J Cutan Pathol 2007: 34: 953–955
doi: 10.1111/j.1600-0560.2007.00736.x
Blackwell Munksgaard. Printed in Singapore

Journal of
Cutaneous Pathology

Commentary

Squamous cell carcinoma *in situ* in skin: what does it mean?

Squamous cell carcinoma *in situ* (SCCIS) is a frequently reported diagnosis by pathologists. The dermatologists base their management of the patient on this diagnosis. However, SCCIS can be seen in a variety of clinical situations. The pathologic diagnosis of SCCIS must be correlated with clinical data to arrive at a correct diagnosis and therefore appropriate management of the patient.

Bhawan J. Squamous cell carcinoma *in situ* in skin: what does it mean? J Cutan Pathol 2007; 34: 953–955. © Blackwell Munksgaard 2007.

Jag Bhawan

Dermatopathology Section, Department of Dermatology, Boston University School of Medicine, Boston, MA, USA

Jag Bhawan, MD, Dermatopathology Section, Department of Dermatology, Boston University School of Medicine, 609 Albany Street, J-309, Boston, MA 02118, USA
Tel: +1 617 638-5570
Fax: +1 617 638-5575
e-mail: jbhawan@bu.edu

Accepted for publication January 17, 2007

Squamous cell carcinoma *in situ* (SCCIS) is a histological diagnosis. Most authors believe that this represents a transepidermal (skin) or transepithelial (mucosa) keratinocyte atypia, with loss of polarity, numerous mitotic figures, dyskeratotic cells, hyperchromasia, lack of maturation and nuclear crowding.[1] Clinically, however, similar findings can be seen also in a variety of noncancerous and other cancerous processes (Table 1). These entities have variable prognoses and different management options. Therefore, faced with these lesions clinically, a clinicopathologic correlation (CPC) is imperative to arrive at an accurate diagnosis and to initiate proper management of the patient. Lack of clinicopathologic correlation can lead to gross mismanagement as exemplified by a bilateral vulvectomy performed for bowenoid papulosis on a 27-year-old woman which was interpreted as SCCIS by a pathologist.[2]

Historically, if the dermatopathologist signed out a case as consistent with a SCCIS, the dermatologist will generally excise the lesion; however, the same lesion will be treated with liquid nitrogen or a topical chemotherapeutic agent such as fluorouracil (5FU)[3] or imiquimod[4] if the lesion is signed out as an actinic keratosis by the dermatopathologist. In our practice of dermatopathology, we frequently see excisions of 'SCCIS' from the face of 70, 80 or 90-year-old patients after biopsy. Interestingly, both these lesions frequently appear similar clinically, as in most cases, the submitting clinical diagnosis is 'rule out actinic keratosis'. There are no distinctive clinical criteria to differentiate some actinic keratoses from some squamous cell carcinomas.[5] Furthermore, this distinction histologically can be based upon finding, even a small, focus of transepidermal atypia. The yield of finding a focus of full-thickness atypia often depends upon the number of sections examined.[6] If multiple cuts were made, one would find areas of full-thickness atypia in many actinic keratosis. Because many of these lesions are curetted or frozen by liquid nitrogen, they cannot be evaluated for full-thickness atypia.[7] We do not know how many of these lesions were histologically 'actinic keratosis' and how many were in fact SCCIS. Furthermore, many dermatologists treat even SCCIS with imiquimod[4] and 5FU.[3]

It may not be a good clinical practice to treat histologic 'SCCIS' more aggressively than actinic keratosis. This does not mean that actinic keratosis should be left alone or that they may not be associated with squamous cell carcinoma. In fact, most squamous cell carcinomas in sun-exposed areas arise in association with actinic keratosis.[8,9]

Table 1. Squamous cell carcinoma *in situ*

Actinic solar keratosis
Bowen's disease
Arsenical keratosis
Bowenoid papulosis
Erythroplasia of Queyrat

Guenthner et al. reported a 97.2% incidence of SCCIS in 1011 cases of squamous cell carcinoma. However, they defined actinic keratosis as SCCIS, not necessitating full-thickness atypia.[10] Bowen's disease was originally described as having histological features of SCCIS. For many years, Bowen's disease was considered to be associated with visceral malignancy;[11] however, some authors believe that Bowen's disease in sun-exposed areas is not associated with an increased risk of internal malignancy.[12] Likewise, there is a history of increased arsenical ingestion in Bowen's disease in non-sun-exposed sites.[13] In large studies, Bowen's disease is considered to be most commonly seen in sun-exposed skin.[14] What then is the difference between an actinic/solar keratosis and Bowen's disease arising in sun-exposed skin in view of the fact that many authors believe actinic keratosis is the earliest form of squamous cell carcinoma?[15,16] Another way to approach this issue would be to classify all lesions on sun-damaged skin that are histologically SCCIS and called Bowen's disease as actinic keratoses. Additionally, we use the term Bowen's disease only for lesions from non-sun-exposed skin which are histologically SCCIS. Thus, SCCIS involving subungual or perianal locations is best classified as Bowen's disease. Erythroplasia of Queyrat is a clinical variant involving the glans penis. Bowen's disease was in the past largely reported to be associated with arsenic ingestion, which would explain the higher incidence of visceral malignancy. Presently, Bowen's disease may arise *de novo* or may be associated with human papillomavirus (HPV).[17,18] It is therefore important to differentiate actinic keratosis and Bowen's disease on a clinical basis, as they may have different prognoses.

The fact that all SCCIS are different is best exemplified by bowenoid papulosis.[2] Many examples of bowenoid papulosis show histologic features of full-blown SCCIS, while others may show changes which lack full focal thickness atypia. For the most part, bowenoid papulosis is considered to be a virally induced benign condition despite the histologic features of SCCIS. Do or should we treat or manage bowenoid papulosis the same as Bowen's disease? I think not!

Arsenical keratosis is another example of SCCIS that needs to be recognized as a distinct entity using CPC. If one saw changes of SCCIS on acral skin (particularly if there were multiple lesions in the absence of solar elastosis), the index of suspicion for an arsenical keratosis should be high.

Variations can be seen in the degree of atypia in any of the clinical entities associated with SCCIS. Thus, there will be instances when full-thickness atypia may not be seen, as the development of SCCIS is a continuum of atypia which starts involving only lower layers of the epidermis and eventually all layers. This concept is well documented and understood in SCCIS of the human uterine cervix, now called as intra-epithelial neoplasia.[19] It was proposed that actinic keratosis is comparable to cervical intra-epithelial neoplasia.[20,21] Cockerell further suggested that the name actinic keratosis be changed to keratinocytic intraepidermal neoplasia.[20] (KIN) and graded on a 1–3 scale, with grade 3 being histologically SCCIS and grades 1 and 2 not being labeled carcinoma. I would suggest that KIN be used for defining the degree of histologic atypia in any of the entities associated with SCCIS.

In conclusion, the distinction between an actinic keratosis and a SCCIS is not just an academic discussion. Each of these diagnoses is associated with a management issue that needs to take into consideration clinicopathologic correlation. In addition, the term Bowen's disease should be applied only to lesions arising in non-sun-exposed areas to alert the clinician to the possibility of arsenic exposure and associated visceral malignancies or an association with HPV. Clinicians must rely upon CPC to determine if the SCCIS/KIN is actinic keratosis, arsenical keratosis, Bowen's disease, bowenoid papulosis or erythroplasia of Queyrat.

Acknowledgements

Authors are grateful for the critical evaluation and helpful suggestions of Dr Jane Grant-Kels and Dr Mina Yaar in preparation of this manuscript.

References

1. Strayer DS, Santa Cruz DJ. Carcinoma in situ of the skin: a review of histopathology. J Cutan Pathol 1980; 7: 244.
2. Bhawan J. Multicentric pigmented Bowen's disease: a clinically benign squamous cell carcinoma in situ. Gynecol Oncol 1980; 10: 201.
3. Dinehart SM. The treatment of actinic keratoses. J Am Acad Dermatol 2000; 42: 25.
4. Patel GK, Goodwin R, Chawla M, et al. Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2006; 54: 1025.

5. Moy RL. Clinical presentation of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 2000; 42: 8.
6. Carag HR, Prieto VG, Yballe LS, Shea CR. Utility of step sections: demonstration of additional pathological findings in biopsy samples initially diagnosed as actinic keratosis. Arch Dermatol 2000; 136: 471.
7. Feldman SR, Fleischer AB Jr, McConnell RC. Most common dermatologic problems identified by internists, 1990-1994. Arch Intern Med 1998; 158: 726.
8. Hurwitz RM, Monger LE. Solar keratosis: an evolving squamous cell carcinoma. Benign or malignant? Dermatol Surg 1995; 21: 184.
9. Mittelbronn MA, Mullins DL, Ramos-Caro FA, Flowers FP. Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma. Int J Dermatol 1998; 37: 677.
10. Guenthner ST, Hurwitz RM, Buckel LJ, Gray HR. Cutaneous squamous cell carcinomas consistently show histologic evidence of in situ changes: a clinicopathologic correlation. J Am Acad Dermatol 1999; 41: 443.
11. Peterka ES, Lynch FW, Goltz RW. An association between Bowen's disease and internal cancer. Arch Dermatol 1961; 84: 623.
12. Sober AJ, Burstein JM. Precursors to skin cancer. Cancer 1995; 75: 645.
13. Yeh S, How SW, Lin CS. Arsenical cancer of skin. Histologic study with special reference to Bowen's disease. Cancer 1968; 21: 312.
14. Kossard S, Rosen R. Cutaneous Bowen's disease. An analysis of 1001 cases according to age, sex, and site. J Am Acad Dermatol 1992; 27: 406.
15. Lober BA, Lober CW. Actinic keratosis is squamous cell carcinoma. South Med J 2000; 93: 650.
16. Ackerman AB, Mones JM. Solar (actinic) keratosis is squamous cell carcinoma. Br J Dermatol 2006; 155: 9.
17. Hara H, Honda A, Suzuki H, Matsukura T. Detection of human papillomavirus type 34 in Bowen's disease on the pubic area. J Eur Acad Dermatol Venereol 2006; 20: 206.
18. Murao K, Kubo Y, Fukuhara K, Matsumoto K, Arase S. Three cases of Bowen's disease on the lower abdomen associated with high-risk types 16, 33, and 59 of human papillomavirus. J Am Acad Dermatol 2005; 52: 723.
19. Arends MJ, Buckley CH, Wells M. Aetiology, pathogenesis, and pathology of cervical neoplasia. J Clin Pathol 1998; 51: 96.
20. Bhawan J. Histology of epidermal dysplasia. J Cutan Aging Cosm Dermatol 1988; 1: 95.
21. Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). J Am Acad Dermatol 2000; 42: 11.