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Case History

A 79-year-old man had a papillomatous lesion removed from the caruncle of his left eye. The lesion recurred at the site of biopsy, and was re-excised six months later.

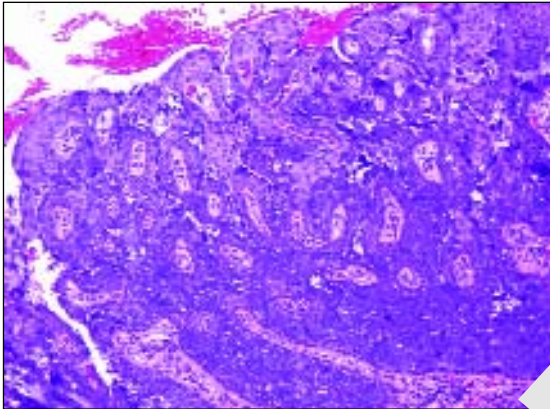


Figure 1

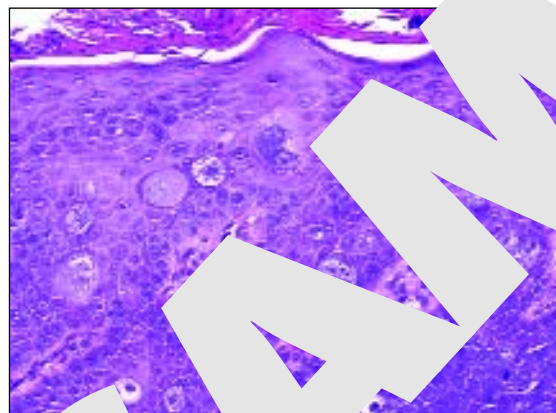
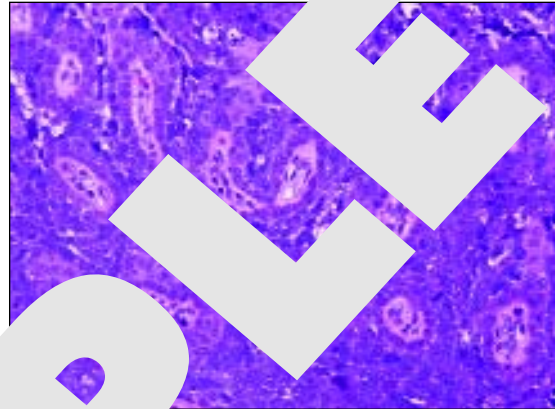


Figure 3

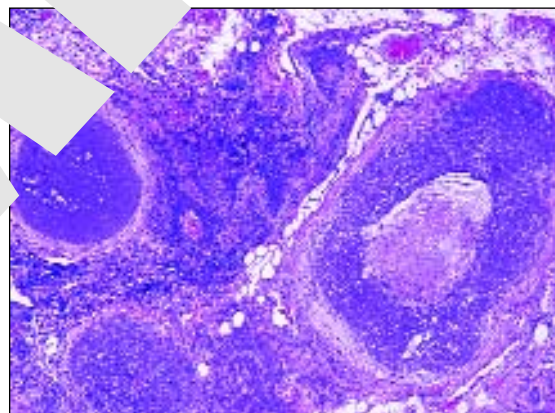


Figure 4

Original lesion, scanning magnification. A proliferation of large cells with a high nuclear to cytoplasmic ratio has replaced the surface epithelium, and exhibits a papillary growth pattern.

Figure 2: Original lesion, intermediate magnification. The surface epithelium is forming slender, short papillae which are infiltrated by large, mitotically active, malignant cells with large nucleoli. In this section, rare cells with a bubbly, foamy cytoplasm and eccentric nuclei are present.

Figure 3: Original lesion, high magnification. Pagetoid spread of single cells adjacent to the surface proliferation is present. The cells are large, and can infiltrate in single cells or clusters. The cytoplasm appears foamy and vacuolated.

Figure 4: Recurrence at site of biopsy, scanning magnification. Several nodules are present in the dermis accompanied by a loose fibrous stroma. Comedonecrosis is present.

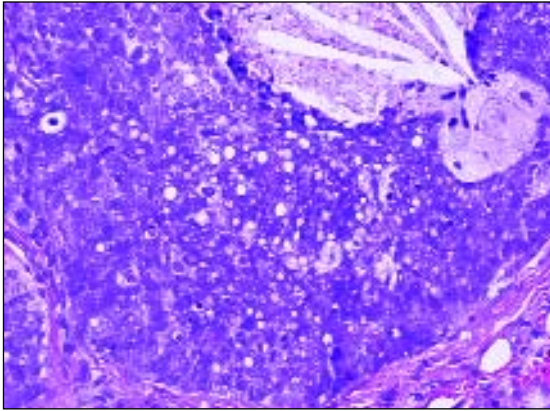


Figure 5

Figure 5: Recurrence at site of biopsy, intermediate magnification. The malignant cells in the dermal nodules are similar to the original biopsy, and exhibit prominent cytoplasmic vacuoles.

Diagnosis

Sebaceous carcinoma.

Commentary

Sebaceous carcinoma is among diagnostically most challenging tumors, and is the most commonly misdiagnosed (both clinically and pathologically) tumor of the eyelid.¹

The clinical and pathological features of sebaceous carcinoma of the eyelid may be misleading and can lead to a delay in diagnosis and treatment. However, early diagnosis is essential to reduce mortality and morbidity. A high index of suspicion for sebaceous carcinoma is needed when dealing with tumors and tumor-like conditions in this location.

Sebaceous carcinoma is defined as a malignant epithelial tumor with sebaceous differentiation showing ability to metastasize to regional lymph nodes and distant sites. This is a common malignancy of the eyelid, and represents 0.2-0.8% of all tumors at this site, and 1-5.5% of all eyelid malignancies.²

Demographics

This malignancy is most common in the elderly, with a median age at diagnosis of 57 to 72 years, and is slightly more common in females. Sebaceous carcinoma is more prevalent in India and China than in North America, however, the etiologic association is unknown.^{1,2} Risk factors for development of sebaceous carcinoma include prior irradiation to the ocular region, and Muir Torre syndrome.

Clinical presentation

Sebaceous carcinoma can arise from all sebaceous glands of the eyelid, including meibomian glands (51-70% of ocular cases), glands of Zeis (10%), and least often in sebaceous glands in caruncle (7%) or the skin (1%).² Extraocular manifestations occur in approximately 25% of all cases of sebaceous carcinoma, most commonly in the head and neck region.²

Ocular sebaceous carcinoma has a varied repertoire of clinical manifestations. The most common presentation is chalazion, which is a hard and painless nodule on the eyelid caused by inflammation of the meibomian glands or glands of Zeis (**Figure 6**). The tumor can have a distinct yellow color (**Figure 7**) due to lipid accumulation. The second-most common manifestation is a diffuse unilateral thickening of the tarsus, which can mimic blepharitis (**Figure 8**). Sebaceous carcinoma can also exhibit a pedunculated growth pattern, mimicking a cutaneous horn that usually occurs at the eyelid margin at the glands of Zeis. At the caruncle, sebaceous carcinoma can appear as an irregular yellow mass in soft tissues, which is covered by intact epithelium. As the tumor progresses, there are loss of lashes (**Figure 9**), and widespread involvement of both eyelids, conjunctiva, and anterior orbital tissues. Since sebaceous carcinoma has a varied clinical presentation, a clinical suspicion for malignancy may arise after failure of conventional treatment. This 'masquerade syndrome' is usually seen in cases that present as persistent unilateral conjunctivitis, blepharitis, meibomitis, or blepharoconjunctivitis.

Clinical Course, Treatment and Prognosis

Sebaceous carcinoma of the eyelid is slow-growing, and commonly spreads to the conjunctiva, orbital soft tissue, the lacrimal gland, or lacrimal excretory system. Local recurrence tends to occur within five years in about 9-36% of cases with resection margins that are less than 5 mm.¹ However, achieving clear margins is difficult due to the Pagetoid spread of the tumor, and 'skip lesions' or multifocal disease is common. Lymphatic and vascular invasion is also seen, which leads to regional lymph node metastasis in about 30% of cases.

The overall mortality of sebaceous carcinoma of the eyelid varies from 15-30% depending on several prognostic indicators. A negative outcome is strongly associated with multicentric origin, vascular and lymphatic invasion, involvement of the upper and lower eyelids, involvement of both meibomian glands and glands of Zeis, and tumor diameter greater than 2 cm.¹ A delay of one to six months from presentation is associated with a 14% mortality rate, whereas a delay of more than six months has a 38% mortality rate. The development of metastatic disease is associated with a 50-67% five-year mortality rate. Histologic features that are associated with a poor prognosis include poor sebaceous differentiation, intraepithelial pagetoid distortion of the epithelium, and a highly infiltrative growth pattern.¹

Histological Features

Histological patterns:

- *In situ* growth pattern with or without Pagetoid spread
- Invasive growth pattern, lobular (most common) or infiltrative
- Comedo-carcinoma

Histological differentiation:

- Sebaceous: vacuolated cytoplasm filled with lipid droplets, nuclear pleomorphism, and high mitotic activity
- Squamous: keratinization *without* internuclear bridging
- Basaloid: palisading growth pattern

Histological differential diagnosis:

- Sebaceous adenoma and sebaceoma
- Squamous cell carcinoma
- Basal cell carcinoma
- Other primary (sweat gland carcinoma) or metastatic (clear cell renal carcinoma) tumors with clear cell cytological features

Histological clues that favor sebaceous over squamous cell carcinoma:

- Obvious sebaceous differentiation of malignant cells
- Presence of cytoplasmic fat on Oil Red O stain (requires frozen section)
- High cytological grade with frequent single cell necrosis
- Nested growth pattern with comedonecrosis
- Foamy, bubbly cytoplasm
- Indented scalloped nuclei
- Pagetoid growth in conjunctiva
- *In situ* involvement of hair follicles or sebaceous units
- More foamy sebaceous differentiation in the center
- Microvesicular pattern on EMA staining

Immunohistochemical techniques can also aid in the differential diagnosis. Most cases of sebaceous carcinomas stain for EMA (epithelial membrane antigen), CAM5.2 (low molecular weight keratin) and HMFG-1 (human milk fat globule-1) and do not stain for S-100 or HMB-45.³ Basal cell carcinomas are usually negative for EMA and HMFG-1, whereas squamous cell carcinomas are CAM5.2 negative.³ Androgen receptor staining, although suggested to be helpful as a marker of sebaceous differentiation⁴ is also seen in basal cell carcinomas, and thus is not a useful marker in the differential diagnosis.⁵

Another characteristic which may aid in narrowing the differential diagnosis is the anatomic site. Two thirds of sebaceous carcinomas more frequently arise in the upper eyelid due to the increased concentration of meibomian glands, whereas basal cell and squamous cell carcinomas arise more frequently in the lower lid.⁶ Therefore,

sebaceous carcinoma should be the most likely diagnosis for a malignancy arising in the upper eyelid.

This case illustrates how sebaceous carcinoma can often be misdiagnosed as squamous cell carcinoma. Several cases have described how sebaceous carcinoma can be erroneously diagnosed as Bowen's disease or squamous cell carcinoma *in situ*.^{6,7} One retrospective study showed that 50% of sebaceous carcinomas were misdiagnosed as squamous cell carcinomas at initial biopsy.¹

Management

Wide surgical excision, with 5-6 mm margins is the primary management of sebaceous carcinoma. However, local recurrence is common due to Pagetoid spread, and thus map biopsies and subsequent cryotherapy of intraepithelial lesions is also performed. Topical chemotherapy with mitomycin C is also employed as an option to orbital exenteration for selected cases of conjunctival Pagetoid spread.² Irradiation is also used as an alternative to surgical exenteration or for selected cases of recurrence. Regional lymph node metastases can be treated by surgical dissection, and distant metastases are often treated with systemic chemotherapy.



Figure 6



Figure 7

Figure 6: Clinical picture of chalazion, the most common clinical presentation of sebaceous carcinoma, is a painless nodule on the eyelid.

Figure 7: Sebaceous carcinomas usually have a yellow coloration due to lipid accumulation.