Histopathologic assessment of depth of follicular invasion of squamous cell carcinoma (SCC) in situ (SCCis): Implications for treatment approach

Sean R. Christensen, MD, PhD,[a] Jennifer M. McNiff, MD,[a] Alicia J. Cool, MD,[a] Sumaira Z. Aasi, MD,[b] Allison M. Hanlon, MD, PhD,[a] and David J. Leffell, MD[a]
New Haven, Connecticut, and Palo Alto, California

Background: Squamous cell carcinoma in situ (SCCis) has been reported to involve the hair follicle epithelium. Deep follicular invasion is often cited as a cause of treatment failure.

Objective: We sought to define the frequency and the depth of hair follicle invasion by SCCis.

Methods: The study included both a retrospective review of intraoperative pathology specimens from 42 SCCis cases treated with Mohs micrographic surgery and a prospective evaluation of serially sectioned SCCis tissue from 12 additional patients. Pathology specimens were analyzed for follicular invasion of SCCis.

Results: SCCis invasion of the superficial hair follicle infundibulum was observed in 61.3% to 87.5% of cases in the 2 cohorts, whereas invasion of the isthmus and lower follicle was observed in only 8.3% to 12.5% of cases. In most tumors the depth of follicular invasion was comparable with the thickness of the surrounding epidermis. The maximum observed depth of follicular invasion was 0.82 mm.

Limitations: The study was performed on a limited number of cases referred for surgery at a single institution.

Conclusions: Although SCCis invasion of the upper hair follicle infundibulum is common, deep invasion below the level of the surrounding epidermis is rare. This may have implications for optimal therapy of this condition. (J Am Acad Dermatol 2016;74:356-62.)

Key words: adnexal structure; Bowen disease; cutaneous; depth; hair follicle; histology; Mohs micrographic surgery; pathology; sebaceous gland; squamous cell carcinoma in situ.

Cutaneous squamous cell carcinoma (SCC) in situ (SCCis) (also known as Bowen disease) is an intraepidermal malignancy characterized by cellular atypia and disordered maturation of the full thickness of the epidermis without dermal invasion or breaching of the basement membrane.[1,2] SCCis typically presents in the sixth to ninth decade of life as a slowly growing, scaly, red plaque on sun-exposed skin. Although the tumor does not exhibit a significant gender bias, SCCis in men favors the ears and scalp, whereas SCCis in women favors the cheeks and lower aspect of legs.[3] It has been

Abbreviations used:

ICC:	intraclass correlation coefficient
SCC:	squamous cell carcinoma
SCCis:	squamous cell carcinoma in situ

From the Departments of Dermatology at Yale University School of Medicine, New Haven,[a] and Stanford University School of Medicine, Palo Alto.[b]

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Reprint requests: Sean R. Christensen, MD, PhD, Department of Dermatology, Yale University School of Medicine, 40 Temple St, Suite 5A, New Haven, CT 06510. E-mail: sean.christensen@yale.edu.

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reported that SCCis has a 3% to 10% risk of progression to invasive SCC,[4-8] although this may be an overestimate caused by publication bias.[9,10]

SCCis is commonly encountered on skin with a high density of hair follicles. A defining pathologic feature of SCCis is malignant involvement of the entire interfollicular epidermis and frequent involvement of epidermal-derived adnexal structures such as hair follicles.[2,11] The lower portion of human terminal follicles may extend more than 4 mm in depth[12] and is hypothesized to serve as a deep reservoir of SCCis. It has been repeatedly suggested in the literature that deep follicular invasion of SCCis is a direct cause of treatment failure or tumor recurrence when superficial destructive treatments are used.[1,4,8,11,13-16] Despite these claims, the true frequency and depth of follicular invasion in SCCis has not been systematically examined and this aspect of the disease remains undefined.

CAPSULE SUMMARY

- Cutaneous squamous cell carcinoma in situ is reported to invade hair follicles and adnexa.
- Squamous cell carcinoma in situ typically involves the upper portion of the hair follicle but rarely invades below the level of the surrounding epidermis.
- The lack of deep follicular extension in most cases of squamous cell carcinoma in situ may have therapeutic implications.

Similar to other types of nonmelanoma skin cancer, SCCis is increasing in prevalence worldwide. A recent epidemiologic study of the Alberta Cancer Registry revealed that SCCis comprises 10% to 15% of all nonmelanoma skin cancer, and thus could represent over 350,000 cases per year in the United States.[17,18] Given the financial burden associated with treatment of nonmelanoma skin cancer,[19] therapy should not only be highly effective in terms of clinical outcome, but also practical and cost-effective. In this study, we sought to define the frequency and depth of hair follicle invasion in SCCis. This characterization of histopathologic behavior has potential implications for the selection of optimal therapy, because deep follicular invasion has been hypothesized to contribute to recurrence of SCCis.

METHODS

For the first study cohort, all cases with a diagnosis of SCCis treated with Mohs micrographic surgery at our institution from July to December 2010 (n = 175) were retrospectively reviewed, and cases with positive margins on the first stage (n = 59) were selected for analysis. For the second cohort, patients with SCCis on nonglabrous skin with clinical evidence of gross tumor treated with Mohs micrographic surgery between October 2011 and April 2012 were prospectively selected for the study (n = 18). Excised fresh-frozen tissue blocks from Mohs micrographic surgery were paraffin-embedded and serially sectioned through the entire tumor at 1-mm intervals. SCCis was defined as disordered epidermal maturation with cytologic atypia affecting the entire thickness of the interfollicular epidermis. Cases that did not meet criteria for SCCis, cases with evidence of another malignancy, and cases without follicular units within 2 mm of SCCis were excluded. All pathologic specimens with evidence of SCCis were independently scored by 3 Mohs surgeons and 1 dermatopathologist for the presence of SCCis in the follicular infundibulum and in the follicular isthmus/lower follicle (including the sebaceous gland). SCCis in the follicle or sebaceous gland was defined as disordered maturation and cytologic atypia affecting a majority of the cells within the adnexal structure. In the second cohort, every second slide was measured with a micrometer to determine the maximum linear thickness (from the granular layer of the epidermis) of SCCis in the interfollicular epidermis compared with the depth of SCCis extending down hair follicles.

Clinical parameters including preoperative lesion size, postoperative defect size, number of Mohs stages, and anatomic location were extracted from patient records in a deidentified manner. This study was granted an exemption from formal review by the Human Investigation Committee and Human Research Protection Program at Yale University. Statistical tests included paired t test to compare infundibulum versus lower follicle involvement, unpaired t test to compare epidermal versus follicular depth and to compare clinical parameters in cases with and without lower follicle invasion, and χ^2 test to determine association of lower follicle invasion with anatomic site. Interobserver (reader) agreement was calculated by total percent agreement, pairwise kappa coefficient and Spearman correlation coefficient, and intraclass correlation coefficient (ICC) (model 1). Correlation coefficients were calculated after converting binary reader data (SCCis present or absent) into ordinal data for follicular invasion (none, infundibulum, or isthmus/lower follicle).