins were obtained, but no recurrence if 5.0 mm of margins were taken. Caruncular masses may not lend themselves for wide margin resection and thus extensive cryotherapy may be involved. When the resection is performed, surrounding epithelia must be evaluated for signs of malignancy, in which a map biopsy may be employed.

Management

- Incisional biopsy: This is the preferred method of diagnosis for advanced primary lesions that will require extensive reconstruction. It should involve full-thickness piece of the eyelid including tarsus, skin and palpebral conjunctiva. This type of procedure can be performed in an office with local anesthesia.
- Frozen section or Mohs microsurgery: In the primary excision or for subsequent excisional procedures, frozen sections or Mohs microsurgery may be performed to ensure clear margins. The decision between one or the other remains up to the clinician. Freezing artifact may complicate the diagnosis, as it may appear similar to the vacuolated, frothy cytoplasm of the SC cells. Permanent analysis must always be performed subsequently.

Management

- Map biopsy: Due to the diffuse involvement of the ocular epithelia in SC, map biopsies are indicated to determine extend of disease. Usually 10-15 biopsies are taken. The most common method involves: eversion of the eyelids and taking 4 specimens from the palpebral conjunctiva, six specimens from the bulbar conjunctiva. Retrobulbar anesthesia is preferred to local anesthesia due to the sparring of disruption of conjunctival/eyelid anatomy.

Management

- Cryotherapy: Useful in cases of SC with pagetoid spread to the conjunctival surface. It is used during map biopsies and during definitive surgical excision.
- Topical chemotherapy: Has been used in select cases of pagetoid spread involving the conjunctival epithelium.
- Irradiation: The general belief is that irradiation is not useful and complete excision of the tumor is preferred. Plaque brachytherapy has been advocated by some reports for residual lacrimal gland malignancies and for orbital invasion of eyelid and conjunctival tumors. This technique involves placing a plaque that provides 500 Gy to the target region. This has not been tested for SC, and remains subject of research.

Management

- Orbital exenteration: Widely believed to be the best option for SC that diffusely involves the conjunctiva and with invasion into the orbit. Recently has become less common due to other management options. Appropriate for orbital invasion cases of SC with no evidence of distant metastasis. Lid-sparing exenteration is an option that must be considered if the eyelid contains no tumor, as the benefits of faster healing and a better fitting prosthesis are substantial.

References

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References

1. Plaza JA, Mackinnon A, Carrillo L, Prieto VG, Sanguenza M, Suster S. Role of immunohistochemistry in the diagnosis of sebaceous carcinoma: a clinicopathologic and immunohistochemical study. *Am J Dermatopathol*. 2015;37(11):809-21.
2. Chen WS, Chen PL, Li J, Lind AC, Lu D. Lipid synthesis and processing proteins ABHD5, PGRMC1 and squalene synthase can serve as novel immunohistochemical markers for sebaceous neoplasms and differentiate sebaceous carcinoma from sebaceoma and basal cell carcinoma with clear cell features. *J Cutan Pathol*. 2013;40(7):631-8.
3. Asadi-amoli F, Khoshnevis F, Haeri H, Jahanzad I, Pazira R, Shahsiah R. Comparative examination of androgen receptor reactivity for differential diagnosis of sebaceous carcinoma from squamous cell and basal cell carcinoma. *Am J Clin Pathol*. 2010;134(1):22-6.
4. Jakobiec FA, Mendoza PR. Eyelid sebaceous carcinoma: clinicopathologic and multiparametric immunohistochemical analysis that includes adipophilin. *Am J Ophthalmol*. 2014;157(1):186-208.e2.
5. Mulay K, White VA, Shah SJ, Honavar SG. Sebaceous carcinoma: clinicopathologic features and diagnostic role of immunohistochemistry (including androgen receptor). *Can J Ophthalmol*. 2014;49(4):326-32.
6. Ansai S, Takeichi H, Arase S, Kawana S, Kimura T. Sebaceous carcinoma: an immunohistochemical reappraisal. *Am J Dermatopathol*. 2011;33(6):579-87.
7. Ansai S, Arase S, Kawana S, Kimura T. Immunohistochemical findings of sebaceous carcinoma and sebaceoma: retrieval of cytokeratin expression by a panel of anti-cytokeratin monoclonal antibodies. *J Dermatol*. 2011;38(10):951-8.
8. Sramek B, Lisle A, Loy T. Immunohistochemistry in ocular carcinomas. *J Cutan Pathol*. 2008;35(7):641-6.
9. Mittal R, Araujo I, Czanner G, Coupland SE. Perforin expression in eyelid sebaceous carcinomas: a useful and specific immunomarker for the differential diagnosis of eyelid carcinomas. *Acta Ophthalmol*. 2016;94(5):e325-30.
10. Uhlenhake EE, Clark LN, Smoller BR, Shalin SC, Gardner JM. Nuclear factor XIIIa staining (clone AC-1A1 mouse monoclonal) is a sensitive and specific marker to discriminate sebaceous proliferations from other cutaneous clear cell neoplasms. *J Cutan Pathol*. 2016;43(8):649-56.
11. Mulay K, White VA, Shah SJ, Honavar SG. Sebaceous carcinoma: clinicopathologic features and diagnostic role of immunohistochemistry (including androgen receptor). *Can J Ophthalmol*. 2014;49(4):326-32.
12. Jakobiec FA, Werdich X. Androgen receptor identification in the diagnosis of eyelid sebaceous carcinomas. *Am J Ophthalmol*. 2014;157(3):687-96.e1-2.
13. Boussahmain C, Mochel MC, Hoang MP. Perilipin and adipophilin expression in sebaceous carcinoma and mimics. *Hum Pathol*. 2013;44(9):1811-6.
14. Milman T, Schear MJ, Eagle RC. Diagnostic utility of adipophilin immunostain in periocular carcinomas. *Ophthalmology*. 2014;121(4):964-71
15. Shields JA, Demirci H, Marr BP, Eagle RC, Shields CL. Sebaceous carcinoma of the ocular region: a review. *Surv Ophthalmol*. 2005;50(2):103-22.

16. Deprez M, Uffer S. Clinicopathological features of eyelid skin tumors. A retrospective study of 5504 cases and review of literature. *Am J Dermatopathol.* 2009;31(3):256-62.
17. Dasgupta T, Wilson LD, Yu JB. A retrospective review of 1349 cases of sebaceous carcinoma. *Cancer.* 2009;115(1):158-65.
18. Izumi M, Mukai K, Nagai T, et al. Sebaceous carcinoma of the eyelids: thirty cases from Japan. *Pathol Int.* 2008;58(8):483-8.
19. Fan YS, Carr RA, Sanders DS, Smith AP, Lazar AJ, Calonje E. Characteristic Ber-EP4 and EMA expression in sebaceoma is immunohistochemically distinct from basal cell carcinoma. *Histopathology.* 2007;51(1):80-6.
20. Bayer-garner IB, Givens V, Smoller B. Immunohistochemical staining for androgen receptors: a sensitive marker of sebaceous differentiation. *Am J Dermatopathol.* 1999;21(5):426-31.
21. Ostler DA, Prieto VG, Reed JA, Deavers MT, Lazar AJ, Ivan D. Adipophilin expression in sebaceous tumors and other cutaneous lesions with clear cell histology: an immunohistochemical study of 117 cases. *Mod Pathol.* 2010;23(4):567-73.
22. Poniecka AW, Alexis JB. An immunohistochemical study of basal cell carcinoma and trichoepithelioma. *Am J Dermatopathol.* 1999;21(4):332-6.
23. Metze D, Soyer HP, Zelger B, et al. Expression of a glycoprotein of the carcinoembryonic antigen family in normal and neoplastic sebaceous glands. Limited role of carcinoembryonic antigen as a sweat gland marker. *J Am Acad Dermatol.* 1996;34(5 Pt 1):735-44.
24. Heyderman E, Graham RM, Chapman DV, Richardson TC, Mckee PH. Epithelial markers in primary skin cancer: an immunoperoxidase study of the distribution of epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) in 65 primary skin carcinomas. *Histopathology.* 1984;8(3):423-34.
25. Beer TW, Shepherd P, Theaker JM. Ber EP4 and epithelial membrane antigen aid distinction of basal cell, squamous cell and basosquamous carcinomas of the skin. *Histopathology.* 2000;37(3):218-23.
26. Clark LN, Elwood HR, Uhlenhake EE, Smoller BR, Shalin SC, Gardner JM. Nuclear factor XIIIa staining (clone AC-1A1 mouse monoclonal) is a highly sensitive marker of sebaceous differentiation in normal and neoplastic sebocytes. *J Cutan Pathol.* 2016;43(8):657-62.
27. Khandelwal P, Liu S, Sullivan DA. Androgen regulation of gene expression in human meibomian gland and conjunctival epithelial cells. *Mol Vis.* 2012;18:1055-67.
28. Kiyosaki K, Nakada C, Hijiya N, et al. Analysis of p53 mutations and the expression of p53 and p21WAF1/CIP1 protein in 15 cases of sebaceous carcinoma of the eyelid. *Invest Ophthalmol Vis Sci.* 2010;51(1):7-11.
29. Rangel J, Mccalmont TH. Intracytoplasmic adipophilin immunopositivity: a pitfall in the distinction of metastatic renal carcinoma from sebaceous carcinoma. *J Cutan Pathol.* 2010;37(12):1193-5.
30. Muthusamy K, Halbert G, Roberts F. Immunohistochemical staining for adipophilin, perilipin and TIP47. *J Clin Pathol.* 2006;59(11):1166-70.