UC Davis
Dermatology Online Journal

Title
Signet-ring squamous cell carcinoma: a report of a rare variant and review of the literature

Permalink
https://escholarship.org/uc/item/4dg131j1

Journal
Dermatology Online Journal, 26(5)

Authors
Haghayeghi, Koorosh
Telang, Gladys
Robinson-Bostom, Leslie

Publication Date
2020

DOI
10.5070/D3265048777

Copyright Information
Copyright 2020 by the author(s).This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at https://creativecommons.org/licenses/by-nc-nd/4.0/

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Signet-ring squamous cell carcinoma: a report of a rare variant and review of the literature

Koorosh Haghayeghi[1] MD PharmD, Gladys Telang[2] MD, Leslie Robinson-Bostom[2] MD

Affiliations: [1]Department of Pathology, Warren Alpert Medical School of Brown/Rhode Island Hospital, Providence, USA, [2]Department of Dermatology, Warren Alpert Medical School of Brown/Rhode Island Hospital, Providence, USA

Corresponding Author: Koorosh Haghayeghi MD PharmD, Department of Pathology and Laboratory Medicine, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903, Email: hkoorosh@gmail.com

Abstract

Signet-ring squamous cell carcinoma is a rare histological subtype of squamous cell carcinoma. The distinct morphologic appearance of this variant can mimic metastatic adenocarcinoma and impose a diagnostic challenge. Unlike its glandular counterpart, signet-ring cell variant of squamous cell carcinoma has a poorly characterized histopathogenesis with no known prognostic implication. We describe an additional case and review the literature.

Keywords: squamous cell carcinoma, signet ring cell

Introduction

Numerous histopathologic variants of cutaneous squamous cell carcinomas (SCC) have been described. Low-grade variants include keratoacanthoma and verrucous SCC whereas more aggressive subtypes include spindle cell SCC and adenosquamous carcinoma. Some uncommon variants include clear cell SCC and lymphoepithelioma-like carcinoma of the skin [1]. Signet ring cell squamous cell carcinoma (SRSCC) is a rare variant of cutaneous SCC with few cases reported to date [2-8].

Case Synopsis

A 71-year-old immunocompetent man with a history of numerous keratinocytic carcinomas presented with a non-healing ulcerated lesion of left ear. Examination revealed a 1.5×1.0cm pink ulcerated plaque in the left conchal bowl (**Figure 1**). Punch biopsy showed an ulcerated tumor extending from the epidermis, composed of pleomorphic hyperchromatic keratinocytes arranged in lobules and infiltrating cords (**Figure 2**). The atypical keratinocytes showed compact peripheral nuclear localization with centrally-located intracytoplasmic vacuoles consistent with signet ring morphology (**Figure 3A, B**). The signet ring cells stained positive for keratin cocktail and were negative for S-100, carcinoembryonic antigen, and calponin. Mucicarmine and Alcian blue were negative for intracytoplasmic mucin. Signet cells stained only focally with periodic acid–Schiff and periodic acid–

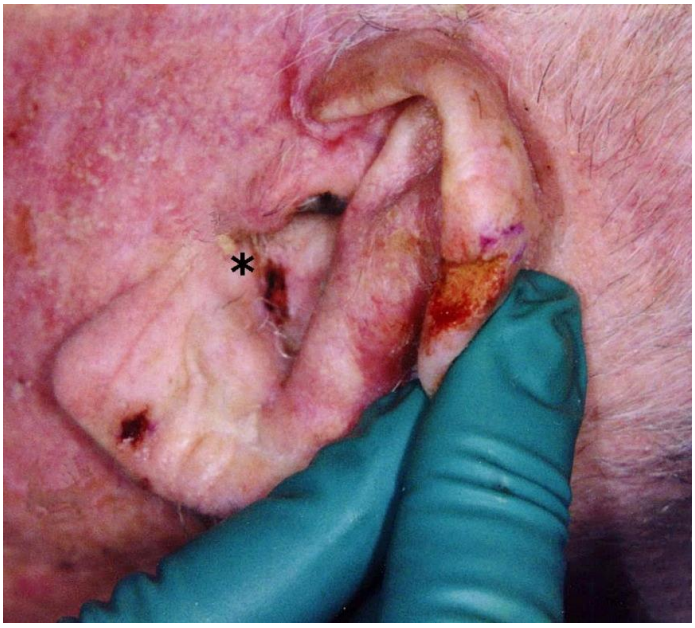

Figure 1. *Clinical appearance of the left conchal bowl lesion (*) and helix with ulcerated plaque.*

Schiff–diastase stains (**Figure 3C)**. Perineural invasion was not identified. Patient underwent Mohs micrographic surgery.

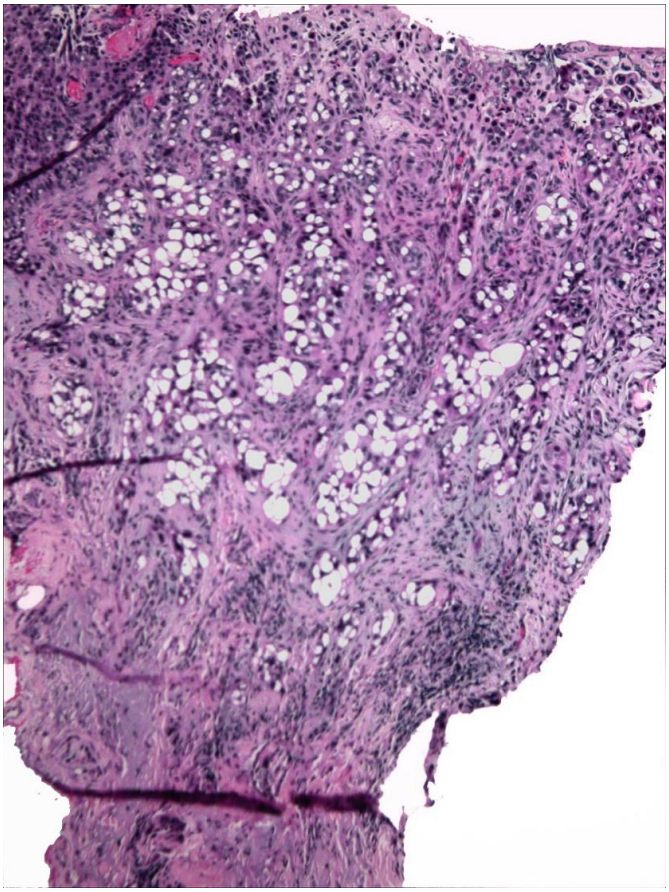

Figure 2. *Low power view of the conchal bowl lesion showing cords of keratinocytes with cytoplasmic vacuolization extending down the dermis (H&E, 100×).*

Case Discussion

Signet ring squamous cell carcinoma is a rare histological variant originally described by Cramer and Heggeness in 1989 that exhibits a group of monodispersed cells with concentric rings originating from a field of actinic keratosis [2]. To date, a total of 14 cases have been reported with a mean age of 76 (age range: 50-84 year) affecting males and females in approximately 3:1 ratio (**Table 1**). The head and neck region has been most commonly implicated (85.7%, 12/14) and in up to 92.8% of the cases (13/14), SRSCC manifested in sun-exposed anatomical sites. The intracytoplasmic vacuoles were negative for mucin in all of the cases (0/14), whereas PAS stain was positive in 23% of the cases (3/13). Despite the aggressive clinical behavior of SRSCC reported by Cramer and Heggeness, this

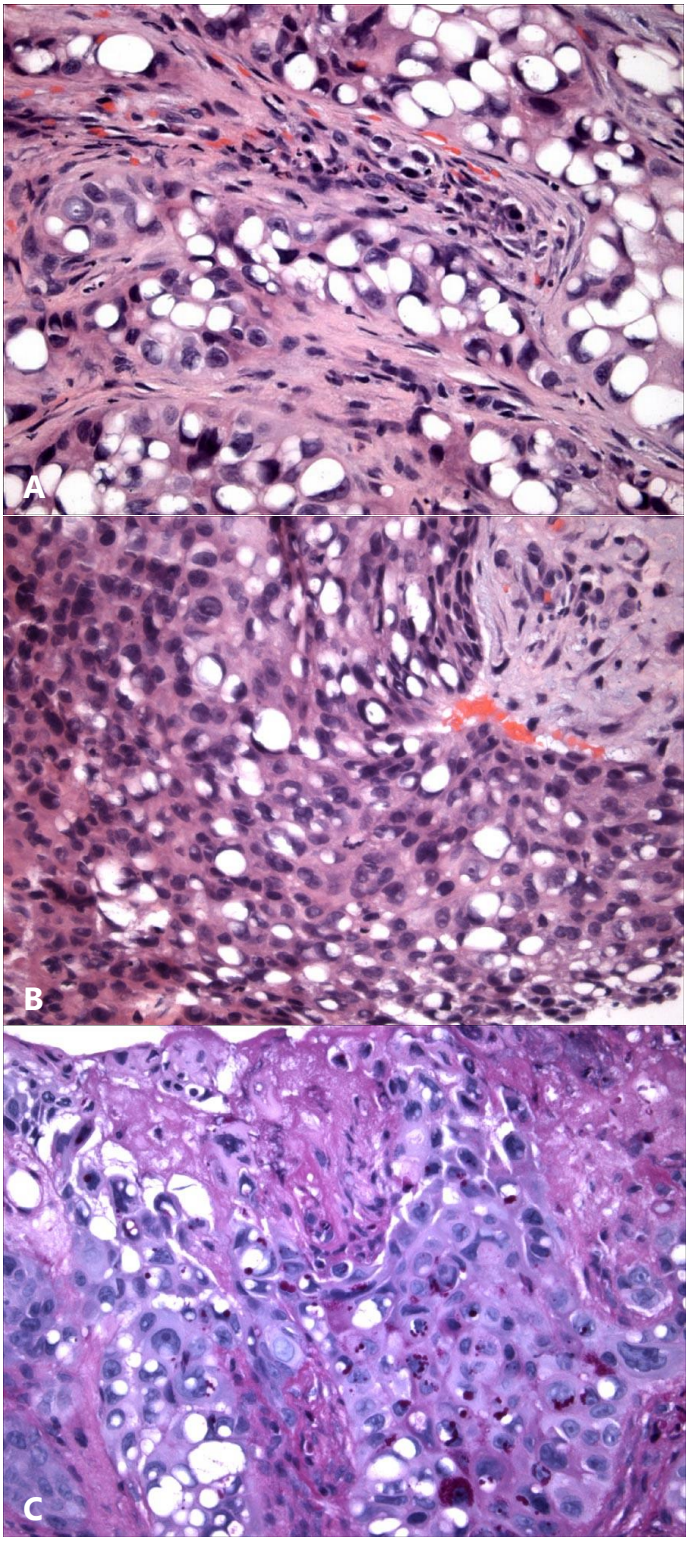

Figure 3. ***A)*** *and* ***B)*** *High power view of the lesion exhibiting signet ring morphology (H&E, 400×).* ***C)*** *PAS with diastase stain showing only focal positivity of signet ring cells (PAS stain, 400×).*

unusual variant appears to bear no specific prognostic significance.

Signet ring carcinomas are characterized by eccentrically-located nucleus compressed against the cell periphery by accumulation of cytoplasmic vacuole or substance such as mucin or glycogen [5]. Neoplasms with signet ring morphology were traditionally presumed to be exclusively glandular with aggressive clinical behavior [10, 11]. Non-cutaneous signet ring neoplasms have been described in thoracic [12], gastric [13], ovarian [14], and mammary proliferations [15] with variable demographics and clinical course. A number of primary cutaneous neoplasms with signet ring features have also been reported in basal cell carcinoma [16], melanoma [17], dermatofibroma [18], epithelioid angiosarcoma [19], cutaneous lymphoma [20], and primary cutaneous signet ring carcinoma of the eyelid [21]. Owing to the diversity of neoplasms exhibiting signet ring morphology, accurate identification of these tumors can be diagnostically challenging. Other histopathological cutaneous mimics of SRSCC include trichilemmal carcinoma, sebaceous carcinoma, and clear cell variants of eccrine carcinoma, melanoma, and atypical fibroxanthoma.

Biologically, cytoplasmic vacuolization in mammalian cells is a morphologic phenomenon related to a wide range of etiologies including exposure to bacterial, viral, or chemical agents [22]. Pore-forming protein toxins of bacteria have been shown to generate vacuolization of different organelles including endosomes, lysosomes, and endoplasmic reticulum. In virally induced instances, vacuolization results from dysfunction of endoplasmic reticulum or endosomal-lysosomal organelles caused by viral capsids [23]. In some signet-ring carcinomas including adenocarcinomas, the intracytoplasmic vacuolizations are specifically caused by accumulation of substances such as mucin, glycogen, and intermediate filaments [24]. In all the SRSCC cases reported to date, only a small percentage are associated with glycogen (21.4%) and none are associated with mucin accumulation (**Table 1**).

Conclusion

In summary, we report an exceedingly rare case of SRSCC in a sun-exposed skin of an elderly patient with extensive sun damage. The mucin negativity and minimal glycogen staining seen in our case supports the prospect of other cytoplasmic processes or processing artifact to be involved in formation of signet ring variant of cutaneous squamous cell carcinoma. These changes do not appear to have impact on prognosis but may cause diagnostic difficulty.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. *Yanofsky VR, Mercer SE, Phelps RG. Histopathological variants of cutaneous squamous cell carcinoma: a review. J Skin Cancer. 2011;2011:210813. [PMID: 21234325].*
2. *Cramer SF and Heggeness LM. Signet-ring squamous cell carcinoma. Am J Clin Pathol. 1989;91:488-91.[PMID: 2467552].*
3. Mckinley E, Valles R, Bang R, Bocklage T. Signet-ring squamous cell carcinoma: a case report. *J Cutan Pathol.* 1998;25:176-81.[PMID: 9550318].
4. El demellawy D, Onuma K, Alowami S. Signet ring squamous cell carcinoma--the forgotten variant: case report and review of the literature. *J Cutan Pathol.* 2011;38:306-8. [PMID: 19751229].
5. Lortscher DN, Satter EK, Romero LS. Signet ring-like cells: no longer a "signature" of glandular differentiation. *Dermatol Online J.* 2012;18:3. [PMID: 22559018].
6. Bastian BC, Kutzner H, Yen Ts, Leboit PE. Signet-ring cell formation in cutaneous neoplasms. *J Am Acad Dermatol.* 1999;41:606-13. [PMID: 10495385].
7. Bartoš V, Kullová M. Cutaneous squamous cell carcinoma in situ with extensive clear cell change - A report of two cases. *Our Dermatol Online.* 2017;8:311-314. [DOI: 10.7241/ourd.20173.89].
8. Wang NR, Wang MM, Zhou L. Cutaneous clear cell/signet-ring cell squamous cell carcinoma arising in the right thigh of a patient with type two diabetes: combined morphologic, immunohistochemical, and etiologic analysis. *Diagn Pathol.* 2016;11:36. [PMID: 27066782].
9. Sirjusingh L, Imhagwe G. Signet ring squamous cell carcinoma – a case report. *Pathology J.* 2019;51(Suppl 1): S99. [DOI: 10.1016/j.pathol.2018.12.269].

10. Huh CW, Jung DH, Kim JH. Signet ring cell mixed histology may show more aggressive behavior than other histologies in early gastric cancer. *J Surg Oncol.* 2013;107:124-9. [PMID: 22991272].
11. Kang H, O'connell JB, Maggard MA, Sack J, Ko CY. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. *Dis Colon Rectum.* 2005;48:1161-8. [PMID: 15868237].
12. Roxas, R. B. S., Bernardo, M. C. F., Jacoba, A. P., Lim-Dy, J., Alvarado, A. C, et al. (2019). Primary Thymic Signet Ring Cell Adenocarcinoma: A Currently Unrecognized Variant. *Intl J Surg Path 27*, 315–321. [PMID: 30259765].
13. Dobrițoiu M, Stepan AE, Vere CC, Simionescu CE. Evaluation of Gastric Carcinomas Histological Patterns in Relation to Tumors Aggressiveness Parameters. *Curr Health Sci J.* 2018;44:342-346. [PMID: 31123609].
14. Chen PH, Hui P, Buza N. Bilateral Signet-Ring Stromal Tumor of the Ovary: A Case Report With Next-generation Sequencing Analysis and FOXL2 Mutation Testing. *Int J Gynecol Pathol.* 2019. [PMID: 30676431].
15. Singh K, Diazgomez B, Wang Y, Ou J, Hansen K. Invasive Lobular Carcinoma With Extracellular Mucin: Not All Mucinous Mammary Carcinomas Are Ductal!. *Int J Surg Pathol.* 2019;27:55-58. [PMID: 31695973].
16. Aroni K, Lazaris AC, Nikolaou I, Saetta A, Kavantzas N, Davaris PS. Signet ring basal cell carcinoma. A case study emphasizing the differential diagnosis of neoplasms with signet ring cell formation. *Pathol Res Pract* 2001; 197:853-856. [PMID: 11795835].
17. Kocovski L, Alowami S. Signet-ring cell melanoma: a potential diagnostic pitfall. *Am J Dermatopathol.* 2014;36:985-8. [PMID: 25321087].
18. Garrido-Ruiz MC, Carrillo R, Enguita AB, Peralto JL. Signet-ring cell dermatofibroma. *Am J Dermatopathol* 2009; 31:84-87. [PMID: 19155733].
19. Salviato T, Bacchi CE, Luzar B, Falconieri G. Signet ring cell angiosarcoma: a hitherto unreported pitfall in the diagnosis of epithelioid cutaneous malignancies. *Am J Dermatopathol.* 2013;35:671-5. [PMID: 23538897].
20. Papalas JA, Kulbacki EL, Park HK, Howell ER. Signet ring cell primary cutaneous CD30+ lymphoproliferative disorder presenting as a monomorphic T-cell posttransplant lymphoproliferative disease. *Am J Dermatopathol.* 2012;34:e94-6. [PMID: 22534639].
21. Requena L, Prieto VG, Requena C, et al. Primary signet-ring cell/histiocytoid carcinoma of the eyelid: a clinicopathologic study of 5 cases and review of the literature. *Am J Surg Pathol.* 2011;35:378-91. [PMID: 21317710].
22. Shubin AV, Demidyuk IV, Komissarov AA, Rafieva LM, Kostrov SV. Cytoplasmic vacuolization in cell death and survival. *Oncotarget.* 2016;7:55863-55889. [PMID: 27331412].
23. Patient R, Hourioux C, Sizaret P-Y, Trassard S, Sureau C, et al. Hepatitis B virus subviral envelope particle morphogenesis and intracellular trafficking. *J Virol.* 2007;81:3842–3851. [PMID: 17267490].
24. Kim do Y, Cho SB, Chung KY, Kim YC. Clear cell basal cell carcinoma with sialomucin deposition. *Yonsei Med J.* 2006; 47:870-872. [PMID: 17191318].

Table 1. *Clinical and histopathologic characteristics of reported cases of signet ring squamous cell carcinoma.*

Case	Age/Sex	Location	Mucin	PAS	Reference
1	69 M	Forehead	Negative	Positive	[2]
2	50 M	Neck	Negative	Focal	[3]
3	84 F	Upper lip	Negative	Negative	[4]
4	67 M	Canthus	Negative	Negative	[5]
5	79 F	Cheek	Negative	Negative	[6]
6	82 M	Temple	Negative	Negative	[6]
7	83 M	Ear	Negative	Negative	[6]
8	80 M	Forehead	Negative	Negative	[6]
9	87 M	Frontal scalp	Negative	Negative	[6]
10	76 M	Forehead	Negative	Negative	[6]
11	78 M	Cheek	Negative	Weak	[7]
12	79 F	Neck	Negative	Negative	[7]
13	78 F	Thigh	Negative	Septal only	[8]
14	78 M	Ear	NA	NA	[9]