

Acantholytic squamous cell carcinoma is usually associated with hair follicles, not acantholytic actinic keratosis, and is not “high risk”: Diagnosis, management, and clinical outcomes in a series of 115 cases

Toru Ogawa, MD, PhD,^a Maija Kiuru, MD, PhD,^{a,b} Thomas H. Konia, MD,^{a,b} and Maxwell A. Fung, MD^{a,b}
Sacramento, California

Background: Acantholytic squamous cell carcinoma (aSCC) is regarded as a high-risk variant of cutaneous squamous cell carcinoma (SCC). Acantholytic actinic keratosis (aAK) has been regarded as a precursor risk factor for aSCC. However, supporting evidence is limited.

Objective: We sought to document clinical features, histologic features, management, and outcomes in a series of aSCC cases.

Methods: Definitions of aSCC, aAK, and aSCC arising in association with aAK were applied to a consecutive series of aSCC cases. Clinical characteristics and outcomes were obtained from electronic medical records.

Results: Of 115 aSCC cases (103 patients, mean age 71.8 years), actinic keratosis was present in 23% (27/115) but only 7.8% (9/115) exhibited associated aAK. Ten cases (10/115, 9%) fulfilled strict histologic criteria for follicular SCC as previously defined, but 50 of 115 (43%) of our aSCC cases exhibited predominant involvement of follicular epithelium rather than epidermis. Clinical outcome (median follow-up, 36 months) was available in 106 of 115 (92%). One patient experienced regional extension (parotid), and 1 patient experienced a local recurrence (nose). No disease-related metastases or deaths were documented.

Limitations: This was a single-institution retrospective study from the United States.

Conclusions: The presence of acantholysis in cutaneous SCC does not specifically confer aggressive behavior, a finding that may inform clinical practice guidelines. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2016.09.024>.)

Key words: acantholysis; acantholytic actinic keratosis; cutaneous oncology; dermatopathology; follicular squamous cell carcinoma; nonmelanoma skin cancer; outcomes; prognosis; squamous cell carcinoma.

Squamous cell carcinoma (SCC) is the second most common form of skin cancer and most common cause of death from nonmelanoma

skin cancer.¹⁻³ Acantholytic SCC (aSCC) is a distinctive histologic subtype of SCC first described by Lever⁴ in 1947 as a form of sweat gland carcinoma.

From the Departments of Dermatology^a and Pathology and Laboratory Medicine,^b University of California Davis.

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Correspondence to: Maxwell A. Fung, MD, Department of Dermatology, University of California Davis, 3301 C St, Suite 1400, Sacramento, CA 95816. E-mail: maxfung@ucdavis.edu.

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Synonyms in the literature include adenoid SCC (adenoacanthoma of Lever) or pseudoglandular SCC. aSCC also encompasses the rare histologic subsets of pseudovascular SCC, pseudoangiosarcomatous SCC, and small-cell SCC.^{1,5-10} aSCC has long been regarded as an intermediate- to high-risk form of SCC.^{1,11} A frequently cited reference in support of the high-risk nature of aSCC is the case series published in 1989 by Nappi and coworkers,¹¹ who reported that 19% of their 49 patients developed fatal metastases. Case reports and small case series have also documented aggressive behavior.¹²⁻¹⁵ However, comparatively lower mortality was reported by other institutions, with the largest published series of 155 patients by Johnson and Helwig¹⁶ reporting only 3% mortality.¹⁷ Garcia and Crowson¹⁸ recently questioned whether aSCC is truly an aggressive tumor. However, aSCC remains classified as a high-risk form of SCC in the 2016 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for cutaneous SCC (v1.2016)¹⁹ and current clinical practice guidelines from the European Organization for Research and Treatment of Cancer (EORTC).²⁰ The emerging role for sentinel lymph node biopsy for high-risk SCC magnifies the importance of accurate risk stratification for cutaneous SCC.³

As a histologic variant of SCC, the diagnosis of aSCC is necessarily a histologic diagnosis. aSCC is regarded as a rare variant of cutaneous SCC. Although diagnosing aSCC has not historically been controversial, there are no validated or standardized minimal criteria for the diagnosis of aSCC. Similarly, a definition of aSCC arising in association with acantholytic actinic keratosis (aAK) (or SCC arising in association with actinic keratosis [AK] generally) has not been proposed. Moreover, acantholysis has been documented in other variants of SCC, including follicular SCC,²¹ spindle-cell SCC,^{22,23} and even rarely as an incidental finding in keratoacanthoma (KA),²⁴ despite the fact that some investigators definitionally exclude KA if acantholysis is present.²⁵ Cassarino and colleagues,¹ in their comprehensive review of the histopathology of cutaneous SCC, characterized aSCC as exhibiting intratumoral acantholysis “At least focally, but often extensively....” In

the largest series to date, Johnson and Helwig¹⁶ noted that aSCC tumors typically arose from the upper portion of follicular outer root sheath, but characteristic involvement of follicular epithelium was not mentioned in subsequent descriptions of aSCC^{11,26} or follicular variants of SCC.^{21,27,28} Of note, Carr and coworkers²⁹ identified a central acantholytic mucin pool in over half of their series of 30 cases of follicular SCC and contrasted this finding with the characteristic suprabasilar acantholysis that typifies aAK and aSCC. Multiple authorities state that aSCC is often present in association with aAK.³⁰⁻³² AK is a widely accepted precursor to, and risk factor for, cutaneous SCC,³³ with aAK representing the presumptive precursor of aSCC.¹⁶ However, a formal evaluation of the degree of association between aAK and aSCC has not been reported. Similar

to aSCC, aAK is a rare variant of AK, representing less than 5% of 402 AKs in the series of Carapeto and Garcia-Perez³⁴ and 10% in the series of 300 AKs by Pensley and Sims.³⁵

In this study, we developed and uniformly applied definitions of aSCC, aAK, and aSCC arising in association with AK/aAK to facilitate review of the associated clinical features, management, and clinical outcomes in aSCC.

METHODS

A natural language search for “acantholytic squamous cell carcinoma” and “squamous cell carcinoma, acantholytic” was performed on the database of an academic medical center’s dermatopathology laboratory to identify a consecutive sampling of tissue specimens with a diagnosis of aSCC (2006-2011). Study material was fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin-eosin for histologic diagnosis. All cases were originally interpreted by a board-certified dermatopathologist.

Study definitions were developed to be compatible with existing descriptions in published studies and reviews.^{1,5,11,16,17} The study definitions were as follows.

Acantholytic SCC

This was defined as SCC containing atypical keratinocytes associated with loss of cohesion

CAPSULE SUMMARY

- Acantholytic actinic keratosis has been regarded as a precursor of acantholytic squamous cell carcinoma (SCC), a reportedly aggressive high-risk form of SCC.
- In this series of 115 cases, acantholytic SCC was more commonly associated with follicular epithelium than acantholytic actinic keratosis and did not display aggressive behavior.
- The presence of acantholysis, per se, in cutaneous acantholytic SCC does not confer aggressive clinical behavior.

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