Cutaneous signet-ring cell squamous cell carcinoma

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ABSTRACT

Cutaneous signet-ring cell squamous cell carcinoma (SRCSCC) is a rare variant, most commonly occurring in the head and neck. We report a case of a 66-year-old transgender woman with an ulcerated growing facial mass measuring $5.6 \times 4.0 \times 2.0$ cm. Histological analysis showed features consistent with SRCSCC. Immunohistochemical analysis showed positive staining for high-molecular-weight cytokeratin, estrogen receptor (1-2+ in 10%), E-cadherin (mostly positive with partial loss), and p40 and negative staining for Ber EP-4, cytokeratin 7, low-molecular-weight cytokeratin, mucicarmine, Alcian blue PAS, HER2, and MUC4. The tumor had invaded the perineurium, lymphovascular spaces, and subcutaneum. Additionally, microsatellite instability testing was negative. This case adds to the limited knowledge of this poorly characterized entity.

KEYWORDS Signet-ring cell squamous cell carcinoma; signet squamous cell

Signet-ring cell squamous cell carcinoma (SRCSCC) is an uncommon variant of squamous cell carcinoma (SCC) with only 15 prior cases reported to date to the authors' knowledge. Histologically, the neoplasm has the characteristic features of keratin pearls in addition to signet ring morphology. In the gastrointestinal tract, a signet ring morphology portends a poor prognosis; however, it is unknown if this is also true in cutaneous SRCSCC. Immunohistochemical stains for MUC4, HER2, and E-cadherin were done to evaluate whether there is a similar protein distribution to that of gastrointestinal signet ring tumors,¹ which may suggest analogous aggressive behavior.

CASE PRESENTATION

A 66-year-old transgender Caucasian woman presented with a 3-month history of weight loss and a growing mass involving the skin overlying the left parotid. Limited past medical history included skin cancer (unknown location and histologic type), tobacco use (40 pack-years), and heavy alcohol use. Clinical exam identified a 3 cm ulcerated mass involving the left cheek with left-sided regional adenopathy (level 1 and 2 A). Parotidectomy with left modified neck dissection

was performed. Grossly, the resection revealed a $5.6 \times 4.0 \times 2.0$ cm red-tan nodular mass with central ulceration involving the overlying skin.

Sections of tumor revealed a contiguous biphasic carcinoma, which focally extended from the overlying epithelium (*Figure 1a*). There were areas of predominantly irregularly shaped pseudoglandular structures associated with keratinization and intraluminal eosinophilic material (*Figure 1b*) as well as a solid vaguely nested architecture. Both components had conspicuous individual cells with abundant clear cytoplasm and eccentrically displaced nuclei, recapitulating signet ring cells (*Figure 1c*). Immunohistochemistry stains for p40 (*Figure 2a*) and high-molecular-weight keratin were diffusely positive. Ber EP-4, cytokeratin 7, low-molecular-weight cytokeratins, mucicarmine, Alcian blue PAS, and HER2 (*Figure 2b*) were negative by immunohistochemistry. MUC4 was focally positive in dysplastic surface epithelium but diffusely negative within the tumor (*Figure 2c*). E-cadherin was mostly positive, with focal partial loss (*Figure 2d*). Estrogen receptor was positive (1-2+ in 10%). Polymerase chain reaction testing for microsatellite instability was negative.

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Figure 1. (a) Overlying squamous epithelium transitioning into invasive component, 40 $\times$. (b) Cleared out cells visible adjacent to invasive squamous component, 100 $\times$. (c) Glandular-like structures with signet ring cells, 200 $\times$.

DISCUSSION

In the initial case report of cutaneous SRCSCC, Cramer and Heggeness wrote that “better documentation of additional cases will be necessary before it can be stated with certainty that a signet-ring pattern is a reliable marker for aggressive behavior in squamous cell carcinoma.”² Subsequent published case reports have shown conflicting

Figure 2. (a) p40 positive staining, 40 $\times$. (b) HER2 negative staining, 200 $\times$. (c) MUC4 negative staining, 200 $\times$. (d) E-cadherin positive staining (focal loss not pictured), 200 $\times$.

evidence of whether cutaneous SRCSCC is indeed linked to aggressive tumor behavior (*Table 1*).^{2–9}

Previous investigators have hypothesized that signet-ring morphology may be due to interactions between basolateral ErbB2/ErbB3 and apical MUC4.¹ This interaction is postulated to be due to the loss of E-cadherin, which prevents the interaction between the two proteins by assisting in cell polarization.¹ In the current case, staining for E-cadherin was positive with partial loss, and HER2 (ErbB2) was negative, as was MUC4. It is unknown whether the negative staining reflects a true absence of MUC4 and/or HER2 or is due to a conformational protein change preventing anti-body binding.

Lin et al¹⁰ showed that when examining head and neck SCC cases, microsatellite instability was correlated to margin recurrence. In our case, the tumor was microsatellite stable and clinically there was no recurrence 6 months postoperatively.

Oral SCC has been shown to express estrogen receptor (ER α),¹¹ with some evidence that estrogen is involved with the invasive properties of head and neck SCC.¹² Tamoxifen, a selective estrogen receptor modulator, has been shown to inhibit growth of a gingival SCC cell line.¹¹ Assuming our case's primary site is skin and not the upper aerodigestive tract, loss of estrogen receptor in the majority of cells supports the hypothesis that estrogen may have a potential role in protecting against cutaneous SCC. Of note, oral malignancy was on the initial differential diagnosis; however, histologically, the parotid gland was not involved and adenocarcinoma was ruled out by mucicarmine and Alcian blue PAS negativity.

Table 1. Summary of published cases of cutaneous signet-ring cell squamous cell carcinoma

First author/year	Age (years)/sex	Location	Size (cm)	Additional clinical history	Procedure	Outcome
Cramer (1989) ²	69	Forehead and scalp	—	Arising from AK with multiple recurrences	—	LN metastasis and death
McKinley (1998) ³	50 M	L lateral neck	0.6	EtOH use, history of SCC and BCC	Shave biopsy and excision	—
Bastian (1999) ⁴	79 F	R cheek	—	—	—	—
Bastian (1999) ⁴	82 M	L temple	—	—	—	—
Bastian (1999) ⁴	83 M	R ear	—	—	—	—
Bastian (1999) ⁴	80 M	Forehead	—	—	—	—
Bastian (1999) ⁴	87 M	Frontal scalp	—	—	—	—
Bastian (1999) ⁴	—	—	—	—	—	—
Bastian (1999) ⁴	76 M	Forehead	—	—	—	—
Proia (2006) ⁵	93 F	R lower eyelid	1.7 × 1.4 × 0.9	HTN, arthritis, pseudoexfoliation syndrome	Resection with graft flap	—
El Demellawy (2011) ⁶	84 F	Upper lip	—	Previous punch biopsy with SCC	Excisional biopsy	Died at 1 y (Alzheimer's disease)
Lortscher (2012) ⁷	67 M	L lateral canthus	1.5	Hx lung cancer	Mohs surgery	NSR (13-mo f/u)
Nakajima (2013) ⁸	83 M	Back of the finger	3.1 × 2.1	—	Excision with skin graft	NSR (3-y f/u)
Wang (2016) ⁹	78 F	R thigh	5 × 3 × 1.5	Diabetes mellitus type 2 for 30 y	Resection	—
Our case	66 transgender F	Skin over L parotid	5.6 × 4.0 × 2.0	Hx EtOH, tobacco, skin cancer (unknown type); weight loss	Wide local excision, L parotidectomy and neck dissection	NSR 6 mo postop

AK indicates actinic keratosis; BCC, basal cell carcinoma; EtOH, alcohol; f/u, follow-up; HTN, hypertension; Hx, history of; L, left; LN, lymph node; met, metastasis; NSR, no signs of recurrence; R, right; SCC, squamous cell carcinoma.

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