

Letter to the Editor

Merkel cell carcinoma in situ associated with actinic keratosis: fortuitous or serendipitous?

To the Editor,

Merkel cell carcinoma (MCC) commonly presents as a malignancy confined to the dermis. Fewer than 10% of cases show varying degrees of epidermal involvement.¹ Only a small number of cases of entirely intraepidermal 'in situ' MCC (MCCIS) have been reported.^{2–8} All but one⁷ of these cases were encountered as an incidental histopathological finding in the presence of an otherwise common cutaneous lesion, such as squamous cell carcinoma in situ,^{2–5} trichilemmal cyst⁶ or seborrheic keratosis.⁸

Figure 1A illustrates a gritty, indurated plaque above the upper lip in a 68-year-old woman, skin-type I, who was followed regularly because of a history of multiple actinic keratoses and basal cell carcinomas. The clinical differential diagnosis included actinic keratosis and squamous cell carcinoma. A shave biopsy specimen disclosed rare intraepidermal nests of hyperchromatic basaloid cells with nuclear moulding set in a background of a characteristic actinic keratosis (Fig. 1B and C). Immunohistochemically, the basaloid cells expressed cytokeratin-20 (CK20) in a paranuclear dot-like pattern (Fig. 1D) and neuron-specific enolase and lacked expression of S100 protein. A diagnosis of MCCIS in association with actinic keratosis was thus made. The patient underwent subsequent excision by micrographic surgery, which disclosed residual squamous cell carcinoma but not MCCIS.

Table 1 summarizes the clinicopathological features of the present case compared with those from previous reports of MCCIS. This highly uncommon malignancy seems to favor sun-exposed areas, as with conventional MCC, and is associated with more common sun-induced lesions, such as actinic keratosis and squamous cell carcinoma. In the present case, the keratinocytic component of this association defined the clinical picture, but we can speculate that the latter could vary case by case depending on the quantitative representation of each component.

Cases associated with a scant MCCIS component are incidental, and are thus due to a fortuitous histopathological discovery.

Serendipity refers to a fortuitous and fortunate finding during the search for something unrelated.⁹ Therefore, most, if not all of the cases of MCCIS reported to date could be considered serendipitous. There is, however, one major aspect of Horace Walpole's original definition of serendipity,⁹ which does not apply here, namely, the ability of linking findings to reach a valuable conclusion. How can we link actinic keratosis and squamous cell carcinoma with MCCIS? We can speculate that this association simply represents a chance collision between two ultraviolet-induced neoplasms. Curiously, the present case is the first example of MCCIS associated with actinic keratosis located on

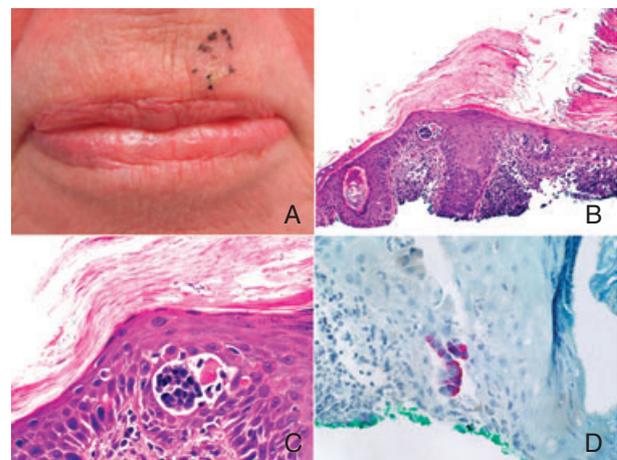


Fig. 1. A gritty plaque above the upper lip (A) histopathologically featuring an actinic keratosis and a few intraepidermal nests of hyperchromatic basaloid cells (B: hematoxylin and eosin, ×100) showing nuclear moulding (C: hematoxylin-eosin, ×400); cytokeratin 20-positivity of a cluster of cells in a paranuclear dot pattern, consistent with Merkel cell carcinoma in situ (D: ×400).

Letter to the Editor

Table 1. Clinicopathologic features of the reported cases of Merkel cell carcinoma in situ

Reference	Sex, age (years)	Site	Associated lesion	Outcome
Smith et al. ²	Male, 84	Arm	Squamous cell carcinoma in situ	Dermal recurrence with regional metastases
Brown et al. ³	Male, 74	Index finger	Squamous cell carcinoma in situ (focal)	No dermal involvement on re-excision
Al-Ahmadie et al. ⁴	Male, 79	Dorsal wrist	Squamous cell carcinoma in situ	Not reported
Ferringer et al. ⁵	Male, 76	Dorsal hand	Squamous cell carcinoma in situ	No residual tumor on re-excision
Su et al. ⁶	Male, 72	Fourth finger	Trichilemmal cyst	No residual tumor on re-excision; sentinel node biopsy negative
Reese et al. ⁷	Male, 73	Posterior neck	None	Not reported
Kitagawa et al. ⁸	Male, 62	Scalp	Seborrheic keratosis	No metastasis on radical lymph node dissection
Present case	Female, 68	Upper lip	Actinic keratosis	Residual squamous cell carcinoma; no residual MCCIS on re-excision

MCCIS, Merkel cell carcinoma in situ.

the face, an area where both neoplasms are more frequent.

We know Merkel cells arranged in single units can be highlighted with the anti-cytokeratin antibody featuring a hyperplastic pattern secondary to actinic damage¹⁰, and in the setting of a hyperplastic actinic keratosis.¹¹ Hence, while we recognize that both MCCIS and squamous cell neoplasms may represent a common response to ultraviolet light, we speculate that their simultaneous occurrence could derive either from divergent differentiation of a common pluripotential stem cell or from metaplasia of neoplastic keratinocytes ('neometaplasia') with the acquisition of the phenotype of Merkel cells. The well-recognized occurrence of MCC with squamous cell differentiation¹² would be considered as in keeping with this hypothesis.

Gerardo Ferrara, MD¹

Samuel D. Goos, MD²

Catherine M. Stefanato, MD, FRCPath³

¹Department of Oncology,
Anatomic Pathology Unit,

Gaetano Rummo General Hospital,
Benevento, Italy,

²Adult & Pediatric Dermatology,
Concord, MA, USA, and

³Dermatopathology Section,
Department of Dermatology,
Boston University School of Medicine,
Boston, MA, USA

Present address:

Department of Dermatopathology,
St. John's Institute of Dermatology,
St. Thomas' Hospital,
London, UK

e-mail: catherinestefanato@gmail.com

This case was presented at the 14th Congress of the European Academy of Dermatology and Venereology, October 12–16, 2005, London, UK.

References

1. McKee PH, Calonje E, Granter SR. Pathology of the skin with clinical correlations, 3rd ed. China: Elsevier Mosby, 2005.
2. Smith K, Skelton HG III, Holland TT, Morgan AM, Lupton GP. Neuroendocrine (Merkel cell) carcinoma with an intraepidermal component. *Am J Dermatopathol* 1993; 15: 528.
3. Brown HA, Sawyer DM, Woo T. Intraepidermal Merkel cell carcinoma with no dermal involvement. *Am J Dermatopathol* 2000; 22: 65.
4. Al-Ahmadie HA, Mutasim DF, Mutema GK. A case of intraepidermal Merkel cell carcinoma within squamous cell carcinoma in situ: Merkel cell carcinoma in situ? *Am J Dermatopathol* 2004; 26: 230.
5. Ferringer T, Rogers HC, Metcalf JS, et al. Merkel cell carcinoma in situ. *J Cutan Pathol* 2005; 32: 162.
6. Su W, Kheir SM, Berberian B, Cockerell CJ. Merkel cell carcinoma in situ arising in a trichilemmal cyst: a case report and literature review. *Am J Dermatopathol* 2008; 30: 458.
7. Reese J, Elenitsas R. Merkel cell carcinoma in situ. *J Cutan Pathol* 2010; 37: 165 [abstract].
8. Kitagawa K, Phadke P, Puri P, Selim M. Merkel cell carcinoma arising in a seborrheic keratosis. *J Cutan Pathol* 2010; 37: 188 [abstract].
9. Lewis WS. Horace Walpole's correspondence. In Remer TG, ed. Serendipity and the three princes from the Peregrinaggio of 1557. University of Oklahoma Press, 1965.
10. Moll I, Bladt U, Jung EG. Presence of Merkel cells in sun exposed and not sun exposed skin: a quantitative study. *Arch Dermatol Res* 1990; 282: 213.
11. Merot Y, Mooy A. Merkel cell hyperplasia in hypertrophic varieties of actinic keratosis. *Dermatologica* 1989; 178: 189.
12. Iacocca MV, Abernethy JL, Stefanato CM, Allan AE, Bhawan J. Mixed Merkel cell carcinoma and squamous cell carcinoma of the skin. *J Am Acad Dermatol* 1998; 39: 882.