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MAJOR REVIEW

Sebaceous Carcinoma of the Ocular Region: A Review

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Abstract. Sebaceous carcinoma of the ocular region is a malignant neoplasm that is being recognized more frequently and managed by innovative techniques of local resection, cryotherapy, topical chemotherapy, and radiotherapy, resulting in improved visual and systemic prognosis. (**Surv Ophthalmol 50**:103–122, 2005. © 2005 Elsevier Inc. All rights reserved.)

Key words. amniotic membrane graft • blepharitis • blepharoconjunctivitis • chalazion • chemotherapy • conjunctiva • conjunctivitis • cryotherapy • frozen sections • irradiation • meibomian gland • mitomycin C • Mohs microsurgery • pagetoid • plaque radiotherapy • sebaceous gland • surgical resection • Zeis gland

I. Introduction

Sebaceous carcinoma is an important malignant neoplasm that occurs most often in the periorbital area, usually in the eyelid.[9,10,25,28,33,56,60,91,92,98,103,129,133] It can exhibit aggressive local behavior and can metastasize to regional lymph nodes and distant organs. Historically, this neoplasm was notorious for masquerading as other benign and less malignant lesions, resulting in delays in diagnosis and relatively high morbidity and mortality. Hence, the ophthalmologist should be cognizant of the clinical features and current therapy of periorbital sebaceous carcinoma. In recent years, greater awareness of this neoplasm has resulted in earlier diagnosis and has provided the opportunity for less aggressive therapy. Even though ophthalmologists have become more familiar with the clinical variations of periorbital sebaceous carcinoma, we have observed that serious delays in diagnosis are still common. This review provides an update on sebaceous carcinoma of the ocular region, with emphasis on current options in management.

A. DEFINITIONS

Sebaceous glands are generally associated with hair follicles and, hence, are most abundant in skin where more hair is present. They are characterized by holocrine secretion in which the entire cell is desquamated into the lumen and secreted through a duct to the skin surface. Even though cells within sebaceous glands demonstrate a high mitotic activity, the development of malignant sebaceous neoplasms is uncommon.[56]

The terms sebaceous carcinoma, sebaceous gland carcinoma, and sebaceous cell carcinoma and meibomian gland carcinoma have all been used in the literature to describe the malignant neoplasm discussed in this review. In speaking with several ophthalmic pathologists, we found that there is no general agreement on terminology. However, in most

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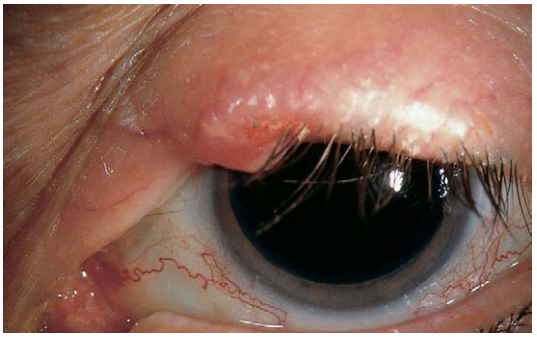

Fig. 1. Sebaceous carcinoma arising from meibomian glands of left upper eyelid.

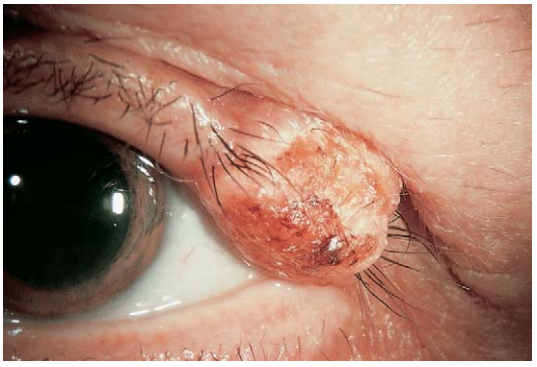

Fig. 2. Sebaceous carcinoma arising from Zeis glands of left upper eyelid.

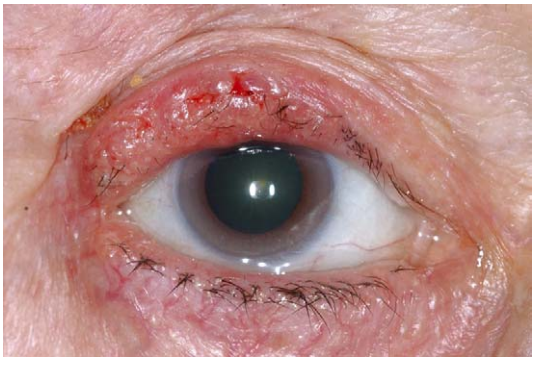

Fig. 3. Sebaceous carcinoma of right upper eyelid causing diffuse loss of cilia.

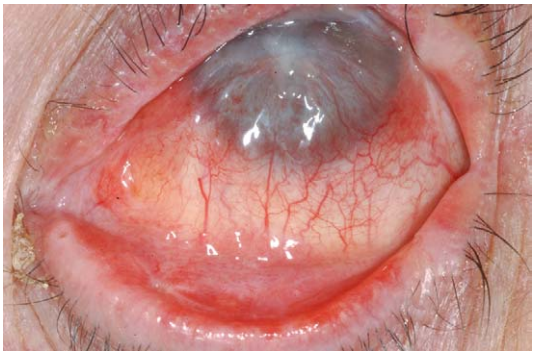

Fig. 4. Diffuse involvement of conjunctiva and cornea by pagetoid growth.

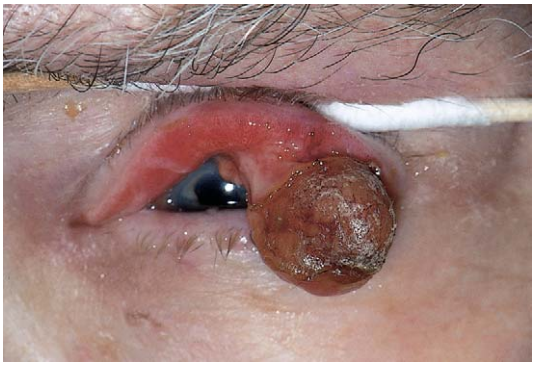

Fig. 5. Pedunculated sebaceous carcinoma seen arising from upper tarsus.

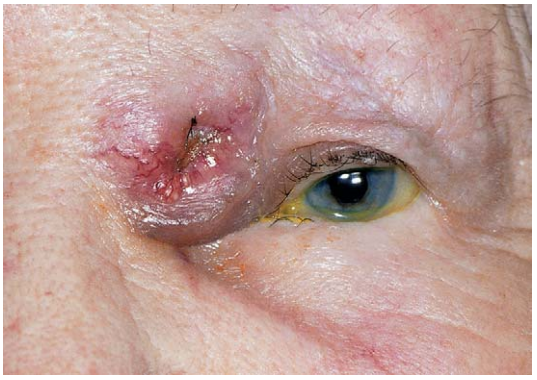

Fig. 6. Ulcerated sebaceous carcinoma. Note the suture at site of prior biopsy.

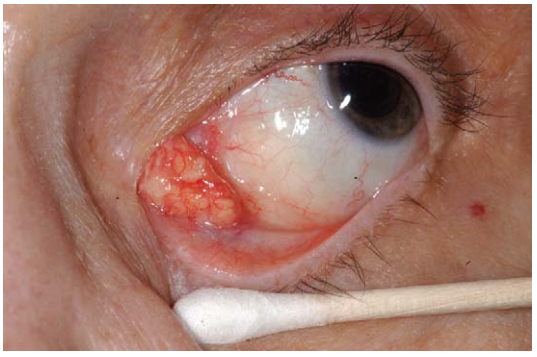

Fig. 7. Sebaceous carcinoma arising from caruncle. Initial biopsy elsewhere was misdiagnosed histopathologically as squamous cell carcinoma, but yellow appearance without papillary changes or leukoplakia led to clinical suspicion of sebaceous carcinoma.

recent articles, the term sebaceous carcinoma has been employed and most ophthalmic pathologists seem to prefer that term. Hence, the term sebaceous carcinoma is used in this article.

Sebaceous carcinoma is a malignant neoplasm that originates from cells that comprise sebaceous glands.[9,10,25,28,33,56,60,91,92,103,129,133] There is an unusual abundance of sebaceous glands in the ocular region, particularly in the tarsus (Meibomian glands)

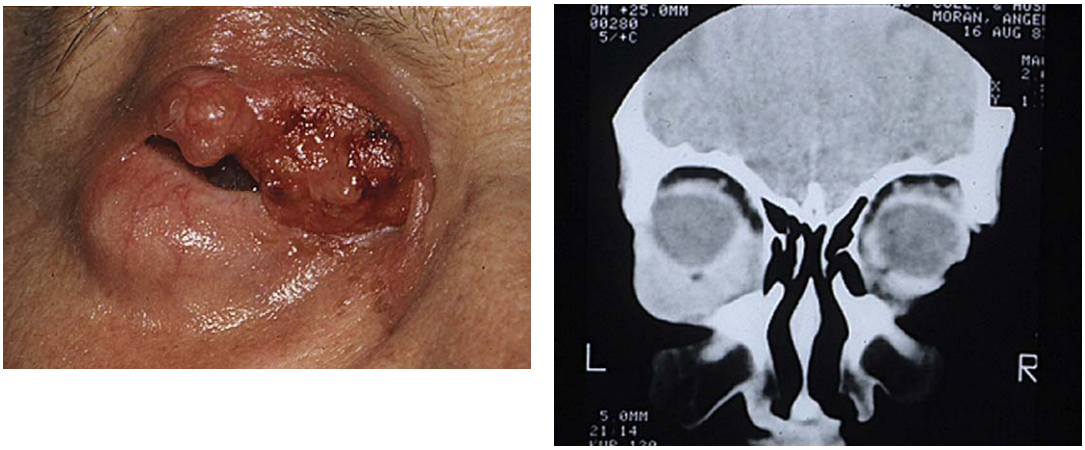

Fig. 8. *Left:* Advanced recurrent sebaceous carcinoma with extensive involvement of upper and lower eyelid and orbital soft tissue. *Right:* Coronal computed tomography of the same patient, showing diffuse orbital involvement particularly in the inferior aspect of the orbit.

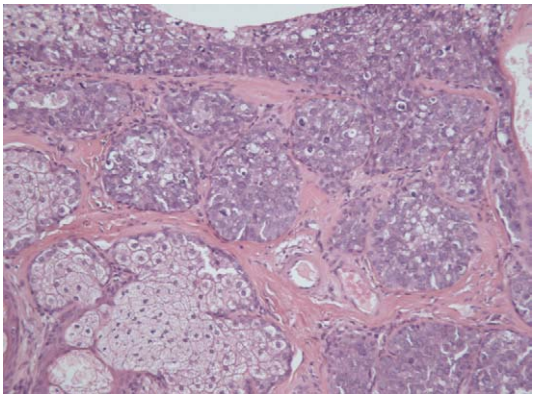

Fig. 9. Lobular growth pattern of sebaceous carcinoma. Note the malignant lobules (up and right) and the normal meibomian glands (down and left) (hematoxylin-eosin × 50).

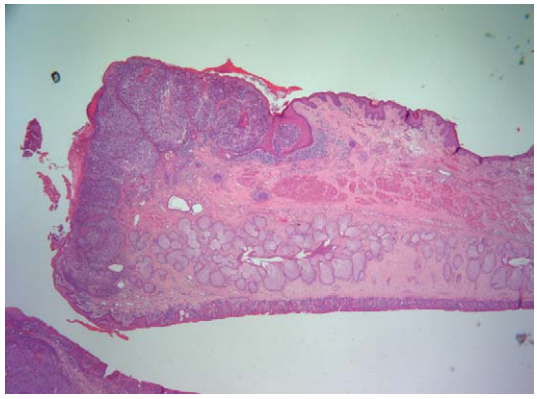

Fig. 11. Localized sebaceous carcinoma near the eyelid margin, arising from gland of Zeis. This is the same case as shown in Fig. 2 (hematoxylin-eosin × 5).

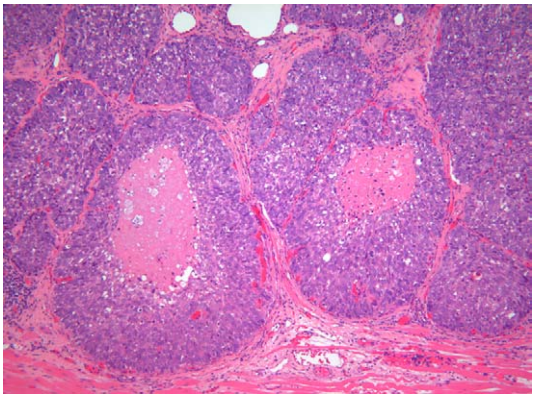

Fig. 10. Comedocarcinoma pattern of sebaceous carcinoma. Note that the larger tumor lobules have central necrosis (hematoxylin-eosin × 25).

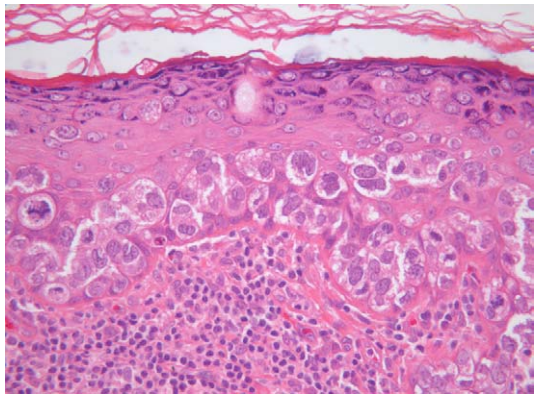

Fig. 12. Pagetoid involvement of the eyelid skin. The basal epidermis contains cells with foamy, vacuolated cytoplasm (hematoxylin-eosin × 200).

and in association with the cilia (Zeis glands). The caruncle is also endowed with sebaceous glands that are associated with fine lanugo hairs of that structure. Sebaceous glands are also present in the eyebrow region. Therefore, all of these periorbital sites are capable of spawning sebaceous neoplasms.[56]

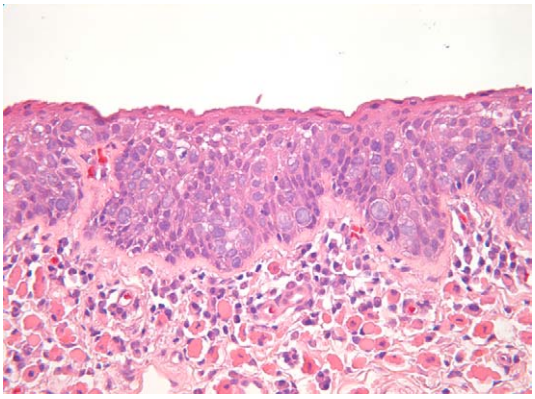

Fig. 13. Pagetoid growth pattern in the conjunctiva. Note the intact basement membrane and the intense chronic inflammatory reaction in the stroma (hematoxylin-eosin × 100).

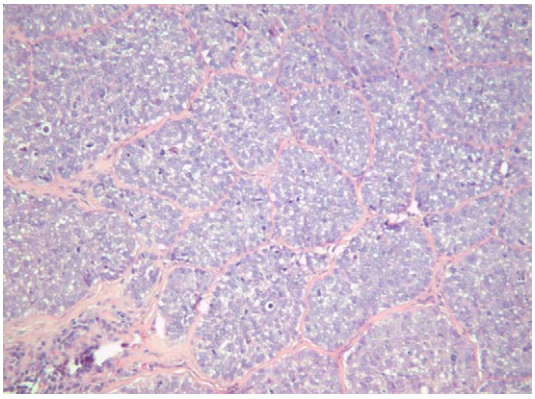

Fig. 14. Sebaceous carcinoma with numerous lipid globules within the cytoplasm of the tumors cells, seen as clear spaces (hematoxylin-eosin × 100).

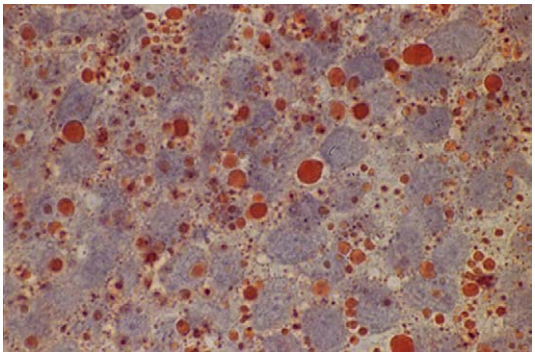

Fig. 15. Accentuation of the lipid using oil red-O stain. The lipid globules have a red color (frozen sections, oil red-O × 250).

B. HISTORICAL ASPECTS

A historical review of periorbital sebaceous carcinoma was provided by Kass and Hornblass in 1989.[60] Based on their review, the first case may have been reported by Thiersch in 1865 and another case was reported by Baldauf in 1870. However, Allaire is generally credited with reporting the first reasonably well-documented case in 1891.[60] There were several subsequent reports including one by Hagedoorn, who recognized the aggressive nature and metastatic potential of this neoplasm.[43]

Most of our modern understanding of eyelid sebaceous carcinoma was initiated by the review of Straatsma in 1956, who reported 16 cases in which he clarified the origin and clinical behavior of this neoplasm.[143] Subsequently, other publications contributed to our understanding of this neoplasm.[9,10,18,26,28,91,92,95,103,129,145,147,155,168]

C. EXTRAORBITAL PRIMARY LOCATIONS

Although sebaceous carcinoma has a marked tendency to arise in the ocular region, particularly in the eyelids, it does occur in other locations.[3,5–7,100,158] It is estimated that approximately 25% of sebaceous carcinomas occur in extraorbital sites, about 70% of which are in the head and neck region.[158] The parotid gland is the most common extraorbital origin and accounts for almost 30% of all cases.[158] In that location, the tumor may arise either from pleuripotential cells with capacity for sebaceous differentiation or from ectopic sebaceous cells that are displaced in the parotid gland during embryologic development. An incomplete list of other reported sites of origin include the submandibular gland, chest, extremities, great toe, sole of the foot, penis, external auditory canal, and anterior neck region.[5,90,101] The demographics, clinical course, pathology, management, and prognosis are similar for extraorbital and periorbital sebaceous carcinoma.

II. Incidence

About 5–10% of all skin malignancies occur on the eyelid and basal cell carcinoma is the most common malignant eyelid tumor.[24] Although the incidence varies from series to series, in the United States it is generally acknowledged that basal cell carcinoma accounts for about 90% of malignant eyelid tumors, sebaceous carcinoma for about 5%, squamous cell carcinoma for about 4%, and others, including melanoma, for only about 1%.

The incidence of sebaceous carcinoma shows a puzzling variation according to the geographic area surveyed and, hence, appears to have racial preferences. A study of malignant eyelid tumors that included patients from Florida suggested that the annual incidence of eyelid sebaceous carcinoma was 0.5 per million in the white population older than 20 years.[81] Reports from China and India show that sebaceous carcinoma accounts for a higher percent of malignant eyelid tumors in those countries, a subject to be discussed in the next section.

It has been suggested that the incidence of sebaceous carcinoma of the periorbital area may be increasing.[64] If that is true, there are several possible explanations for this change. First, there is greater awareness of eyelid sebaceous carcinoma among pathologists, ophthalmologists, and dermatologists, resulting in increase frequency of accurate diagnosis. Second, there may be more referrals to institutions where patients are enrolled into studies. Third, the average life span has increased and sebaceous carcinoma is generally a disease of older individuals. Fourth, in the United States, there has been an increase in individuals of Asian origin, in whom the disease is presumably more common. Fifth, it may be related to delayed effects or irradiation to the face area employed at an earlier age.[52,64]

III. Demographics and Risk Factors

Some relative risk factors for periocular sebaceous carcinoma include older patient age, female sex, race, prior irradiation, systemic associations, prolonged use of diuretics, and immunosuppression.

A. AGE

Sebaceous carcinoma is generally a disease of older individuals. The mean patient age at diagnosis in reported series has ranged from 57 years to 72 years.[18,23,45,60,92,103,129,163] However, it can occur in older children and young adults, particularly those with prior irradiation for hereditary retinoblastoma, in whom the mean age of diagnosis is 14 years.[67] Sebaceous carcinoma has been reported in a 20-year-old with no known risk factors.[8]

B. SEX

Although reports regarding sex have varied, most authors have found sebaceous carcinoma to be more common in women than men, with over 70% occurring in women.[10,60,92,103,129,140,160] The reason for this apparent predisposition is unknown.

C. RACE

In North America, sebaceous carcinoma appears to be more common in whites than in African-Americans.[160] One report of 75 patients included only four blacks.[103] The presumed higher incidence of sebaceous carcinoma in Asians and Indians is well known.[1,19,20,91] In 1982, Ni and associates reported that sebaceous carcinoma accounted for 33% of all malignant eyelid tumors in a Chinese population.[92] They compared the incidence to a series collected in Boston in which it accounted for only 1.5% of malignant eyelid tumors.

Recent studies from India have shown that sebaceous carcinoma accounts for 40–60% of malignant eyelid tumor from that country (Unpublished poster data, abstracts from International Society of Ocular Oncology Meeting, Hyderabad, India, January 2003). A published review of 85 malignant eyelid tumors from that country disclosed that basal cell carcinoma accounted for 39%, sebaceous carcinoma for 28%, and squamous cell carcinoma for 22%.[1] To our knowledge, it is currently undetermined whether there is an increased incidence of this tumor in Asians who have lived only in Western countries.

D. IRRADIATION

Prior irradiation also is an important risk factor. There are several reports of cases of sebaceous carcinoma occurring in patients with familial retinoblastoma who were treated with ocular irradiation (mean 46 Gy).[10,53,67,73,111] A review of nine such cases revealed that all cases were hereditary retinoblastoma and the sebaceous carcinoma developed in the field of irradiation at a mean age of 14 years and at a mean of 11 years after the irradiation.[67] It was of interest that the same authors mentioned two cases of eyelid sebaceous carcinoma that occurred in survivors of hereditary retinoblastoma, but who had no prior irradiation.[67] This suggests that sebaceous carcinoma may be one of the so-called second neoplasms that can occur with familial retinoblastoma, regardless of whether irradiation had been used. Sebaceous carcinoma can also develop following facial irradiation for other benign conditions, including acne, cutaneous hemangioma, and eczema.[118,158] A remarkable case was reported by Rumelt and associates in 1998.[110] Their patient, who had prior whole face irradiation for eczema, developed bilateral sebaceous carcinoma that involved all four eyelids.

E. MUIR-TORRE SYNDROME

There are no systemic conditions that convincingly predispose to sebaceous carcinoma. The Muir-Torre syndrome is an autosomal dominant condition in which patients develop cutaneous sebaceous adenomas, keratoacanthomas, and internal malignancies, mainly of stomach and duodenum.[34,55,57,106,109,149,153] Occasional patients with the Muir-Torre syndrome have developed periocular sebaceous carcinoma.[142]

F. DIURETICS

A presumed relationship between the use of diuretic medications and development of sebaceous carcinoma has been described. In a report of 20 patients with sebaceous carcinoma, eight were taking

diuretics.[65] The mechanism of thiazide diuretic-induced carcinogenesis was postulated to be related to the production of carcinogenic N-nitroso compounds, (i.e., nitrosamine) which occur during interactions of orally ingested thiazides with nitrites in the gastric fluids.[64] Although this is an interesting observation, there is still no firm evidence of a relationship between diuretic use and sebaceous carcinoma.[90]

G. IMMUNOSUPPRESSION

It is well known that patients infected with the human immunodeficiency virus (HIV) are at an increased risk for developing malignancies, which occur at a younger age and often are highly aggressive. In one report, a 36-year-old woman and a 24-year-old man, both of whom were HIV positive, developed sebaceous carcinoma of the eyelid and caruncle, respectively.[164] As mentioned earlier, there is a report of an immunosuppressed patient with Muir-Torre syndrome who developed an eyelid sebaceous carcinoma.[142] Our group managed a woman with thrombocytopenia who was treated for 14 years with corticosteroids who developed sebaceous carcinoma at the age of 33 years.[50]

IV. Ocular Origins

As mentioned earlier, the periorbital area is particularly well-endowed with sebaceous glands any of which can spawn sebaceous carcinoma. The clinical features of sebaceous carcinoma that develops from these specific glands are discussed in the subsequent section.

A. MEIBOMIAN GLANDS

Most sebaceous carcinomas arise from the meibomian glands, within the tarsus. In a review of reported cases, Kass and Hornblass found that 63% occurred in the upper eyelid, 27% in the lower eyelid, and 5% diffusely involved both eyelids.[60] A recent study from our department has revealed similar findings.[129]

B. ZEIS GLANDS

The Zeis gland associated with the cilia can also give rise to sebaceous carcinoma. In the series by Rao and associates, about 10% arose from the Zeis glands.[103]

C. CARUNCLE

The caruncle has abundant sebaceous glands associated with the hairs that emanate from that structure. Overall, sebaceous carcinoma accounts for a very low percent of caruncular tumors.[128] However, 5–10% of sebaceous carcinomas arise in the caruncle.[103,129]

D. EYEBROW

There is little mention in the ophthalmic literature about sebaceous carcinoma of the eyebrow. Although it seems to be rare, it is possible that such cases are managed more often by dermatologists and do not come to the attention of ophthalmologists or ophthalmic pathologists and are under-represented in the ophthalmic literature.

E. CONJUNCTIVA

There have been reported cases in which sebaceous carcinoma is confined to the conjunctival epithelium or the epidermis, with no demonstrable deeper involvement of the tarsus or dermis (Freeman LN, Iliff WJ, Iliff NT, Green WR: Extramammary Paget's disease/pagetoid change of the conjunctiva without underlying sebaceous gland carcinoma [abstract]. Invest Ophthalmol Vis Sci 29[Suppl]:321, 1988).[50,79,80] It appears that these truly represent primary sebaceous carcinoma of the conjunctiva without origin in eyelid or caruncular sebaceous glands.

F. MULTICENTRIC ORIGIN

There has been considerable concern among clinicians about the tendency of sebaceous carcinoma to exhibit multicentric origins.[17,156] In some cases, these may represent "skip areas" within pagetoid invasion. In the series of 104 cases reported by Rao and associates, 12 were judged to be of multicentric origin, which the authors believed to arise from both the meibomian and Zeis glands.[103] It is believed that up to 18% of advanced sebaceous carcinomas are multicentric.[56,140]

It was mentioned earlier that sebaceous carcinoma occasionally can arise primarily in the parotid and submandibular glands. It is of ophthalmic interest that the lacrimal gland, a minor salivary gland, can rarely spawn a sebaceous neoplasm.[14,46,131] Before one can make such a diagnosis, it is necessary to exclude a diffuse eyelid sebaceous carcinoma that has secondarily invaded the lacrimal gland.[131,135]

V. Clinical Features

Historically, sebaceous carcinoma of the eyelid is notorious for masquerading as a more common benign condition ("masquerade syndrome"), often resulting in a long delay before the correct diagnosis is made (Brownstein S, Gariepy EL, Codere F: Sebaceous carcinoma masquerading as a chalazion. Ophthalmic Practice 5:123–6, 1987).[4,10,15,28,86,103,129,157] Such a delay in diagnosis can increase the chance of local recurrence, metastasis, and death. Consequently, ophthalmologists, dermatologists, and other

professionals must be familiar with its clinical variations.

A. SOLITARY EYELID NODULE

The most common clinical variant is a painless, firm, sessile to round, subcutaneous nodule in the eyelid (Fig. 1).[56,108,129,133] It is initially deep to the epidermis and fixed to the tarsus.[62] The skin over the lesion is generally smooth and fairly movable. As the tumor enlarges and encroaches on the epidermis, it assumes a yellow color due to the presence of lipid in the mass. When the tumor arises from the Zeis gland, it can appear as a rounded mass at the eyelid margin, without such a firm attachment to the tarsus (Fig. 2). Sebaceous carcinoma eventually causes loss of cilia, a finding seen with other malignant eyelid tumors (Figs. 1–3).[61,132]

B. DIFFUSE PSEUDOINFLAMMATORY PATTERN

The second most frequent presentation is a diffuse unilateral thickening of the eyelid (Fig. 3). This diffuse type is more likely to extend into the epithelium of the forniceal or bulbar conjunctiva and even the corneal epithelium (Fig. 4). The lack of a distinct nodule, as seen with most neoplasms, causes the clinician to suspect an inflammatory condition, rather than a neoplasm.[35,71,117] It must be stressed that sebaceous carcinoma should be a diagnostic consideration in a middle-aged or older patient with a unilateral "blepharitis" that does not respond to standard treatment. In such cases, biopsy should be considered. If the blepharitis is bilateral and symmetrical, then sebaceous carcinoma is less likely.

C. PEDUNCULATED LESION

Although sebaceous carcinoma is usually round to oval, it can sometimes grow outward and become pedunculated (Fig. 5).[10,44,133] Such lesions can show keratinization and even appear as a cutaneous horn.[13,123] This is more likely to occur with an eyelid margin lesion, presumably from the glands of Zeis.[10,13] Occasionally, a sebaceous carcinoma can become ulcerated, simulating a basal cell carcinoma (Fig. 6).

D. CARUNCULAR MASS

When sebaceous carcinoma develops in the caruncle, it appears as an irregular yellow mass in the medial canthal region (Fig. 7). It is more likely to be in soft tissues and less likely to be fixed to adjacent structures.[132,133] Wherever the origin, sebaceous carcinoma can sometimes replace the entire eyelid and invade the orbit (Fig. 8).

E. EYEBROW MASS

Sebaceous carcinoma that originates in the eyebrow area generally appears as a deep cutaneous mass that may be indistinguishable from the more common epidermal inclusion or "sebaceous" cyst.

F. LACRIMAL GLAND MASS

In rare instances the initial manifestation of sebaceous carcinoma is a progressively enlarging mass in the lacrimal gland region.[14,46,107,131] Careful history and examination of most such patients reveals findings of a chronic unilateral blepharoconjunctivitis that was either not previously recognized or was treated locally as a benign inflammatory lesion.[2] As mentioned earlier, primary sebaceous carcinoma can rarely develop primarily in the lacrimal gland.

G. EXTENSIVE INVASION

Regardless of the gland(s) of origin, sebaceous carcinoma can sometimes present with widespread involvement of both eyelids, conjunctiva, and even the anterior orbital tissues (Fig. 8). This is more likely to occur in neglected or recurrent cases.

VI. Clinical Differential Diagnosis

Because sebaceous carcinoma can resemble a number of inflammatory and neoplastic conditions, it is important for the clinician to be familiar with the clinical variations of sebaceous carcinoma and the simulating conditions. As mentioned earlier, confusion with benign conditions such as chalazion and blepharoconjunctivitis has led to the term "masquerade syndrome" to characterize this lesion.[15,37,42,161]

A. CHALAZION

Chalazion can be remarkably similar to early sebaceous carcinoma.[10,94,103,147] In contrast to sebaceous carcinoma, chalazion generally occurs in younger individuals, is more painful or tender, is more circumscribed without diffuse involvement, and usually does not produce loss of cilia. Nevertheless, any older patient with a chalazion, particularly one that is in any way atypical, or one that recurs after initial curettage, should undergo a biopsy to rule out sebaceous carcinoma.

B. BLEPHARITIS

Because of its tendency for diffuse involvement of the eyelid, sebaceous carcinoma is often misdiagnosed as blepharitis. However, in most cases seborrheic blepharitis is bilateral, and produces dandruff-like deposits on the cilia, and does not cause loss of cilia or appreciable thickening of the eyelids.

C. CONJUNCTIVITIS

When diffuse epithelial involvement by sebaceous carcinoma progresses to involve the palpebral, forniceal, or bulbar conjunctiva, it can simulate conjunctivitis.[18,130,152] In contrast to sebaceous carcinoma, classic conjunctivitis is more likely to be bilateral and does not cause appreciable thickening of the eyelids. A blepharoconjunctivitis appearance predominates in 20–50% of patients with sebaceous carcinoma.[2,35,57,64,163] Pagetoid involvement can be widespread and even extend to involve the nasal cavity.[120]

D. KERATOCONJUNCTIVITIS

As diffuse sebaceous carcinoma progresses, it can extend onto the corneal epithelium, producing the appearance of a keratoconjunctivitis. This is due to a neoplastic pannus that extends onto the cornea.[56,103,167] The same features mentioned above for conjunctivitis also apply to keratoconjunctivitis. Related to all of the above inflammatory conditions, it is noteworthy that diffuse sebaceous carcinoma typically induces secondary inflammation, an important principle when one interprets histopathologic findings. Sebaceous carcinoma has also been known to induce a peripheral ulcerative keratitis in the vicinity of the neoplasm.[114]

E. SUPERIOR LIMBIC KERATOCONJUNCTIVITIS

Sebaceous carcinoma can be misinterpreted as superior limbic keratoconjunctivitis. In one reported case, the patient was treated for several years for superior limbic keratoconjunctivitis. [22] In retrospect, the diffuse thickening of the tarsus should have suggested the diagnosis of sebaceous carcinoma.[22]

F. OTHER INFLAMMATORY CONDITIONS

Because of the diverse clinical manifestations of sebaceous carcinoma, virtually any other inflammatory condition of the eyelid or conjunctiva must be included in the differential diagnosis of that neoplasm. It can simulate a unilateral papillary conjunctivitis[39] or cicatricial pemphigoid.[41] Hence, any granuloma, including sarcoidosis, can have a similar clinical appearance. We have seen a patient with conjunctival involvement with allergic granulomatosis of the Churg-Strauss syndrome in whom the diagnosis of sebaceous carcinoma was a strong diagnostic consideration.[127]

G. OTHER TUMORS

Several other malignant and benign tumors can have a similar clinical appearance to sebaceous carcinoma.[75,121,123] In all of these conditions, an excisional or incisional biopsy is also warranted. However, findings on clinical examination should assist in establishing a preoperative diagnosis.

1. Basal Cell Carcinoma

The nodular or noduloulcerative form of basal cell carcinoma usually presents as solitary nodule but it is more common in the lower eyelid. It generally is more white or translucent rather than yellow, has vascular elevated margins, and is more likely to become ulcerated at an early stage. Ulceration is uncommon in sebaceous carcinoma.[150] The diffuse sclerosing or morpheaform basal cell carcinoma may closely simulate sebaceous carcinoma. However, it is unlikely to exhibit simultaneous diffuse invasion of the conjunctiva and is more likely to show erosion or ulceration.

2. Squamous Cell Carcinoma

Squamous cell carcinoma may also be more common in the upper eyelid but is usually more superficial, lacks a yellow color, and is more likely to be seen in association with actinic keratosis of the facial skin.[105] Conjunctival intraepithelial neoplasia can be quite similar to the diffuse epithelial invasion by sebaceous carcinoma, except eyelid involvement is less likely to be present.

3. Melanoma

Cutaneous melanoma can also occur in the eyelid or conjunctiva and can assume a nodular or diffuse growth pattern. It is generally pigmented and has a black or brown, rather than yellow color. An interesting clinical paradox is that the recurrence of eyelid or conjunctival melanoma after prior excision is frequently amelanotic and thus can resemble sebaceous carcinoma.[126]

4. Merkel cell carcinoma

Eyelid Merkel cell carcinoma (cutaneous neuroendocrine carcinoma) also occurs most often as a solitary subcutaneous nodule in the upper eyelid of older individuals. In contrast to sebaceous carcinoma, it has a red or red blue color.[99]

5. Lymphoma

Lymphoma of the eyelid or conjunctiva is more common than sebaceous carcinoma.[121] In the eyelid area it is usually deep to the epidermis and the skin moves freely over the lesion. In the conjunctiva, it has the typical pink "salmon patch" and usually is located deep to the epithelium and does not have the inflammatory signs that are seen with sebaceous carcinoma.[124]

6. Sweat Gland Neoplasms

Benign adenomas and malignant adenocarcinomas of eccrine and apocrine sweat gland origin are rare tumors that can be confused clinically with sebaceous carcinoma. Moll gland neoplasms arise within the substance of the eyelid beneath intact epidermis and may also be confused initially with a chalazion.[33]

7. Other tumors

As mentioned earlier a number of other benign and malignant tumors can assume a similar clinical appearance to sebaceous carcinoma. Hence the differential diagnosis must include eyelid or conjunctival squamous papilloma,[85] hereditary benign intraepithelial dyskeratosis,[125] metastatic carcinoma,[66] and other rare lesions.

VII. Methods of Spread

One of the more clinically challenging aspects of sebaceous carcinoma is its ability to extend beyond its original site to affect other structures. This can occur in the form of direct local extension, regional metastasis, or distant metastasis.

A. LOCAL EXTENSION

Sebaceous carcinoma can invade the adjacent epithelia or the orbital soft tissues, lacrimal secretory system, lacrimal excretory system and, in advanced cases, the cranial cavity.

B. EPITHELIAL INVASION

Sebaceous carcinoma is well known to exhibit flat, superficial involvement of the eyelid or conjunctival epithelium.[18,33,56,103,130] This is usually referred to as pagetoid growth pattern because of the microscopic similarity to pagetoid spread of some breast cancers. This is addressed in more detail later in the Pathology section.

C. ORBITAL SOFT TISSUE

With time, sebaceous carcinoma can extend posteriorly into orbital soft tissues[98] (Fig. 8). This appears to be more frequent in advanced cases or in those that arise in the caruncle. In a recent series of 1,264 orbital masses, orbital extension of sebaceous gland carcinoma accounted for only 4 cases (<1% of all orbital tumors and for 3% of all secondary orbital tumors).[137] Patients with neglected cases can rarely present initially with advanced tumor that replaces all of the orbital contents.[56]

D. LACRIMAL SECRETARY SYSTEM (LACRIMAL GLAND)

Eyelid sebaceous carcinoma can secondarily involve the lacrimal gland.[88,131] This could feasibly occur either from direct epithelial extension from the conjunctiva or from free-floating dissemination of tumor cells through lacrimal gland ducts that open into the conjunctival fornix. Such ductal dissemination may account for tumor recurrences in the lateral canthal region with "clear" surgical margins.[64]

E. LACRIMAL EXCRETORY SYSTEM (LACRIMAL SAC)

Eyelid sebaceous gland carcinoma can extend into canaliculus, nasolacrimal sac, nasolacrimal duct, and inferior turbinate bone. It is uncertain whether this occurs via contiguous epithelial spread or whether free-floating cancer cells are implanted into the lacrimal drainage system or whether both mechanisms play a role. The chances of tumor dissemination into the lacrimal drainage system should be kept in mind during surgical management of these neoplasms.

F. INTRACRANIAL EXTENSION

In most cases sebaceous carcinoma with major orbital extension is managed today by orbital exenteration, and local tumor control is achieved.[138] However, in highly aggressive or neglected cases the tumor can breach the internal orbital periosteum and extend through the bony foramina to reach the cranial cavity.[16,21]

G. REGIONAL METASTASIS

The most common method of metastasis of eyelid sebaceous carcinoma is via lymphatic channels to regional lymph nodes. Historically, regional node metastasis occurred in about 30% of cases.[38,64,77,103,119,148] Tumors that originate in the upper eyelid tend to metastasize to preauricular and parotid nodes, which represent the most common sites of metastasis. Tumors of the lower eyelid region tend to metastasize to submandibular and cervical nodes.[10,57,103,129]

H. DISTANT METASTASIS

Advanced cases of eyelid sebaceous carcinoma can occasionally exhibit distant metastasis, probably by hematogenous routes. Organs most often involved are lung, liver, bone, and brain.[16,29,64,68]

VIII. Pathology

Another challenging problem related to sebaceous carcinoma is the difficulty often encountered in

histopathologic diagnosis of this neoplasm. Because the tumor usually occurs in the ocular area, specimens are often sent to ophthalmic pathologists who are more accustomed to seeing this uncommon tumor. General pathologists, particularly those in community hospitals, are unlikely to see a case during their entire career. Hence, it has often been misdiagnosed as squamous cell carcinoma, basal cell carcinoma, or other more common neoplasms. Incorrect initial histopathologic diagnoses have been reported in 40–75% of cases in which the sections were interpreted usually by an inexperienced pathologist.[10,28,64,129,163] Even when the diagnosis is correct, there frequently are misleading histopathologic interpretations of "clear" margins on frozen section and Mohs microsurgery techniques, which may be unreliable in up to 25% of cases.[64] Such misinterpretation can lead to inappropriate undertreatment.[103,112]

A. GROSS PATHOLOGY

There are no specific gross features of sebaceous carcinoma. The excised mass may have a yellow color due to the presence of lipids. Specimens of full thickness eyelid biopsy may show the tumor arising in the tarsal plate.

B. MICROSCOPIC PATHOLOGY

Although there are several methods of classifying sebaceous carcinoma, most authorities recognize four histopathologic patterns; lobular, comedocarcinoma, papillary, and mixed.[33,56,103] Histopathologically, sebaceous carcinoma can be grouped into well-differentiated, moderately differentiated, and poorly differentiated varieties.[33]

The lobular pattern occurs most frequently and mimics the normal sebaceous gland architecture with less differentiated cells situated peripherally, and better differentiated, lipid-producing cells located centrally (Fig. 9). In the comedocarcinoma pattern, the lobules show a large necrotic central core surrounded by peripheral viable cells (Fig. 10). The papillary pattern occurs frequently in small conjunctival tumors characterized by papillary projections and areas of sebaceous differentiation. The mixed pattern can exhibit any combination of the three patterns. When the tumor arises from, and is confined to, the Zeis glands, it appears microscopically to affect the glands near the eyelid margin but spare the tarsus (Fig. 11).

A well-known and highly quoted aspect of sebaceous carcinoma is its ability to exhibit intraepithelial spread into the eyelid epidermis (Fig. 12) and conjunctival epithelium (Fig. 13).[56,103,129,130] This has generally been reported to occur from 44–80% of cases.[18,56,103,129,160] In a review of 52 cases of orbital exenteration for more advanced sebaceous carcinoma, Jakobiec found that some degree of conjunctival epithelial involvement could be identified in 100%.[56] Although three patterns of conjunctival intraepithelial spread of sebaceous carcinoma have been identified,[56] we prefer for simplicity to use the term "pagetoid invasion" to apply to all cases of conjunctival epithelial involvement. Pagetoid spread of this neoplasm represents a peculiar histopathologic pattern that is not fully understood.

Regardless of the growth pattern, sebaceous carcinoma is an unencapsulated infiltrating mass with fairly distinct cytologic features.[56] The individual cells have a finely vacuolated, frothy cytoplasm (Fig. 14). Lipid in the tumor can sometimes incite a foreign body giant cell reaction that may superficially resemble a chalazion. Mitotic activity is usually high and there is pronounced nuclear pleomorphism. Some areas may closely resemble squamous cell carcinoma.

The presence of lipid in normal sebaceous glands and in sebaceous neoplasms can be demonstrated with the oil red-O stain by which lipid has a red color (Fig. 15). Many clinicians and pathologists have long believed that it is necessary to employ frozen sections and oil red-O stain to establish the diagnosis. However it is usually possible to demonstrate oil red-O positivity in sections of formalin-fixed tissue as well, although the staining reaction may not be so intense.[30,56] One must remember that any lipid-containing cell can show a positive oil red-O stain. Hence, the entire histopathologic pattern must be taken into account in arriving at a final diagnosis.

It has been observed that sebaceous carcinoma appears to have a less intense inflammatory response (Figs. 12 and 13) with T-helper cells than basal cell carcinoma, prompting some authorities to speculate that this may be related to the more aggressive behavior of sebaceous carcinoma.[49]

C. IMMUNOHISTOCHEMISTRY

In the hands of pathologists experienced with sebaceous carcinoma, the diagnosis can usually be made readily and immunohistochemistry is not usually necessary. However, there are a few reports on the immunohistochemistry of this neoplasm.[11,58,139,146] Johnson and associates demonstrated dimorphic immunohistochemical staining in sebaceous ocular neoplasms.[58] They found that the central foamy cells expressed human milk fat globule-1 (HMFG1), epithelial membrane antigen (EMA) but not cytokeratins, whereas the small peripheral basal and duct cells generally expressed cytokeratin but not HMFG1 or EMA. They pointed out that use of these markers largely removed the need for fat stains on frozen sections. They believe that their results also support

the concept that ocular sebaceous neoplasms arise from a common stem cell rather than from developed sebaceous cells or basal/ductal cells.[58]

Sinard used immunohistochemistry to differentiate sebaceous carcinoma from basal and squamous cell carcinomas.[139] He found that sebaceous carcinoma generally expressed EMA, Cam 5.2 and BRST-1. Basal cell carcinoma expressed neither EMA or BRST-1 whereas squamous cell carcinoma expressed EMA but not Cam 5.2. He believed that these immunohistochemical studies could be helpful in the differentiation of these 3 important eyelid malignancies.[139] Other authors have reported similar findings.[146]

IX. Histopathologic Differential Diagnosis

As mentioned earlier, the histopathologic diagnosis of sebaceous carcinoma can be challenging and it is often misdiagnosed as other neoplasms, particularly squamous cell carcinoma or basal cell carcinoma. However, based on the typical histopathologic features of these entities and the aforementioned histochemical and immunohistochemical reactions, the diagnosis can generally be established. The following represents some of the light microscopic features that serve to differentiate them.

A. SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma is the lesion most often confused with sebaceous carcinoma histopathologically and about 50% of cases of sebaceous carcinoma have been originally misdiagnosed as squamous cell carcinoma.[69,70,129] Squamous cell carcinoma is generally better differentiated, has more abundant eosinophilic cytoplasm without lipid vacuoles, and may show squamous eddy formation and keratin cysts.

B. BASAL CELL CARCINOMA

Lobules of basal cell carcinoma typically show peripheral palisading of nuclei and retraction artifact, findings that are not seen with sebaceous carcinoma. Basal cell carcinoma is also much less likely to exhibit pagetoid spread.[112] In some cases, basal cell carcinoma can exhibit sebaceous differentiation and be misdiagnosed as primary sebaceous carcinoma.[115] In such instances, the differentiation between the two tumors can be difficult.

C. OTHER TUMORS

The two main neoplasms that should be considered in the histopathologic differential diagnosis of sebaceous carcinoma are squamous cell carcinoma and basal cell carcinoma, which are relatively common tumors. Other less common tumors to be considered in the differential diagnosis include the mucoepidermoid variant of squamous cell carcinoma, Merkel cell carcinoma, melanoma, and lymphoma. Awareness of these lesions, combined with appropriate immunohistochemical studies, can be helpful in differentiating them from sebaceous carcinoma.

X. Pathogenesis

Most sebaceous carcinomas appear to arise de novo, and not from a pre-existing sebaceous adenoma, sebaceous hyperplasia, or sebaceous (organoid) nevus. Other factors that may be pathogenically related, like irradiation, immunosuppression, and use of diuretics, have already been discussed.

Studies have shown that there may be a relationship of sebaceous carcinoma and human papillomavirus (HPV). A report of 21 tumors from Japan revealed that 13 tumors (62%) were positive for HPV DNA using in-situ hybridization techniques.[47] That study also showed that overexpression of P53 protein may be important in carcinogenesis.

XI. Diagnostic Techniques

The diagnostic methods and management of sebaceous carcinoma necessarily overlap, but they are discussed separately here for simplification. The diagnosis of periorbital sebaceous carcinoma (as well as other eyelid neoplasms) necessitates a high index of suspicion based on clinical findings, followed by excisional or incisional biopsy, and histopathologic confirmation of the diagnosis. If an incisional biopsy is done to establish a diagnosis, it is generally preferable to perform a full thickness eyelid biopsy that includes the skin, tarsus, and bulbar conjunctiva. As a general rule, ancillary studies, as used for intraocular and orbital tumors, are not necessary. However, if the eyelid and conjunctival involvement are more diffuse and extensive on the initial examination, orbital imaging studies to rule out posterior tumor extension may be justified, either before or after the initial biopsy.

Fine-needle aspiration biopsy (FNAB) has been employed only rarely in the diagnosis of periocular sebaceous carcinoma.[144] It is not generally advisable because of the limited amount of tissue obtained. It is generally preferable to perform a more extensive biopsy to include the conjunctiva and tarsus in order to provide the pathologist with enough tissue to establish the diagnosis. However, FNAB may be acceptable for making the diagnosis of regional lymph nodes metastasis in cases where the primary diagnosis has been previously established.[51,77]

Impression cytology has been used as a method of detecting conjunctival intraepithelial spread.[116] This

method has limitations because of the small number of cells obtained and the lack of tissue organization. Because the conjunctiva is accessible for standard biopsy, it seems more reasonable to do an incisional biopsy to obtain sufficient tissue for diagnosis.

XII. Management

The following information related to management is derived from personal experience of the authors combined with a review of the literature, and may not necessarily reflect the experience or views of others who manage sebaceous carcinoma.

The first step in management of a patient with periorbital sebaceous carcinoma is to establish the diagnosis and determine the extent of the disease as quickly and as accurately as possible. This requires a comprehensive clinical evaluation of the eyelid, conjunctiva, caruncle, and adjacent areas, looking for the clinical findings discussed previously. Palpation of preauricular and cervical areas should be performed to detect possible lymph node metastasis. The great majority of patents with relatively small lesions confined to the eyelid will have no demonstrable distant metastasis. Therefore, ancillary studies like chest x-ray, blood testing for liver enzymes, and computed tomography and magnetic resonance imaging of the head, chest, and abdomen usually reveal negative results.

The goals of management, in order of importance, should be as follows:

1. Tumor control to save the patients life
2. Globe salvage
3. Vision salvage
4. Patient comfort
5. Acceptable cosmetic appearance

One issue that has not been adequately emphasized in the literature is the importance of combination therapy. Particularly in advanced cases, surgical excision alone may be inadequate to achieve tumor control. In such cases, the clinician may choose to employ surgical excision combined with cryotherapy, topical chemotherapy, radiotherapy, amniotic membrane grafting, and other techniques, depending on the overall clinical circumstances.

A. SURGICAL MANAGEMENT AND OTHER TECHNIQUES

1. Primary Excisional Biopsy

It is generally acknowledged that the most acceptable management of periorbital sebaceous carcinoma is complete surgical removal when possible.[24] If the lesion is relatively small and circumscribed, and malignancy is strongly suspected, then a planned complete excision is often justified even before there is histopathologic verification of the tumor. It has been our observation that many surgeons prefer to do a small biopsy first and then plan further excision or refer the patient for definitive treatment. However, we believe that if a small lesion is highly typical of primary malignancy and can be removed without major risk for cosmetic deformity, then complete removal of the lesion in one initial procedure is preferable.

For suspected sebaceous carcinoma, a full-thickness, pentagonal, eyelid resection is preferable. The surgeon should strive to take at least 5 mm on nasal and temporal margins. One study of 14 patients showed recurrence of 36% if 1–3 mm margins were taken, but no recurrence if margins were 5 mm or greater.[27] Most older patients have considerable laxity of eyelid skin and complete resection and primary closure can be accomplished for lesions 10 mm or less in diameter, but each case should be individualized depending on the clinical circumstances. A lateral semicircular flap (Tenzel flap) is often necessary to mobilize enough skin to facilitate closure. The methods of pentagonal excision and semicircular flaps are discussed in textbooks and articles on the subject.[133]

For relatively circumscribed lesions in the eyebrow or caruncle, an initial attempt should be made to completely excise the lesion. Adequate margins can be achieved in cases of eyebrow lesions. Caruncular lesions may not lend themselves to wide margins, so heavy cryotherapy (discussed subsequently) may be employed as supplemental treatment in the same surgical procedure, immediately after the mass is removed.

When complete excision of a suspicious lesion is undertaken, the palpebral and bulbar conjunctiva should be carefully examined. If they show suspicious changes suggesting diffuse involvement by tumor, then multiple conjunctival map biopsies should be considered. The technique of map biopsies is considered subsequently.

2. Incisional Biopsy

Incisional biopsy is preferred to establish the diagnosis for more advanced primary lesions that will require extensive reconstruction after the diagnosis and extent of the disease is established. It is also indicated when there are clinical signs of diffuse blepharoconjunctivitis. In general, such a biopsy should involve removing a full-thickness piece of the eyelid including the skin, tarsus, and palpebral conjunctiva.[72] This allows the pathologist to determine the extent of the disease, which usually originates in the tarsus and then extends to involve the epidermis or the epithelium of the bulbar conjunctiva. This

can be done by a scalpel followed by primary closure of the eyelid defect. An easier procedure is to use a small (2-, 3-, or 4-mm diameter) round trephine to penetrate the eyelid. Incisional biopsy of this type can be performed in the office with local anesthesia using an eyelid block, and sutures may not be necessary.

3. Frozen Sections or Mohs Microsurgery

At the time of primary excision, or for subsequent excision of residual or recurrent tumor, either frozen section or Mohs microsurgery is often used to promptly check the margins for residual tumor with continuation of the resection until the margins are clear histopathologically.[29,32,45,63,87,104,141,166] Carefully planned surgical repair of the defect is then undertaken. There has been considerable controversy as to whether Mohs microsurgery or frozen section control are preferable and whether either technique is really better than waiting for permanent sections. Because it is more convenient, we prefer standard frozen section techniques and agree with others that it is as effective as Mohs surgery. Because the results are probably similar, the two techniques are discussed collectively for this review.

In contrast to basal cell carcinoma, sebaceous carcinoma is often characterized by patchy epithelial involvement, sometimes with presumed skip areas.[29] In addition, it may be difficult with frozen sections to differentiate between vacuolated cytoplasm and freezing artifact in conjunctival margins. Hence, the pathologist can sometimes have difficulty in interpretation of frozen sections or Mohs microsurgical methods in cases of sebaceous carcinoma. In addition, surgical margins are often interpreted as negative, but residual tumor is detected when the permanent paraffin embedded sections are studied.[32,56,166] This has led some authorities to question the true reliability of these methods and some believe that the surgeon should rely more on results of permanent sections.[32,56] On the other hand, some surgeons are strong advocates of Mohs microsurgery and have reported favorable results on relative short follow-up.[140]

4. Map Biopsies

Because of the tendency for sebaceous carcinoma to exhibit diffuse involvement in the eyelid and conjunctiva, map biopsies are important to determine the extent of the disease and to plan definitive treatment.[31,102,129,130] Putterman reported his technique of taking 16 conjunctival biopsies, which is similar to the technique that we have employed. However, we routinely take 10 to 14 biopsies, depending on whether there is suspected corneal involvement. With the eyelids everted we take four specimens from the palpebral conjunctiva and six from the bulbar conjunctiva just anterior to the fornix. Putterman recommended taking separate biopsies of the palpebral conjunctiva and the adjacent tarsus, whereas we prefer to include both in one biopsy that includes both conjunctiva and tarsus. We also prefer retrobulbar anesthesia and regional nerve block anesthesia, rather than injecting anesthesia directly under the eyelid skin and bulbar conjunctiva, which could disrupt the conjunctival anatomy.

The routine for map biopsies may need to be modified according to the clinical and surgical findings. For example, if a distinct nodule of suspected tumor is detected in the fornix away from the usual biopsy sites, then that lesion should be entirely removed if feasible.

It is extremely important to carefully label and number each biopsy site on a large diagram that accompanies the specimens submitted for histopathologic study. The small map biopsy specimens should be submitted for permanent sections. Frozen sections or Mohs microsurgery should probably not be performed on conjunctival map biopsies. Once the permanent histopathologic results are obtained, then the definitive surgery can be undertaken.

5. Eyelid and Conjunctival Reconstruction

In the past, diffuse involvement of the conjunctiva by sebaceous carcinoma was considered to be an indication for orbital exenteration. However exenteration for cases with pagetoid invasion only, without orbital infiltration, is controversial.[12,28] Exenteration is possibly justified for advanced diffuse disease with anterior orbital soft tissue invasion. However, many affected patients are elderly, have excellent vision in the affected eye, and the conjunctival involvement is not extensive. In such cases, local resection and reconstruction are probably justified.

Improvements have been made in techniques of eyelid and conjunctival replacement using rotational tarsal flaps and grafting with material like buccal mucosa or preserved amniotic membrane, sometimes combined with cryotherapy or topical chemotherapy. The availability of such methods has stimulated a trend toward more conservative treatment in cases that are not far advanced.

If there is stromal invasion on map biopsies, we now perform local excision of all affected eyelid and conjunctiva. In these cases, it has been possible to remove the posterior lamella of the affected eyelid and the affected conjunctival tissue, followed by repair using rotational or advancement tarsal flaps and buccal mucosa or amniotic membrane grafting. We have used this approach in the overall repair of

about 15 patients with conjunctival involvement by sebaceous carcinoma. With longest follow up of 3 years and mean follow-up of 1 year, no patients have yet required orbital exenteration for recurrence. At the time of surgery and after tumor removal and cryotherapy, the defect is measured, and the amniotic membrane is fashioned to fill the bulbar conjunctival defect and sutured in place with interrupted and running 8-0 vicryl sutures. The tarsal conjunctival defect is closed with buccal mucosa or rotational conjunctival flaps, combined with tarsal replacement. Occasionally a plastic symblepharon ring is employed to prevent adhesions and left in place for about 2 weeks.

6. Cryotherapy

Cryotherapy has been used frequently in recent years as a supplemental treatment for eyelid sebaceous carcinoma, particularly for pagetoid invasion of the conjunctiva. Lisman and associates advocated it as an alternative to exenteration for selected cases.[74] Others have challenged the use of cryotherapy because of the complications, pointing out that in some cases, pagetoid invasion regresses on it own.[28,59] However, we do not believe that conjunctival pagetoid invasion should be ignored. We routinely employ cryotherapy to most of the bulbar and palpebral conjunctiva in these cases both at the time of map biopsy and definitive surgical excision.

7. Topical Chemotherapy

Topical chemotherapy has been found recently to be useful for intraepithelial conjunctival squamous cell carcinoma and primary acquired melanosis.[36,84,162] It has also been found to be very effective as an option to orbital exenteration and complete conjunctivectomy for selected cases of pagetoid invasion of the conjunctiva by sebaceous carcinoma.[122,154] It is probably not effective if there is stromal invasion. The technique of topical chemotherapy using mitomycin C has been reported.[122]

8. Irradiation

There is a general belief that irradiation is not highly effective in the management of sebaceous carcinoma and that surgical excision is preferable.[16,45,48,78,93,151] However, some authors have advocated radiotherapy in selected cases.[83,93,96,97,165] In 1979, Hendly and associates reported short term follow-up on three cases in which irradiation was used as primary treatment for biopsy proven sebaceous carcinoma.[48] Two patients showed no recurrence on short term follow up and one patient required orbital exenteration. In 2000, Yen and associates described two patients who declined further surgical excision and who had tumor control after 39 and 46 months, respectively.[164] Based on their cases and a literature review, those authors concluded that >55 Gy is curative for eyelid sebaceous carcinoma. However, the role of irradiation is not determined, and most authorities believe that surgical management is the appropriate primary treatment. Irradiation may be used as an alternative to exenteration in older patients for selected cases of recurrence following exenteration.[54]

Plaque brachytherapy has recently been advocated for some residual lacrimal gland malignancies and for orbital invasion of malignant eyelid and conjunctival tumors. This method involves the surgical placement of a radioactive plaque in the region of orbital residual tumor to deliver about 500 Gy to the target area.[136] This technique has not been adequately tested in cases of sebaceous carcinoma, but will probably prove to be a reasonable option to exenteration in selected cases.

9. Orbital Exenteration

Until recently orbital exenteration was widely believed to be the only reasonable option in the management of sebaceous that involved most of the conjunctiva and invaded the orbit. With the more recent aforementioned options, orbital exenteration is currently performed less often. However, it is probably the most appropriate option for cases of unresectable orbital extension and no evidence of distant metastasis. Contrary to popular belief, it is not always necessary to completely remove the eyelid skin in such cases. If the eyelid skin is free of disease on frozen sections, it is reasonable to spare the skin and adjacent orbicularis muscle by performing an eyelid sparing exenteration.[134] The advantage of eyelid-sparing exenteration is that socket healing occurs in 2–3 weeks, allowing earlier fitting of a prosthesis.

B. MANAGEMENT OF REGIONAL METASTASIS

Fine-needle aspiration biopsy has been used to make the diagnosis of regional lymph node metastasis from sebaceous carcinoma.[51,77] Cytopathology reveals characteristic epithelial cells with lipid-rich cytoplasm.[51,113] The most frequent sites of regional metastasis include preauricular, parotid, and cervical nodes.[78,82] If there is localized regional lymph node metastasis, then lymph node dissection may be justified.

There has been considerable recent interest in sentinel lymph node biopsy for certain neoplasms, particularly cutaneous melanoma. The goal of this method is to identify the location of lymph nodes so that the nodes themselves can be removed without subjecting the patient to more extensive regional surgery. In a recent series of 5 patients who underwent sentinel node biopsy for periocular neoplasms, two

of the patients had sebaceous carcinoma.[159] This is a new technique with regard to ocular lesions and it is not yet established as a routine method.

C. MANAGEMENT OF DISTANT METASTASIS

Eyelid sebaceous carcinoma can also exhibit hematogenous metastasis to distant organs.[68,76,103] In such cases liver and lung are the most common metastatic sites. Chemotherapy, under the guidance of an oncologist, may be necessary in an attempt to control metastatic disease.[68]

XIII. Prognosis

The visual prognosis for patients with periorbital sebaceous carcinoma varies with the extent of the disease and the type of treatment employed. The systemic prognosis varies with several factors. In an earlier series of 88 cases submitted to the AFIP, Boniuk and Zimmerman reported 30% mortality.[10] Doxanas and Green reported an 18% tumor-related mortality in their series of 40 patients.[28] Rao and associates reported 104 cases with greater than 5-year follow-up data.[103] Of those, 23 patients died from metastatic disease. The various factors that were associated with a worse prognosis included vascular, lymphatic, and orbital invasion; involvement of both upper and lower eyelids, poor differentiation; multicentric origin; duration of symptoms greater than six months; tumor diameter exceeding 10 mm; a highly infiltrative pattern, and pagetoid invasion.

Recent reports have suggested improved survival in patients with periorbital sebaceous carcinoma.[89,129,140] Snow and associates reported 9 patients who were managed by local resection and all 9 patients were alive without recurrence on follow-up ranging from 1 to 14 years.[140] One patient required orbital exenteration because of tumor recurrence. In a review of 60 cases in the authors series there was a 6% mortality.[129] This may represent a falsely high number, because some patients were referred with advanced tumors, after metastasis had developed.

There are other less well-known molecular genetic factors that have been mentioned in the literature. These include hyperexpression of tumor suppressor gene p53, which seems to be associated with progression of sebaceous carcinoma.[40] Another study also showed that p53 accumulation was more often observed in the clinically advanced cases, occasionally in association with recurrence and/or metastasis.[47]

XIV. Summary and Conclusions

Sebaceous carcinoma is a malignant neoplasm that develops most often in the eyelids, usually from the meibomian glands of the tarsus. It has a tendency to be exhibit diffuse, invasive growth in the eyelid and conjunctiva, and can metastasize to regional lymph nodes and distant organs. Historically, this neoplasm is notorious for masquerading as inflammatory disease or other tumors, resulting in delays in diagnosis and higher morbidity and mortality. In recent years, however, greater awareness of this neoplasm has resulted in earlier diagnosis and has provided the opportunity for less aggressive therapy. Today, more cases are being managed by carefully planned map biopsies, local resection, and advanced methods of reconstruction, combined with cryotherapy and topical chemotherapy. Consequently, orbital exenteration is often avoided and patient survival is improving.

Method of Literature Search

Literature selection for this review was based on a Medline database search (1966–2004), using the terms *eyelid, conjunctiva, tumor, sebaceous carcinoma, and sebaceous gland carcinoma.* To supplement this, the medical librarians at Wills Eye Hospital, Thomas Jefferson University, conducted a similar computerized search on the same subjects. Pertinent articles from the English-language literature were primarily selected. Additionally, relevant references contained within those articles were gathered. Pertinent articles from the authors' personal reprint collection were reviewed and included, if not already cited by the aforementioned methods.

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