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Association between melanocytic neoplasms and seborrheic keratosis: more than a coincidental collision?

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ABSTRACT Clinical observations and an expanding knowledge of cell-to-cell communication have led us to speculate that the finding of a melanocytic nevus in conjunction with a seborrheic keratosis is more than a coincidental collision of two lesions. Here we present five cases demonstrating dermoscopic features of both melanocytic lesions and seborrheic keratoses with corresponding histology. Four cases demonstrate dermoscopic features of a melanocytic nevus and seborrheic keratosis, and the final case a melanoma arising in association with a seborrheic keratosis.

Introduction

The presence of a seborrheic keratoses (SK) found in association with a melanocytic nevus has been observed often in our clinical practice. The utilization of dermoscopy highlights the specific features associated with both the nevus component and seborrheic keratosis found in these "collision" lesions. The occurrence of this finding, which is more readily appreciated with dermoscopy, has led us to speculate whether this is a coincidental finding or phenotypic expression of underlying melanocyte cell-signaling. Here we present five cases with histology, collected retrospectively, highlighting the association between melanocytic lesions and SK.

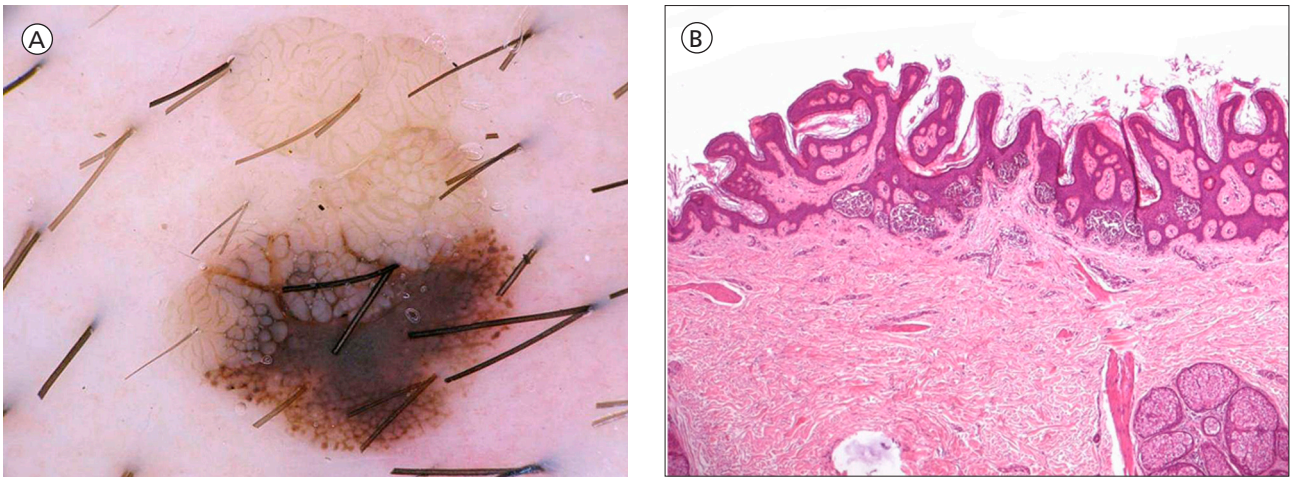


Figure 1A, B. Dermoscopy (1A) demonstrates a melanocytic nevus with reticulated network and an overlapping or colliding seborrheic keratosis with cerebriform pattern. On histology (1B), junctional melanocytic nests are located at the tips of rete ridges of a papillomatous seborrheic keratosis (hematoxylin and eosin [H&E], x25). [Copyright: ©2012 DeFazio et al.]

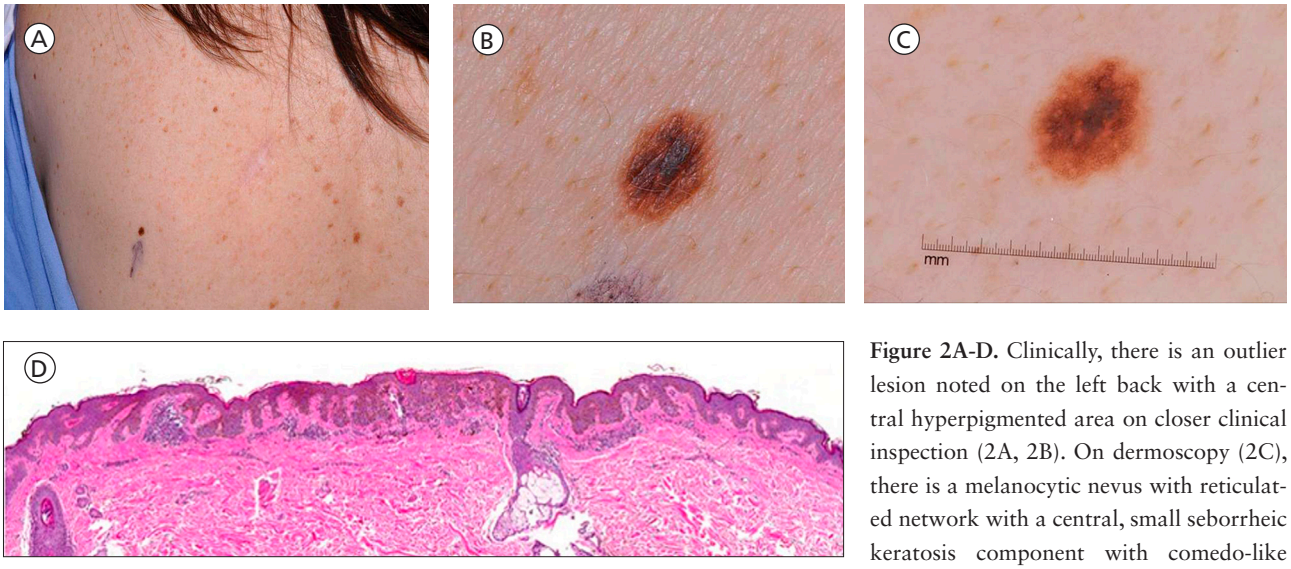


Figure 2A-D. Clinically, there is an outlier lesion noted on the left back with a central hyperpigmented area on closer clinical inspection (2A, 2B). On dermoscopy (2C), there is a melanocytic nevus with reticulated network with a central, small seborrheic keratosis component with comedo-like openings. On H&E (2D), there are focal seborrheic keratosis changes arising in association with the nevus (x20). [Copyright: ©2012 DeFazio et al.]

Case 1

A 31-year-old male with history of multiple nevi presented for routine skin surveillance. On exam a lesion of the pectoral region was noted by the physician and examined with dermoscopy. Dermoscopy (Figure 1A) revealed a macular lesion with a heavily pigmented center and peripheral reticulated network, partially occluded by a second raised component with a distinctive cerebriform appearance. A biopsy was performed. On histology (Figure 1B), the seborrheic keratosis showed papillomatous epidermal hyperplasia with delicate basket-weave hyperkeratosis. A melanocytic nevus involves part of the seborrheic keratosis. It was characterized by a proliferation of nests of melanocytes along the dermoepidermal junction.

Case 2

A 46-year-old female with history of dysplastic nevi, no personal history of melanoma, was noted to have a clinically suspicious lesion of the left back on routine skin surveillance. The lesion was considered to be an outlier lesion (Figure 2A, 2B) prompting closer examination with dermoscopy. On dermoscopic exam (Figure 2C), the lesion was noted to have a reticulated network with a central hyperpigmented area with subtle, small comedo-like openings appreciated. Given the overall clinical appearance, a shave removal of the lesion was performed. On histology (Figure 2D), there were focal features of seborrheic keratosis found arising within the melanocytic nevus, including a small keratin-filled invagination, which correlated with the comedo-

like opening on comparison to the dermoscopic image. The nevus was well circumscribed with junctional and dermal melanocytic nests.

Case 3

A 38-year-old female with history of many nevi was noted by the dermatologist to have a changed lesion on routine skin examination. Clinically (Figure 3A, 3B) the lesion was asymmetric with a heavily pigmented papular component. On dermoscopy (Figure 3C), the area correlating to the heavy pigmentation was noted to have multiple areas consistent with comedo-like openings. In the macular component of the lesion, there was a reticulated network consistent with a melanocytic lesion. Due to the history of change, an excision of the lesion was performed. On histology (Figure 3D, 3E), there were features of a reticulated seborrheic keratosis with associated melanocytic nests of a lentiginous compound dysplastic nevus with slight atypia.

Case 4

A 48-year-old male with no history of melanoma was referred to the dermatology clinic by his primary care physician for evaluation of a lesion on the abdomen (Figure 4A) suspicious for melanoma. Clinically, this was an asymmetric pigmented lesion. On dermoscopy (Figure 4B), there was a cerebriform pattern with multiple comedo-like openings and a few milia-like cysts appreciated. However, there was also a reticulated network noted. This appeared to be almost completely masked by the features of a seborrheic keratosis. A biopsy was performed. On histology (Figure 4C), a seborrheic keratosis showed papillomatous epidermal hyperplasia and a thickened stratum corneum. A part of the seborrheic

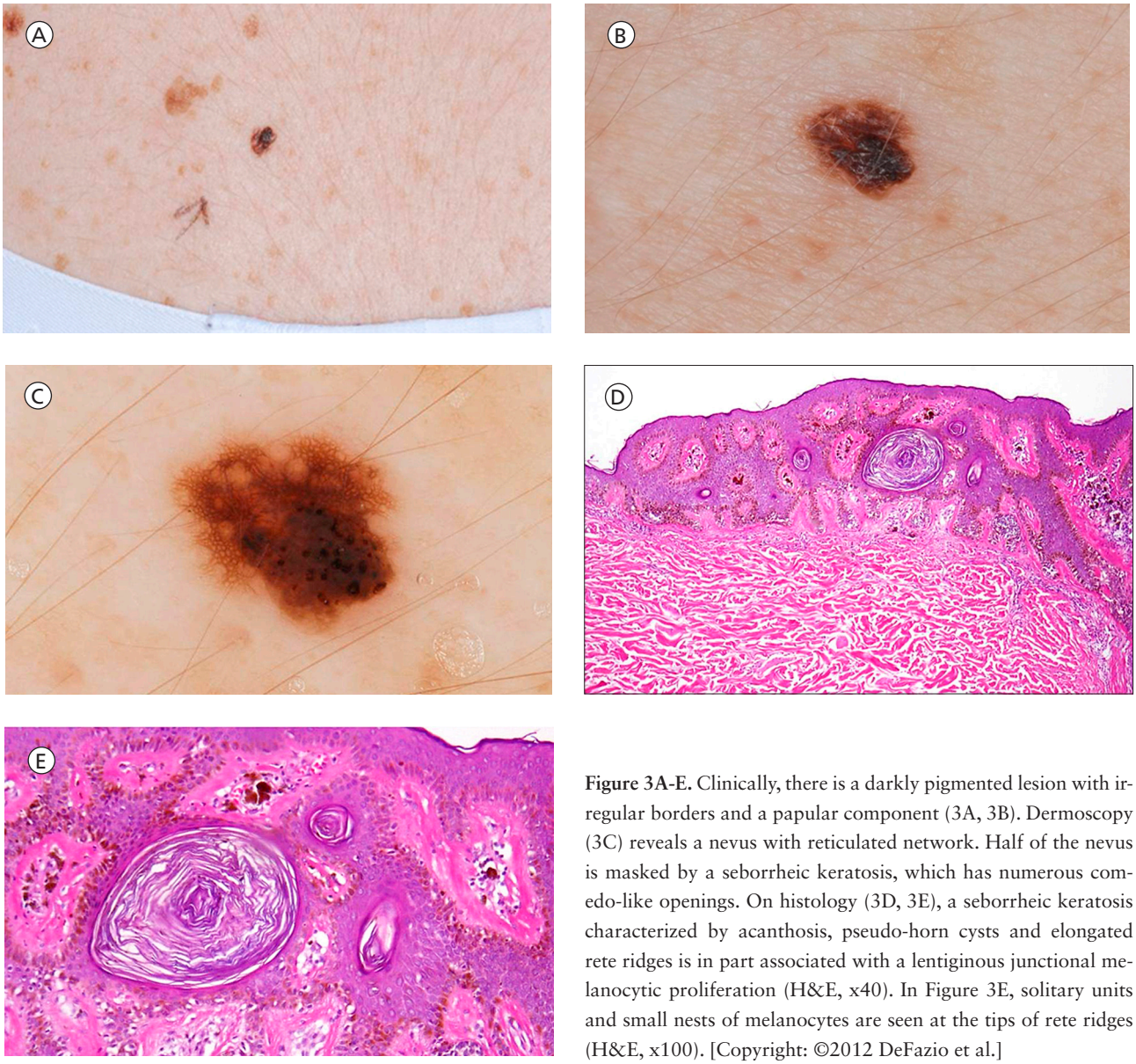
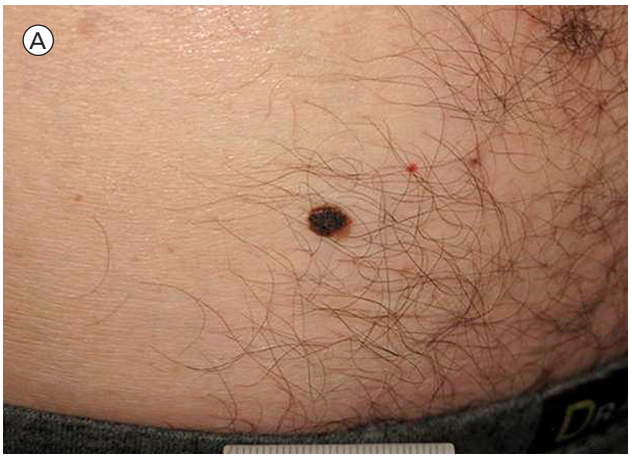
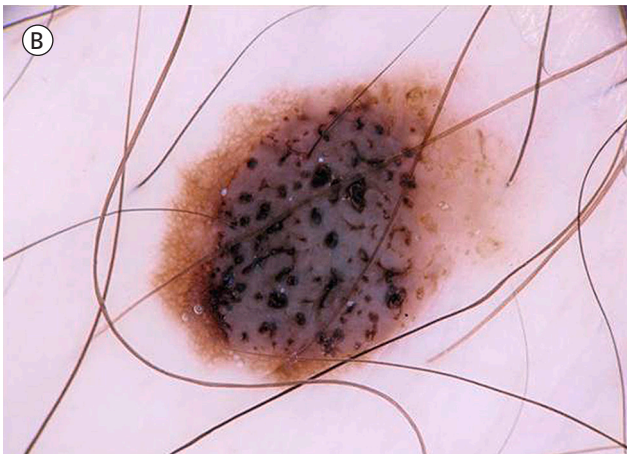


Figure 3A-E. Clinically, there is a darkly pigmented lesion with irregular borders and a papular component (3A, 3B). Dermoscopy (3C) reveals a nevus with reticulated network. Half of the nevus is masked by a seborrheic keratosis, which has numerous comedo-like openings. On histology (3D, 3E), a seborrheic keratosis characterized by acanthosis, pseudo-horn cysts and elongated rete ridges is in part associated with a lentiginous junctional melanocytic proliferation (H&E, x40). In Figure 3E, solitary units and small nests of melanocytes are seen at the tips of rete ridges (H&E, x100). [Copyright: ©2012 DeFazio et al.]





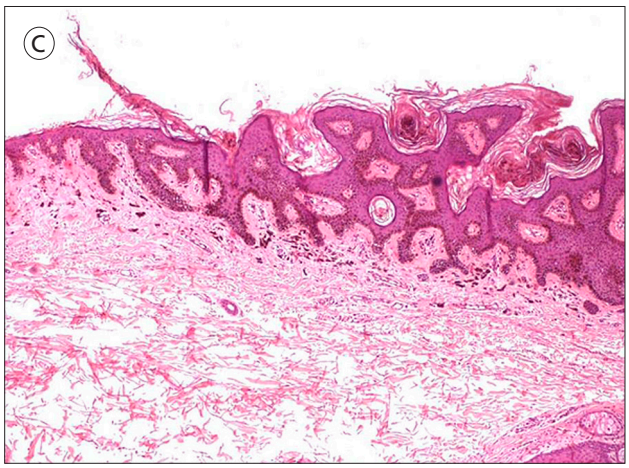


Figure 4A-C. The clinical image (4A) reveals a large, asymmetric pigmented lesion with a papular component. On dermoscopy (4B), the seborrheic keratosis with cerebriform pattern and comedo-like openings has almost completely masked the reticulated network of the melanocytic nevus. Histopathology (4C) shows an increased number of melanocytes, some of them arranged in small nests at the base of a seborrheic keratosis (H&E, x40). [Copyright: ©2012 DeFazio et al.]

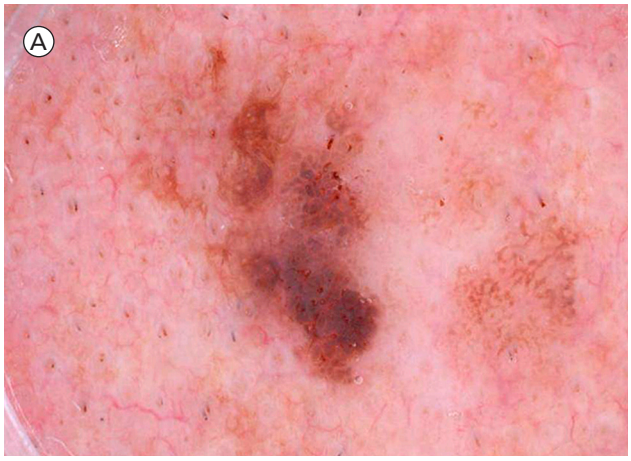
keratosis was involved with a lentiginous junctional melanocytic proliferation, consisting of melanocytes as solitary units and small nests. Melanocytes and melanophages were focally present in the papillary dermis.

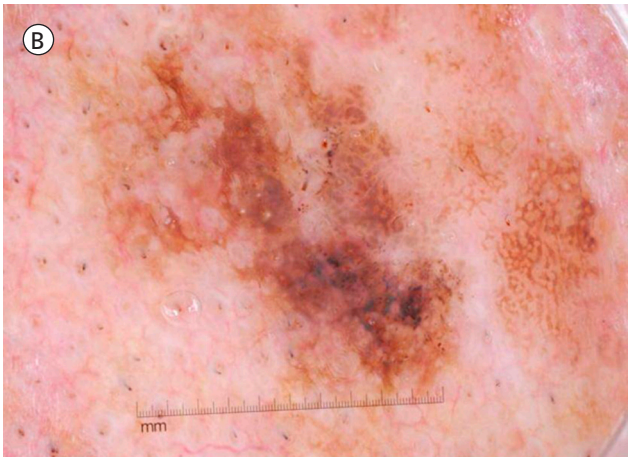
Case 5

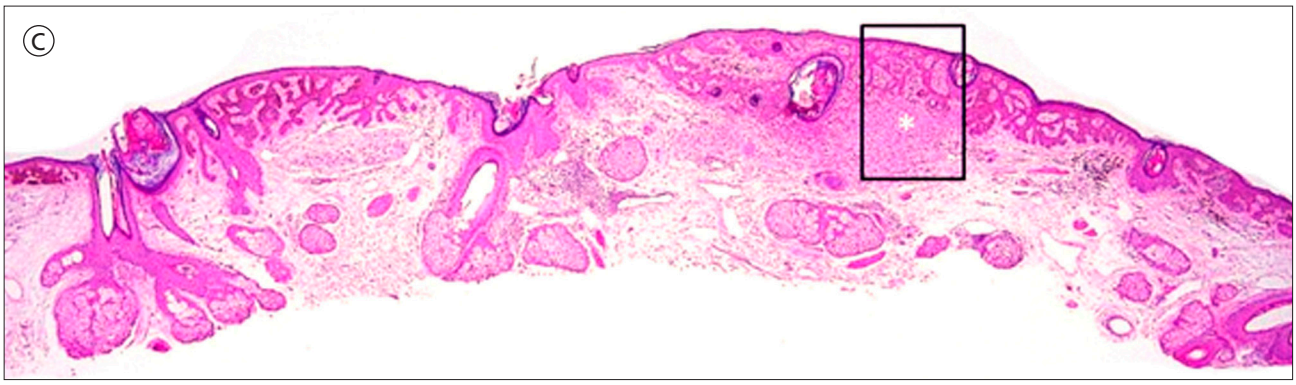
A 69-year-old male with history of invasive melanoma of the left upper arm, melanoma in situ of the upper back, and multiple non-melanoma skin cancers presented to the dermatology clinic for routine skin examination. On examination, a lesion of the right cheek was noted to have changed when compared to prior photography of the site. The initial dermoscopic photo (Figure 5A) demonstrated a cerebriform pattern with comedo-like openings consistent with a seborrheic keratosis. There were no features of a melanocytic lesion present. On dermoscopic comparison, 19 months later, features of melanoma were present including, annular granular, blue-gray and dark brown structures, irregular dots and milky red areas (vascular blush), while features of a seborrheic keratosis could still be appreciated. The lesion was biopsied and histology (Figure 5C, 5D) confirmed the diagnosis of melanoma 1.1 mm in Breslow thickness and Clark level IV, with features of a seborrheic keratosis also present. On greater magnification (Figure 5D, 5E), an invasive melanoma underlying the seborrheic keratosis and melanocytes in pagetoid pattern could be appreciated. The lesion was subsequently treated with wide local excision.

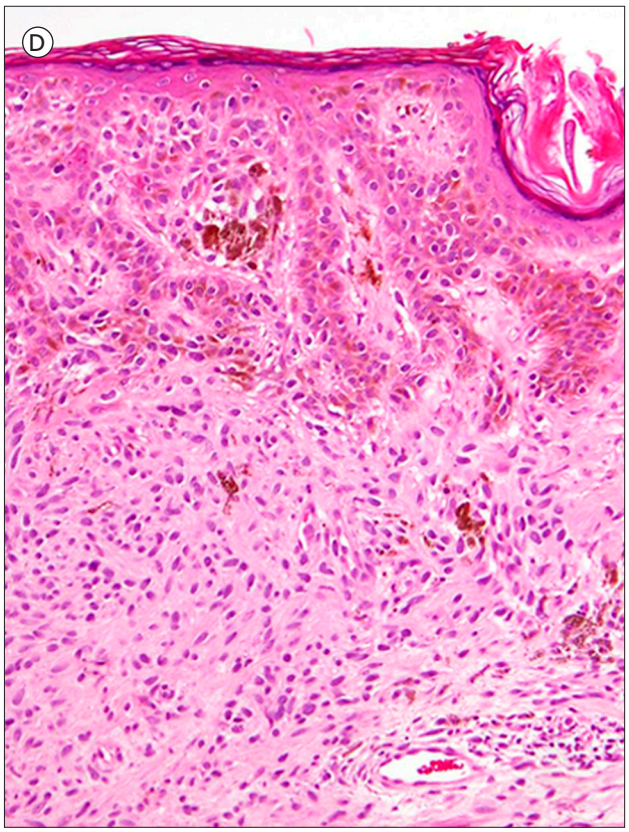
Discussion

Altered cell-cell communication between melanocytes and keratinocytes may result in the proliferation of melanocytes and/or keratinocytes [1,2]. Via dermoscopy, we have come to appreciate that it is not uncommon to encounter melanocytic nevi displaying a seborrheic keratosis (SK) like component. Our clinical experience has led us to speculate that the association between nevi and SK may not simply be due to the coincidental collision between these two benign tumors. It is quite possible that nevi can in fact induce the formation of SK [3]. It is interesting to note that research has also revealed that keratinocyte derived factors can regulate the proliferation of melanocytes, epidermal growth factor mutations are sometimes encountered in melanocytic neoplasms, fibroblast growth factor mutations are common in SK, specifically activating FGFR3 mutation, and fibroblast growth factor can be produced by melanocytic tumors [4-9]. A mutation in the









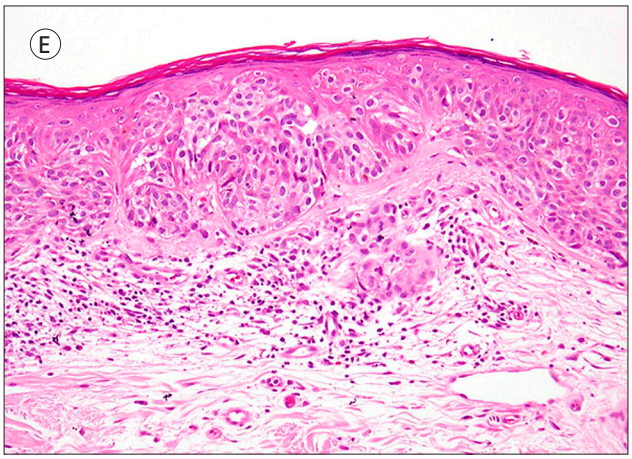


Figure 5A-E. Dermoscopy (5A) of this lesion located on the right cheek demonstrates classic features of the cerebriform pattern seen in seborrheic keratosis along with multiple comedo-like openings. There are no dermoscopic criteria for a melanocytic lesion present. The same lesion, two years later (5B), has dermoscopic features concerning for melanoma including, annular granular, blue-gray and dark brown structures, irregular dots and milky red areas (vascular blush) at the inferior portion of the lesion, while superiorly features of a seborrheic keratosis can still be appreciated. On histology (5C), the silhouette of the lesion shows a seborrheic keratosis with mixed acanthotic and reticulated growth patterns, but a proliferation of melanocytes along the dermoepidermal junction and in the dermis is also apparent. Figure 5D shows a close-up view of the melanoma associated with a seborrheic keratosis (box in 5C). There is an atypical junctional melanocytic proliferation associated with an intradermal spindle cell melanoma.

In Figure 5E, the associated melanoma in situ is characterized by a proliferation of nests of various sizes and shapes and many solitary units of melanocytes at all layers of the epidermis. Melanoma is also noted in the dermis in association with a lymphocytic infiltrate. [Copyright: ©2012 DeFazio et al.]

PI3K pathway has been described in SK [10]. Supplementary to this, it is known that therapies targeting BRAF, which is the most common mutation among nevi, induce eruptive keratinocyte tumors [11].

Mature nevi, which are in a state of senescence, are stable lesions that do not grow. However, SK developing in association with nevi may continue to grow. It is conceivable that the enlarging SK component may eventually mask the underlying nevus. In the unfortunate scenario of the development of a nevus-associated melanoma beneath the SK, the malignancy would of course eventually become visible, as may have occurred in Case 5 presented here [12-15]. Alternative explanations include that some of these lesions may have been melanomas from their inception that were masquerading themselves as SK [16], that normally occurring melanocytes within an SK mutated into melanoma [12], or that the initial lesion was a keratotic melanocytic nevus, which on histology have hyperkeratotic epidermal rete ridges and pseudohorn cysts, and clinically can have a warty appearance [17] mistaken for a seborrheic keratosis. Melanoma may arise from this lesion giving the clinical appearance of a melanoma arising in a seborrheic keratosis or perhaps the association between melanoma and SK is purely due to the coincidental collision between these two entities [18].

Seborrheic keratoses in association with melanocytic nevi and melanoma have been reported previously. In a retrospective study published by Boyd and Rapini, 69 collision tumors were observed after assessing 40,000 cutaneous biopsies. Of those 69, 14 were nevus and seborrheic keratosis [19]. In a retrospective case series by Lim, over a 12-month period, histology of 639 SK was evaluated and 85 (9%) were found in association with other lesions. Seven melanomas (8.2%) were reported with one found to have arisen within the seborrheic keratosis and six adjacent to a seborrheic keratosis. Thirteen melanocytic nevi (15.3%) adjacent to SK were also reported [20]. These findings may be more than coincidental and may suggest a not yet fully understood local phenomenon. This concept has been proposed previously by Brownstein [21], where it was suggested that nevi may interact with the stroma to induce epithelial growths. The melanocytic nevus may alter the local milieu and induce the development of the adjacent seborrheic keratosis, accounting for our clinical observations.

Conclusion

We have presented five cases of melanocytic lesions found in association with SK. Nevus in association with seborrheic keratosis has been observed frequently in our clinical experience and is more readily appreciated with dermoscopic inspection. The frequency with which this has been noted and an ever-increasing understanding of cell-signaling has led us to postulate that this may be more than a chance occurrence. Further exploration of cell-cell signaling of melanocytes and keratinocytes is needed to truly understand this clinical observation.

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