5-1-2022

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Squamoid Eccrine Ductal Carcinoma of the Eyelid: Clinicopathologic Correlation of a Case

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Abstract: **Squamoid eccrine ductal carcinoma (SEDC) is a rare cutaneous neoplasm that often manifests as a plaque or nodule in sun-exposed areas of older patients. Herein, the authors report the first case of SEDC in the eyelid. A 76-year-old man presented with a 2.5 × 1.5 mm area of left upper eyelid erythema, thickening, ulceration, and scaling with madarosis superotemporally just above the lash line. Full-thickness wedge biopsy demonstrated irregular epithelial tubules with nuclear atypia and focal squamous differentiation, consistent with SEDC. The patient underwent Mohs resection and has had no recurrence approximately 27 months after surgical removal. The authors present this case to raise awareness of SEDC to ophthalmologists as all previous cases have been described in the nonophthalmic literature. A full-thickness biopsy is recommended to avoid misdiagnosing SEDC as squamous cell carcinoma (SCC), a less aggressive tumor. With greater awareness, there may be increased recognition of this likely underreported, more malignant entity.**

Skin adnexal carcinomas are rare, with a reported incidence of 5.1 per 1 million person-years in a recent population-based study.[1] Eccrine carcinoma, a subset of adnexal malignancies that originate from the eccrine glands, is the most common form of adnexal carcinoma and represents <0.01% of all cutaneous tumors.[2] Accurate diagnoses of these lesions can be difficult given both their rarity and histologic variability.[3] Furthermore, the histopathology of these entities can resemble metastatic carcinoma from sites such as the breast, lung, and kidney.[4]

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Accepted for publication November 4, 2021.

This research was supported by the Florida Lions Eye Bank, the Bascom Palmer Eye Institute National Institutes of Health Center Core Grant P30EY014801, an unrestricted grant from the Research to Prevent Blindness, and grants W81XWH-09-1-0675 and W81XWH-13-1-0048 ONOVA from the US Department of Defense.

The authors have no financial or conflicts of interest to disclose.

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DOI: 10.1097/IOP.0000000000002116

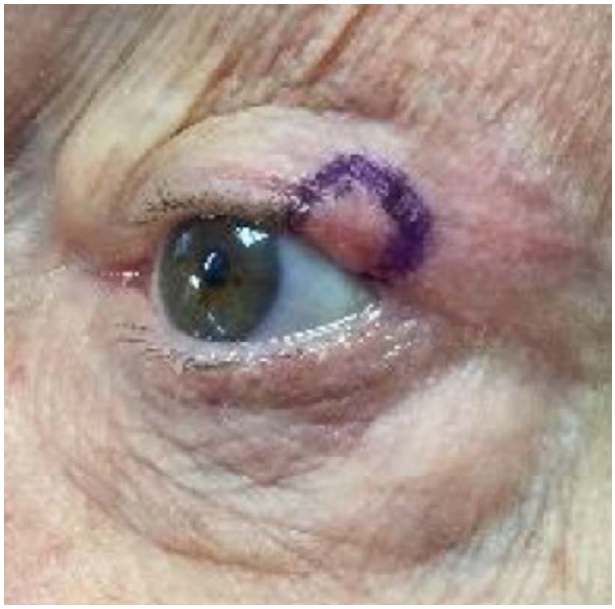

FIG. 1. Clinical photograph after initial incisional biopsy but before wedge resection: A 2.5 × 1.5 mm area of erythema, thickening, ulceration, and scaling with madarosis is present in the superotemporal region of the left upper eyelid just above the lash line.

In the eyelid, 3 distinct subtypes of eccrine carcinoma have been identified: mucinous, adenoid, and ductal.[5] Ductal eccrine carcinoma is the most common subtype and often manifests in middle-aged to older patients as a plaque or nodule on the scalp, trunk, or extremities.[2] Although less commonly identified in the eyelid, a number of cases of ductal eccrine carcinoma have been reported to occur in this area.[6,7]

A variation of ductal eccrine carcinoma that features prominent squamous differentiation, termed squamoid ductal eccrine carcinoma (SEDC), was first described in a series of 3 cases in 1997.[8] Over the course of almost 20 years, less than a dozen subsequent cases of this entity were reported, many in the form of case reports or small case series.[9,10] In 2016, a clinicopathologic study of 30 cases was published and showed that SEDC typically manifests as ulcerated nodules and plaques in sun-exposed areas, primarily the face, in the seventh and eighth decades of life. Histologically, these tumors demonstrate a biphasic appearance. The superficial component displays squamous differentiation with epidermal connection, often in a background of actinic keratosis or SCC in situ. The deeper component is characterized by infiltration of cords and strands in a desmoplastic stroma with cellular atypia and varying amounts of duct differentiation.[11] To date, there has been no published reports of SEDC in the eyelid. Here, the authors present a case of SEDC in the upper eyelid of a 76-year-old man with upper eyelid thickening, ulceration, and madarosis. Of note, the study adhered to HIPAA standards and tenets of the Declaration of Helsinki in the collection and analysis of this patient's protected health information.

CASE PRESENTATION

A 76-year-old Caucasian male was referred to oculoplastics clinic for a left upper eyelid lesion. The patient had been treated with tetracycline ointment for 2 weeks. Past ocular history included central retinal vein occlusion with cystoid macular edema in the left eye (treated with intravitreal aflibercept) and

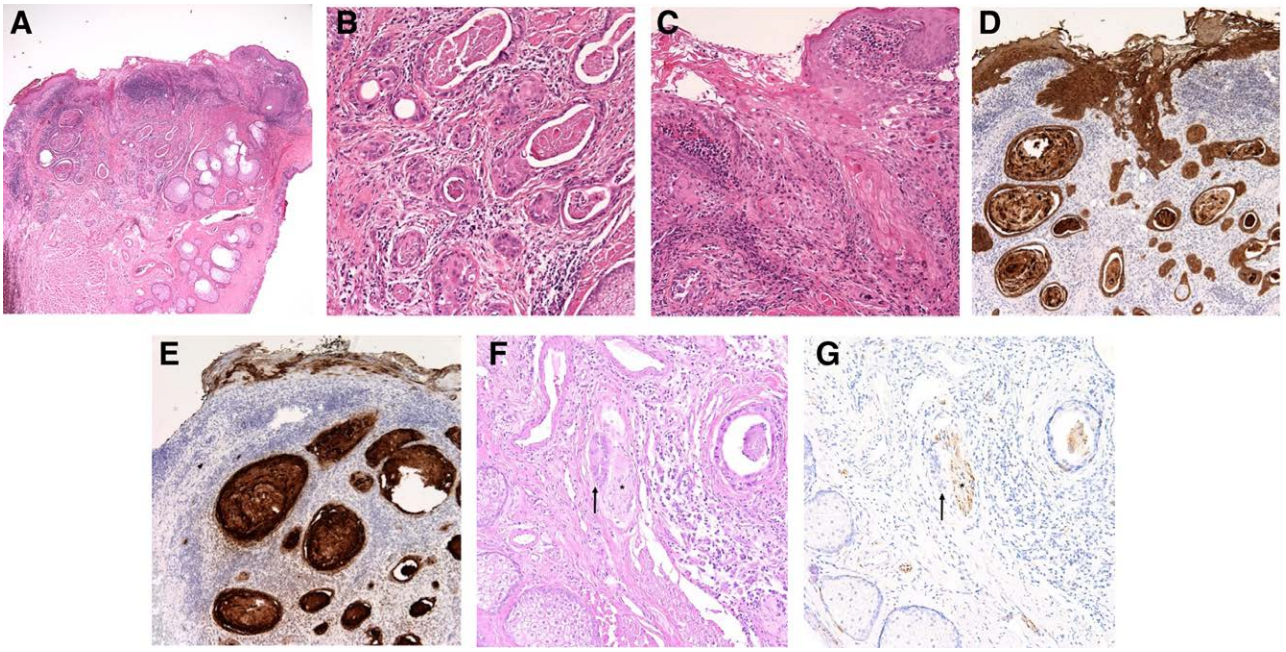

FIG. 2. Histopathology of the eyelid lesion. **A**, Irregular epithelial tubules with nuclear atypia are present in the deeper dermis along with squamous differentiation present superficially (Hematoxylin-eosin, original magnification ×40). **B**, The deeper dermis consists of infiltrative tubules in a desmoplastic stroma with perineural invasion (Hematoxylin-eosin, original magnification ×200). **C**, The superficial portion of the tumor demonstrates focal squamous differentiation with connection to the epidermis (Hematoxylin-eosin, original magnification ×200). **D**, The squamous and ductal portions of the tumor stain positively for pan cytokeratin (Leica) (Pan cytokeratin, original magnification ×100). **E**, The ductal component of the tumor stains positively for CEA (Leica, Agilent Dako), while the squamous portion does not stain for CEA (Carcinoembryonic antigen, original magnification ×100). **F**, Perineural involvement of carcinoma (*arrow*) is present adjacent to the otherwise unremarkable peripheral nerve (asterisk). **G**, The S-100 stain (Leica) highlights the peripheral nerve (asterisk) and the perineural involvement of carcinoma (*arrow*).

cataracts in both eyes. Relevant medical history included significant sun exposure with several nonmelanomatous skin cancers of the face including SCCs of the right naris and right nasal ala skin and basal cell carcinoma of the scalp. On initial examination, the patient's visual acuity, with pinhole, was 20/40 in both eyes. Blepharitis (3+) as well as upper and lower lid laxity were noted bilaterally with no evidence of an eyelid lesion. The patient was managed conservatively with warm compresses, eyelid scrubs, and neomycin/polymyxin B/dexamethasone ointment. Follow-up examination 7 months later revealed similar findings but additionally noted 2 left upper eyelid excoriated lesions accompanied by madarosis, loss of eyelid architecture, and telangiectasias. The patient underwent excisional biopsy of these lesions. Histopathology demonstrated hyperkeratotic and parakeratotic material with acute and chronic inflammation and Gram positive cocci. The patient continued to be managed conservatively and improvement in the patient's eyelid lesions was observed.

Approximately 2 years after the initial biopsy, the patient was noted to have developed a 2.5 × 1.5 mm area of erythema, thickening, ulceration, and scaling with madarosis in the superotemporal region of the left upper eyelid just above the lash line. Repeat biopsy with pentagonal wedge resection was performed at this time given the concern for malignancy. A clinical photograph of the patient's eyelid after initial incisional biopsy but before wedge resection is shown in Figure 1. Histopathology demonstrated irregular epithelial tubules with nuclear atypia as well as focal squamous differentiation present superficially (Fig. 2A, C). Both the squamous and ductal portions of the tumor stained positively for pan cytokeratin (Leica). The eccrine ductal component stained positively for carcinoembryonic antigen (CEA; Leica, Agilent Dako) while the squamous component did not stain for CEA (Fig. 2D, E). The squamous component of the lesion variably stained positively for CK7 (Leica), p63 (Biocare), and CK5/6 (Leica), while the ductal component stained positively for EMA (Cell marque) and CD15 (Leica) (stains not shown). The lesion did not stain for CK20 (Leica) or GCFDP-15 (Leica) (stains not shown). Finally, the tumor demonstrated perineural invasion (Fig. 2F, G). The morphologic and immunohistochemical features of this lesion were consistent with a ductal eccrine adenocarcinoma with focal squamous differentiation.

A PET/CT scan performed 2 months later displayed no clear evidence of metastases. The patient subsequently underwent Mohs resection with reconstruction. After 2 stages of Mohs surgery, the patient's eyelid was free of tumor. At the patient's most recent follow-up visit, approximately 27 months after the wedge resection was performed, the patient presented with no evidence of recurrence, infection, or issues with graft perfusion.

DISCUSSION

SEDC is a very rare entity, and herein, the authors report the first case of this tumor in the eyelid. The presence of this lesion in an individual in the eighth decade of life with a history of evident sun exposure to the face is consistent with that of prior studies.[6,11] Immunosuppression has been suggested as a potential risk factor not only because of the association with older age but also due to the fact that several cases of SEDC have been reported in patients with a history of chronic lymphocytic leukemia or immunosuppression after organ transplant.[3,6] The patient in this study had no history of hematologic malignancy or immunosuppressive medication use. Though the

typical presentation of these lesions include the presence of a nodule, papule, or plaque,[3,6,9–12] there are cases where an ulcerated lesions were described.[6,11]

Histopathology of the case is consistent with that of prior cases of SEDC: the presence of focal squamous differentiation predominately in the epidermis and superficial dermis combined with the growth of ducts and strands in the deeper dermis.[6,11] The immunohistochemical profile is also consistent with that of several prior studies.[11,12] Furthermore, cytologic atypia and perineural invasion are noted in this case. In the largest published series of SEDC (30 cases), these tumors displayed moderate-to-severe atypia, and 27% featured perineural invasion.[11]

The differential diagnosis of this lesion includes SCC, metastatic carcinoma with squamoid features, and other adnexal eccrine carcinomas including microcystic adnexal carcinoma, porocarcinoma with squamous differentiation, and syringoid eccrine carcinoma. Histologically, porocarcinomas may display squamous differentiation but do not typically demonstrate the biphasic pattern seen in SEDC.[12] Microcystic adnexal carcinomas also can exhibit squamoid features but are additionally characterized by keratinous cysts, which are not seen in SEDC.[9,12] Although syringoid eccrine carcinomas are similar to SEDC in that they display a deep infiltrative growth pattern of ducts, they lack squamous differentiation.[11,12] Metastatic carcinoma can be ruled out with the use of immunohistochemistry, namely p63 and CK5/6, whose positivity confirms the primary cutaneous nature of the malignancy.[3,10,12]

The distinction between SEDC and SCC deserves special attention as SEDC can easily be mistaken for SCC. These misdiagnoses have at least, in part, resulted from the use of superficial diagnostic biopsies such as shave or scoop biopsies. These techniques permit examination of only the superficial aspects of the tumor, often resulting in a diagnosis of SCC.[9,12] Such instances highlight the importance of performing an excisional or full-thickness incisional biopsy in situations where an eccrine ductal carcinoma is possible in order not to miss the ductal differentiation that typically predominates in the deeper portions of this tumor. Furthermore, issues with misdiagnosis imply that SEDC is likely an underdiagnosed and underreported entity.

Since only a small number of cases of SEDC have been reported, there is limited information on how to specifically manage this malignancy. The general consensus is similar to that of SCC treatment in that wide surgical excision should be performed with clear margins, with or without Mohs surgery.[2,3,9,10] While these lesions are managed similarly, the prognoses are different. Local recurrence rates for SEDC have been reported to be as high as 70%–80% compared to SCC, which has reported recurrence rates of 3.1%–18.7%.[3] Similarly, metastasis rates for SEDC (up to 50%) are much higher than those for SCC (0.5%).[2] This case study demonstrated no evidence of recurrence approximately 27 months after wedge resection. In the series of 30 cases published by van der Horst et al.,[11] 25% of patients with available follow-up information had local recurrences with a median time to recurrence of 14 months. Thirteen percent of patients at follow-up had regional lymph node metastases with one patient dying of metastases 32 months after the diagnosis.[11] Based on this data, close follow-up with surveillance is recommended for cases of SEDC. Since this is the first time SEDC has been identified in the eyelid, it is not clear to what extent current treatment recommendations and prognosis data for this tumor apply to this scenario.

In summary, the authors present the first case of SEDC in the eyelid with the goal of raising awareness of this entity to ophthalmologists as all previous cases have been described in the dermatology and pathology literature. Our case features a 76-year-old man with left upper eyelid superotemporal thickening with irritation, madarosis, and ulceration. A pentagonal wedge resection was performed, and histopathology demonstrated growth of epithelial tubules in the dermis with nuclear atypia and focal squamous differentiation, consistent with SEDC. This study emphasizes the importance of performing a full-thickness anterior lamellar biopsy or a full-thickness eyelid biopsy when eccrine ductal carcinomas are on the differential to avoid misdiagnosis of these lesions as SCC, an entity with less aggressive behavior. As clinicians become increasingly aware of SEDC, these tumors are likely to be diagnosed more often, providing with more information on how to effectively manage these lesions.

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Bilateral Enophthalmos as an Unusual Presenting Feature of Non-Hodgkin's Orbital Lymphoma

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Abstract: **Lymphoma is the commonest orbital malignancy. The typical presentation is proptosis or swelling, which warrants imaging and confirmation by tissue biopsy. Enophthalmos is a much rarer clinical sign and if bilateral and symmetrical can often present late. We describe a patient who presented with bilateral enophthalmos and**