Squamoid Eccrine Ductal Carcinoma

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PRACTICE **POINTS**

- Squamoid eccrine ductal carcinoma is an aggressive underrecognized cutaneous malignancy that often is misdiagnosed as squamous cell carcinoma (SCC) during initial biopsy.
- Squamoid eccrine ductal carcinoma has a biphasic histologic appearance with a superficial portion resembling well-differentiated SCC and a deeply invasive portion comprised of infiltrative irregular cords with ductal differentiation.
- Excision with complete circumferential peripheral and deep margin assessment with close follow-up is recommended for these patients because of the high risk for recurrence and metastasis.

Squamoid eccrine ductal carcinoma (SEDC) is a rare and underrecognized primary cutaneous tumor with a high risk for local recurrence and metastasis. The tumor has a biphasic histologic appearance consisting of a superficial portion indistinguishable from squamous cell carcinoma (SCC) and a deeper component demonstrating eccrine ductal differentiation. Because of superficial sampling, SEDC often is misdiagnosed as SCC during the initial biopsy. The diagnosis usually is made during complete excision when deeper tissue is sampled. Confirmation of the diagnosis can be achieved by immunohistochemical positivity for carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), cytokeratin (CK) 5/6, and p63. In this article, we review the clinical and histologic details of 5 patients with SEDC who underwent successful treatment with Mohs micrographic surgery (MMS) at a single institution between November 2018 and May 2020. We also review the histologic patterns that helped distinguish SEDC from SCC upon complete excision. Our findings support the use of MMS as the treatment of choice for SEDC, given that all of the patients we reviewed required more than 1 Mohs stage for complete tumor clearance, and none demonstrated evidence of recurrence or metastasis after a mean follow-up period of 11 months.

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Squamoid eccrine ductal carcinoma (SEDC) is an aggressive underrecognized cutaneous malignancy of unknown etiology.[1] It is most likely to occur in sun-exposed areas of the body, most commonly the head and neck. Risk factors include male sex, increased age, and chronic immunosuppression.[1-4] Current reports suggest that SEDC is likely a high-grade subtype of squamous cell carcinoma (SCC) with a high risk for local recurrence (25%) and metastasis (13%).[1,3,5,6] There are as few as 56 cases of SEDC reported in the literature; however, the number of cases may be closer to 100 due to SEDC being classified as either adenosquamous carcinoma of the skin or ductal eccrine carcinoma with squamous differentiation.[1]

Clinically, SEDC mimics keratinocyte carcinomas. Histologically, SEDC is biphasic, with a superficial portion resembling well-differentiated SCC and a deeply invasive portion having infiltrative irregular cords with ductal differentiation. Perineural invasion (PNI) frequently is present. Multiple connections to the overlying epidermis also can be seen, serving as a subtle clue to the diagnosis on broad superficial specimens.[1-3] Due to superficial sampling, approximately 50% of reported cases are misdiagnosed as SCC during the initial biopsy.[4] The diagnosis of SEDC often is made during complete excision when deeper tissue is sampled. Establishing an accurate diagnosis is important given the more aggressive nature of SEDC compared with SCC and its proclivity for PNI.[1,3,6] The purpose of this review is to increase awareness of this underrecognized entity and describe the histologic findings that help distinguish SEDC from SCC.

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Patient Chart Review

We reviewed chart notes as well as frozen and formalin-fixed paraffin-embedded tissue sections from all 5 patients diagnosed with SEDC at a single institution between November 2018 and May 2020. The mean age of patients was 81 years, and 4 were male. Four of the patients presented for MMS with a preoperative diagnosis of SCC per the original biopsy results. Only 1 patient had a preoperative diagnosis of SEDC. The details of each case are recorded in the Table. All tumors were greater than 2 cm in diameter on initial presentation, were located on the head, and clinically resembled keratinocyte carcinoma with either a nodular or plaquelike appearance (Figure 1).

Intraoperative histologic examination of the excised tissue revealed a biphasic pattern consisting of superficial SCC features overlying deeper dermal and subcutaneous infiltrative malignant ductal elements with gland formation in all 5 patients (Figures 2–4). Immunohistochemical staining with cytokeratin AE1/AE3 revealed thin strands of carcinoma in the mid to deeper dermis with

Summary of Selected Characteristics in Patients With SEDC

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, y	82	76	83	82	81
Sex	Female	Male	Male	Male	Male
Location of lesion	Left eyebrow	Left superior occipital scalp	Left superior medial forehead	Medial frontal scalp	Vertex scalp
Histologic diagnosis of original biopsy	Poorly differentiated SCC, recurrent	Moderately differentiated SCC	Well-differentiated SCC	Well-differentiated SCC	SEDC
Depth of invasion, mm	≥3.9	5	NA	2.2	5.45
PNI of large-caliber (0.1-mm) nerve	Yes	Yes	Yes	Yes	Yes
Ulceration	No	No	Yes	Yes	Yes
BWH tumor stage	T2b	T3	T2b	T2b	T2b
Pertinent medical history	Type 2 diabetes mellitus	Active hepatitis B infection	Crohn disease treated with azathioprine, history of melanoma	CLL	HIV, polymyositis treated with tacrolimus and IVIG
Preoperative size, cm	2.3×2	2×1.5	1.5×1	2×2	4.7×4.5
Postoperative size, cm	4.5×3.8	3×2.5	4.1×3	6×5.8	7.5×7.0
No. of Mohs stages	2	2	3	4	2
Repair type	Full-thickness skin graft	Rotation flap	Secondary intention	Secondary intention	Full-thickness skin graft
Adjuvant XRT	Yes	Yes	No	No	No
Imaging findings	Negative for metastatic disease	Incidental parotid cyst	Negative for metastatic disease	Patient declined	Negative for metastatic disease
Approximate follow-up duration to date, mo	18	11	10	6.5	Newly identified case
Recurrence	No	No	No	No	No

Abbreviations: SEDC, squamoid eccrine ductal carcinoma; SCC, squamous cell carcinoma; NA, not available; PNI, perineural invasion; BWH, Brigham and Women's Hospital; CLL, chronic lymphocytic leukemia; IVIG, intravenous immunoglobulin; XRT, radiotherapy.

squamous differentiation and eccrine ductal differentiation (Figure 5), thus confirming the diagnosis in all 5 patients.

The median depth of tumor invasion was 4.1 mm (range, 2.2–5.45 mm). Ulceration was seen in 3 of the patients, and PNI of large-caliber nerves was observed in all 5 patients. A connection with the overlying epidermis was present in all 5 patients. All 5 patients required more than 1 Mohs stage for complete tumor clearance (Table).

In 4 of the patients, nodal imaging performed at the time of diagnosis revealed no evidence of metastasis. Two patients received adjuvant radiation therapy, and none demonstrated evidence of recurrence. The mean follow-up time was 11 months (range, 6.5–18 months) for the 4 cases with available follow-up data (Table).

Literature Review

A PubMed review of the literature using the search term *squamoid eccrine ductal carcinoma* resulted in 28 articles, 19 of which were included in the review based on inclusion criteria (original articles available in English, in full text, and pertained to SEDC). Our review yielded 56 cases of SEDC.[1-19] The mean age of patients with SEDC was 72 years. The number of male and female cases was 52% (29/56) and 48% (27/56), respectively. The most common location of SEDC was on the head or neck (71% [40/56]), followed by the extremities (19% [11/56]). Immunosuppression was noted in 9% (5/56) of cases. Wide local excision was the most commonly employed treatment modality (91% [51/56]), with MMS being used in 4 patients (7%). Adjuvant radiation was reported in 5% (3/56) of cases. Perineural invasion was reported in 34% (19/56) of cases. Recurrence was seen in 23% (13/56) of cases, with a mean time to recurrence of 10.4 months. Metastasis to regional lymph nodes was observed in 13% (7/56) of cases, with 7% (4/56) of those cases having distant metastases.

Comment

Squamoid eccrine ductal carcinoma was successfully treated with MMS in all 5 of the patients we reviewed. Recognition of a distinct biphasic pattern consisting of squamous differentiation superficially with epidermal connection overlying deeper dermal and subcutaneous infiltrative malignant ductal elements with gland formation should lead to consideration of this diagnosis. A

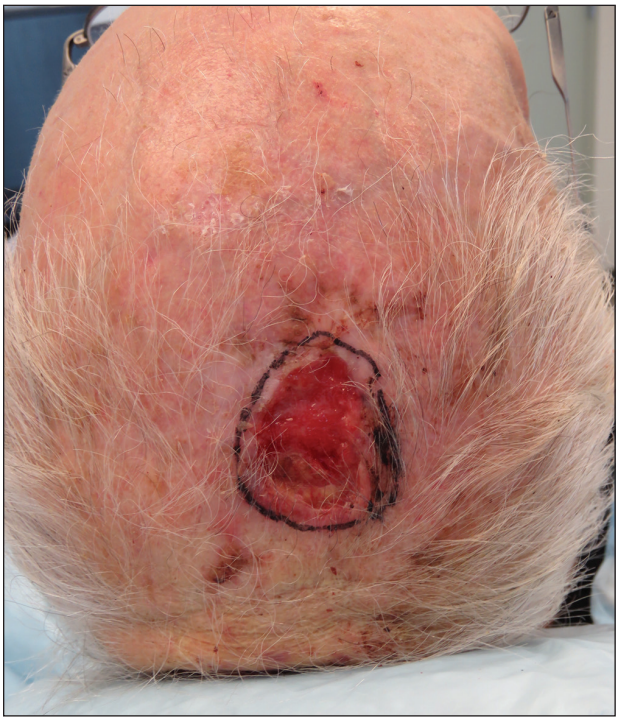

FIGURE 1. Clinical appearance of squamoid eccrine ductal carcinoma in patient 5.

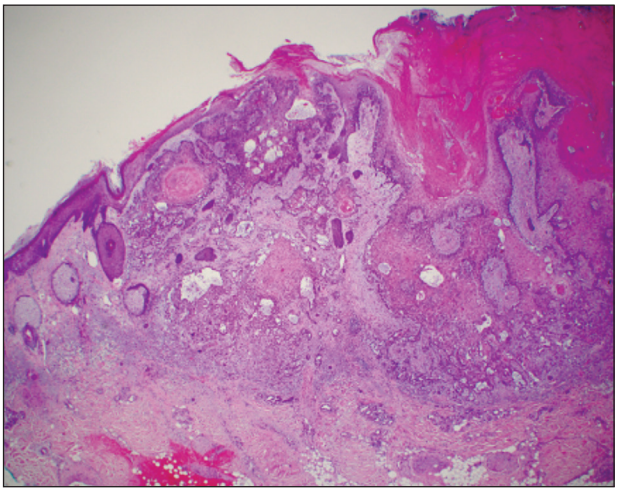

FIGURE 2. Squamous differentiation in the upper dermis and eccrine ductal differentiation in the deeper dermis in patient 2 (H&E, original magnification ×20).

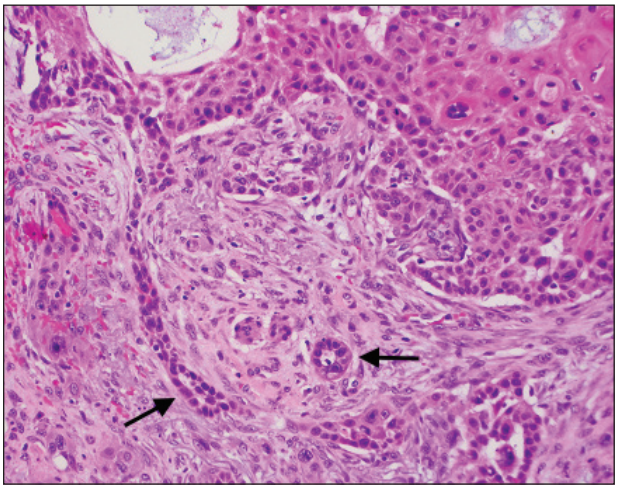

FIGURE 3. Squamous differentiation in the upper portion of the image and eccrine ductal differentiation (arrows) in the lower portion of image in patient 2 (H&E, original magnification ×200).

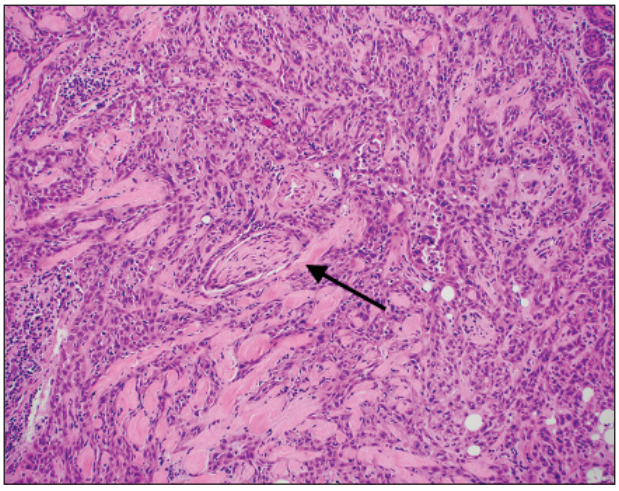

FIGURE 4. Squamous and eccrine ductal differentiation in the mid to deeper dermis in patient 2. Arrow indicates perineural invasion (H&E, original magnification ×100).

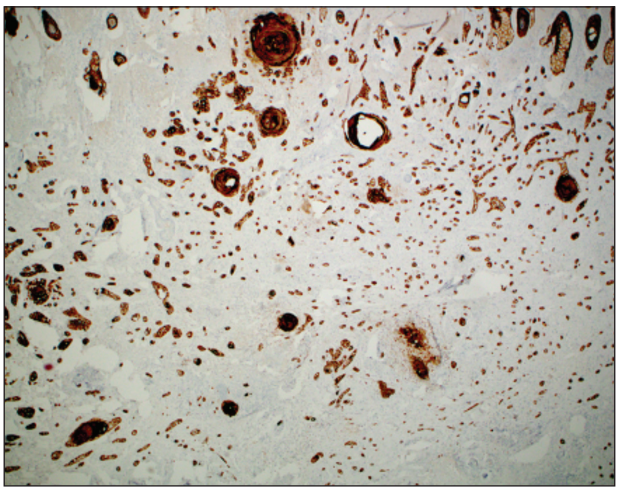

FIGURE 5. Thin strands of carcinoma in the mid to deeper dermis with squamous differentiation and eccrine ductal differentiation in patient 2, best noted by small lumens (cytokeratin AE1/AE3, original magnification ×40).

thorough inspection for PNI also should be performed, as this finding was present in all of 5 cases and in 34% of reported cases in our literature review.

The differential diagnosis for SEDC includes SCC, metastatic adenocarcinoma with squamoid features, and eccrine tumors, including eccrine poroma, microcystic adnexal carcinoma (MAC), and porocarcinoma with squamous differentiation. The combination of histologic features with the immunoexpression profile of carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), cytokeratin (CK) 5/6, and p63 can effectively exclude the other entities in the differential and confirm the diagnosis of SEDC.[1,3,4] While the diagnosis of SEDC relies on the specific histologic features of multiple surface attachments and superficial squamoid changes with deep ductular elements, immunohistochemistry can nonetheless be adjunctive in difficult cases. Positive immunohistochemical staining for CEA and EMA can help to highlight and delineate true glandular elements, whereas CK5/6 highlights the overall contour of the tumor, displaying more clearly the multiple epidermal attachments and the subtle infiltrative nature of the deeper components of invasive cords and ducts. In addition, the combination of CK5/6 and p63 positivity supports the primary cutaneous nature of the lesion rather than metastatic adenocarcinoma.[13,20] Other markers of eccrine secretory coils, such as CK7, CAM5.2, and S100, also are sometimes used for confirmation, some of which can aid in distinction from noneccrine sweat gland differentiation, as CK7 and CAM5.2 are negative in both luminal and basal cells of the dermal duct while being positive within the secretory coil, and S100 protein is expressed within eccrine secretory coil but negative within the apocrine sweat glands.[2,4,21]

The clinical findings from our chart review corroborated those reported in the literature. The mean age of SEDC in the 5 patients we reviewed was 81 years, and all cases presented on the head, consistent with the findings observed in the literature. Although 4 of our cases were male, there may not be a difference in risk based on sex as previously thought.[1] Our literature review revealed an almost equivalent percentage of male and female cases, with 52% being male.

Immunosuppression has been associated with an increased risk for SEDC. Our literature review revealed that approximately 9% (5/56) of cases occurred in immunosuppressed individuals. Two of these reported cases were in the setting of underlying chronic lymphocytic leukemia, 2 in individuals with a history of organ transplant, and 1 treated with azathioprine for myasthenia gravis.[2,4,10,12,13] Our chart review supported this correlation, as all 5 patients had a medical history potentially consistent with being in an immunocompromised state (Table). Notably, patient 5 represents a unique case of SEDC occurring in the setting of HIV. The patient had HIV for 33 years, with his most recent $CD4^+$ count of 794 mm^3 and HIV-1 RNA load of 35 copies/mL. Given that HIV-positive individuals may have more than a 2-fold increased risk of SCC, a greater degree of suspicion for SEDC should be maintained for these patients.[22,23]

The etiology of SEDC is controversial but is thought to be either an SCC arising from eccrine glands or a variant of eccrine carcinoma with extensive squamoid differentiation.[4,6,13,14,17,24] While SEDC certainly appears to share the proclivity for PNI with the malignant eccrine tumor MAC, it is simultaneously quite distinct, demonstrating nuclear pleomorphism and mitotic activity, both of which are lacking in the bland nature of MACs.[12,25]

The exact prevalence of SEDC is difficult to ascertain because of its frequent misdiagnosis and variable nomenclature used within the literature. Most reported cases of SEDC are mistakenly diagnosed as SCC on the initial shave or punch biopsy because of superficial sampling.

This also was the case in 4 of the patients we reviewed. In addition, there are reported cases of SEDC that were referred to by the investigators as cutaneous adenosquamous carcinoma (cASC), among other descriptors, such as ductal eccrine carcinoma with squamous differentiation, adnexal carcinoma with squamous and ductal differentiation, and syringoid eccrine carcinoma.[26-32] While the World Health Organization classifies SEDC as a distinct variant of cASC, which is a rare variant of SCC in itself, the 2 can be differentiated. Despite the similar clinical and histologic features shared between cASC and SEDC, the neoplastic aggregates in SEDC exhibit ductal differentiation containing lumina positive for CEA and EMA.[4] Overall, we favor the term *squamoid eccrine ductal carcinoma*, as there has recently been more uniformity for the designation of this disease entity as such.

It is unclear whether the high incidence of local recurrence (23% [13/56]) of SEDC reported in the literature is related to the treatment modality employed (ie, wide local excision) or due to the innate aggressiveness of SEDC.[1,3,5] The literature has shown that MMS has lower recurrence rates than other treatments at 5-year follow-up for SCC (3.1%–5%) and eccrine carcinomas (0%–5%).[33,34] Although studies assessing tumor behavior or comparing treatment modalities are limited because of the rarity and underrecognition of SEDC, MMS has been used several times for SEDC with only 1 recurrence reported.[4,13,17,24] Given that all 5 of the patients we reviewed required more than 1 Mohs stage for complete tumor clearance and none demonstrated evidence of recurrence or metastasis (Table), we recommend MMS as the treatment of choice for SEDC.

Conclusion

Squamoid eccrine ductal carcinoma is a rare but likely underdiagnosed cutaneous tumor of uncertain etiology. Because of its propensity for recurrence and metastasis, excision of SEDC with complete circumferential peripheral and deep margin assessment with close follow-up is recommended.

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