Ductal eccrine carcinoma with squamous differentiation: apropos a case

Sweat gland carcinomas are rare. Given this, they can pose a diagnostic challenge especially in shave biopsy specimens. We present a case of ductal eccrine carcinoma with extensive squamoid differentiation that was repeatedly misdiagnosed by multiple dermatopathologists as squamous cell carcinoma in the initial few biopsies. As the distinction between these two neoplasms is crucial to patient management, we highlight the histologic features of this uncommon entity to highlight the potential diagnostic pitfalls.


Eccrine carcinomas, a generic term encompassing malignancies originating from the eccrine glands, are relatively rare comprising less than 0.01% of all cutaneous tumors.1 Multiple subtypes of eccrine carcinomas exist and include ductal eccrine carcinoma, eccrine porocarcinoma, mucinous eccrine carcinoma, clear cell eccrine hidradenocarcinoma, adenoid cystic eccrine carcinoma, papillary digital eccrine carcinoma, microcystic adnexal carcinoma, carcinoma ex eccrine spiradenoma, malignant mixed tumor and mucocoeplidemoid eccrine carcinoma.2 Ductal eccrine carcinoma, the most common of these subtypes, typically presents as a nodule or plaque on the scalp, extremities or trunk of middle-aged or elderly individuals.3 Their clinical course is aggressive and is characterized by multiple local recurrences, perineural invasion and even metastasis to regional lymph nodes and distant organs.1,2 Squamous differentiation within ductal eccrine carcinoma, although extremely rare, has been previously reported.2–5 We present a case of ductal eccrine carcinoma, with squamous differentiation that was repeatedly misdiagnosed by more than one dermatopathologist as squamous cell carcinoma. While the histology of the initial shave biopsies did indeed show features typical of a ductal eccrine carcinoma, a unifying confounding feature was the presence of squamous differentiation – extensive enough to obscure the primary diagnosis in the initial few biopsies.

Case report
A 90-year-old man presented initially with a scabby nodule on the left forearm of several months duration. A scoop (deep shave) biopsy of the lesion was signed out as ‘moderately differentiated squamous cell carcinoma, invasive, extending to the tissue edges’ (Fig 1A,B). Immunohistochemical stains (performed retrospectively) showed positive staining of the lesional cells with CD15, carcino-embryonic antigen (CEA), cytokeratin (CK) 5/6 and epithelial membrane antigen (EMA) (not shown). While positive staining with the latter two markers is noncontributory in terms of ascertaining etiopathogenesis (positive in both adnexal and epithelial neoplasms), positive staining with the former two markers, i.e. CD15 and CEA is indeed supportive of an adnexal origin as they are typically negative in epithelial malignancies such as squamous cell carcinoma. Approximately a year later, the patient presented with a hard nodule at the site of the prior biopsy. Microscopic examination of a shave biopsy was again signed out as ‘squamous cell carcinoma, infiltrating, extending to the base of the biopsy’ (Fig 2A, B). Immunohistochemical stains (performed retrospectively) showed positive staining of the lesional cells with CD15, CEA, CK 5/6 and EMA (not shown). Six months later, the patient presented with a hard white nodule again at the site of the previous biopsies. A scoop (deep shave) biopsy
was performed and again signed out as ‘squamous cell carcinoma, infiltrating, extending to the deep edge of the biopsy.’ This time, a note mentioned ‘the lesion appears more differentiated in the superficial dermis and that in the deeper dermis numerous narrow strands of less differentiated cells infiltrating through collagen were present’ (Fig 3A, B). Immunohistochemical stains (performed retrospectively) showed positive staining of the lesional cells with CD15, CEA, CK 5/6 and EMA (not shown). Several months later, an excisional biopsy was performed of a nodular recurrence at the same site. Microscopic examination of the same showed strands and islands of basaloid cells with foci of ductal and squamoid differentiation embedded in mucinous stroma (Figs 4, 5A and 6). Vascular and perineural invasion were noted (Fig 5B). Immunohistochemistry showed positive staining of the lesional cells with CK 5/6, EMA (Fig 7), CEA and CD15 (Fig. 8). Negative staining was observed with CK7, CK 15 and S100 (not shown). A diagnosis of ductal eccrine carcinoma with squamous differentiation rather than squamous cell carcinoma, well-differentiated, infiltrating type (rendered in the prior biopsies) was favored and rendered this time. Criteria favoring the former included a combination of architecture (infiltrating strands and islands of basaloid cells in a mucinous stroma), morphology (foci of ductal differentiation present within atypical squamous islands) and immunohistochemical profile (positive staining with CD15 and CEA). A summary of the sign out of the different biopsies performed with sign-out diagnoses on each is listed in Table 1.

**Discussion**

While ductal eccrine carcinomas are relatively uncommon, ductal eccrine carcinomas with squamous differentiation are extremely rare. A review of the

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**Fig. 1.** Biopsy of lesion in 2003. (A) Low power (highlighting infiltrative nature of the lesion). (B) High power (highlighting foci of ductal differentiation present within atypical squamous islands).

**Fig. 2.** Biopsy of lesion in 2004. (A) Low power (highlighting infiltrative nature of the lesion). (B) High power (highlighting foci of ductal differentiation present within atypical squamous islands and mucinous stroma).

**Fig. 3.** Biopsy of lesion in early 2005. (A) Low power (highlighting infiltrative nature of the lesion). (B) High power (highlighting islands of basaloid cells with foci of ductal differentiation and mucinous stroma).
Ductal eccrine carcinoma with squamous differentiation

English literature shows a total of six cases reported to date.\(^2\)\(^{-}\)\(^5\) In all, evidence of squamous differentiation was evident in the form of scattered keratinizing squamous cysts or dyskeratotic cells.\(^2\)\(^{-}\)\(^5\) In none, however, was the squamous differentiation extensive enough, as in our case, to obscure the primary diagnosis.

Phenotypically distinct variants of ductal eccrine carcinomas that exist include one characterized by abundant fibromyxoid stroma, another characterized by spindled cells arranged concentrically and embedded in an amyloid-like stroma (‘myoepithelial’ differentiation), a basal cell carcinoma-like (‘basaloid’) variant and one, that the case presented best fits into, characterized by squamous metaplasia.\(^1\)

Histologic features of this last subtype, also called squamoid eccrine ductal carcinoma by some, include squamoid nests with dyskeratotic keratinocytes, ductal differentiation and mucinous stroma.\(^2\)\(^,\)\(^5\)

The significance of squamous differentiation in eccrine neoplasms has been a subject of much debate.\(^3\)\(^,\)\(^6\) While some believe that this differentiation delineates a subtype of eccrine neoplasms with a more aggressive biologic behavior, others believe that it is an incidental finding and one of no real clinical significance as it does not appear to have an impact on the biology of the disease.\(^3\)\(^,\)\(^6\) In support of the latter is the study by Kohda et al.,\(^5\) in which both benign and malignant eccrine neoplasms (46\% of 24 cases) had foci of squamous differentiation.

The histologic differential diagnosis of this lesion includes a porocarcinoma with squamous differentiation, microcystic adnexal carcinoma, primary squamous cell carcinoma with ductal differentiation or even a collision lesion of a squamous cell carcinoma and eccrine carcinoma. Porocarcinomas, however, typically present in acral locations and have a prominent intraepidermal component with dermal extensions of basaloid cells and broad anastomosing cords and columns – features not present in our case.\(^1\) While microcystic adnexal carcinoma also has squamoid features, these are typically stratified with a superficial component of keratinous cysts and a deeper component of smaller nests and strands of cells embedded in a markedly hyalinized stroma.\(^7\) The paucity of keratinous cysts

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Fig. 4. Scanning magnification of excisional biopsy in late 2005.

Fig. 5. Biopsy in late 2005 highlighting A) Squamous differentiation. B) Perineural invasion.

Fig. 6. Biopsy in late 2005 highlighting ductal differentiation within atypical squamous islands (A and B).
and absence of a hyalinized stroma makes this a less likely histologic possibility. Critical features crucial to diagnosing ductal eccrine carcinoma with squamous differentiation include a combination of architecture (infiltrating strands and islands of basaloid cells in a mucinous stroma) (Figs 1A, 2A, 3A and 4), morphology (foci of ductal differentiation present within atypical squamous islands) (Figs 5A and 6) and immunohistochemical profile [positive staining with CD15 and CEA (Fig 8) believed to be typical of neoplasms of eccrine origin].1,2,10 Apocrine differentiation, noted in some eccrine neoplasms was not observed in any of our biopsies, lending credence to the concept that apocrine and eccrine neoplasms are distinct in terms of ontogeny.9

In terms of management, given their rarity, limited information is available on these lesions, however, the general consensus is that wide surgical excision (with a view to achieving wide negative margins with or without Mohs’s technique) is the treatment of choice.1,10 Wide excision is recommended primarily because the size of these lesions tends to be underestimated based on the clinical appearance and also eccrine carcinomas, as exemplified by our case, tend to be locally infiltrating and have a propensity for perineural invasion. The recurrence rate for eccrine carcinomas is reported to be as high as 70–80%, and recurrence has been noted even in those cases where the margins were negative histologically.1,2,10 Although the follow-up period is relatively short in this case, 5 months following the final excisional biopsy, the patient does not have evidence of recurrent disease. Despite differing views on the frequency of metastasis seen in these tumors, surveillance with close follow up is recommended based on well-documented cases of metastasis to lymph nodes and distant organs.1,2,10 While no imaging studies were performed to exclude distant metastasis in our case, to date, there is no clinical evidence of lymph node involvement.

The distinction between these two neoplasms, i.e. ductal eccrine carcinoma with squamous differentiation and squamous cell carcinoma is not just semantics, but appears to be crucial to directing appropriate patient management. While conflicting evidence exists regarding their metastatic capabilities, the overwhelming consensus is that ductal eccrine carcinomas are locally more aggressive than squamous cell carcinoma.1,2,10 Regarding their metastatic potential, Wick and Swanson report that

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<tr>
<th>Date</th>
<th>Type of biopsy</th>
<th>Sign-out diagnosis</th>
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<tbody>
<tr>
<td>5/16/03</td>
<td>Scoop (deep shave) biopsy</td>
<td>Moderately differentiated squamous cell carcinoma, invasive</td>
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<tr>
<td>9/30/04</td>
<td>Shave biopsy</td>
<td>Squamous cell carcinoma, infiltrating</td>
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<td>4/29/05</td>
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<td>Squamous cell carcinoma, infiltrating</td>
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<td>12/05/05</td>
<td>Excisional biopsy</td>
<td>Ductal eccrine carcinoma with squamous differentiation</td>
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Fig. 7. Immunohistochemical staining profile of the lesional cells (late 2005 biopsy). A) CK 5/6. B) EMA.

Fig. 8. Immunohistochemical staining profile of the lesional cells favoring an eccrine origin (late 2005 biopsy). A) CEA. B) CD15.
up to 50% of all eccrine carcinomas (in comparison with 0.5% of squamous cell carcinomas) metastasize, while Santa Cruz categorize these neoplasms as having low malignant potential, but with the qualifying statement that these categories may need to be changed after more is known regarding these neoplasms.\textsuperscript{1,10}

In summary, we present a case of an uncommon cutaneous neoplasm – ductal eccrine carcinoma with squamous differentiation that was repeatedly misdiagnosed. Given their rarity, unfamiliarity with the histologic features of this neoplasm may have been a contributing feature, but we believe that a more relevant reason is the kind of biopsy that was repeatedly performed. Despite the fact that all the initial biopsies mentioned that the ‘squamous cell carcinoma’ extended to the tissue margins – the first three procedures performed were all shave or scoop biopsies! For those of us who are confined to making a ‘microscope-based’ diagnosis, what we see and say unfortunately hinges on what we get. Had an excisional biopsy been performed initially, perhaps this misdiagnosis may not have occurred at all.

References