

CONCURRENT OCCURRENCE OF SEBORRHEIC KERATOSIS AND MELANOCYTIC NEVUS IN THE SAME LESIONYosep Chong¹, Dae-Hyun Song², Kee-Taek Jang², Kwang Hwa Park³, Eun Jung Lee¹¹*Department of Hospital Pathology, College of Medicine, The Catholic University of Korea, Seoul, Korea*²*Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*³*Department of Pathology, Yonsei University Wonju College of Medicine, Wonju, Korea*

Source of Support:

Nil

Competing Interests:

None

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Our Dermatol Online. 2014; 5(2): 179-182

Date of submission: 23.12.2013 / acceptance: 28.01.2014

Abstract

Seborrheic keratosis (SK) is common benign epithelial tumor of the skin that can be associated with other cutaneous tumors such as basal cell carcinoma, squamous cell carcinoma and melanoma. On the other hand, melanocytic nevus (MN) is another very common disease, showing anecdotal association with other cutaneous tumors such as trichoepithelioma, syringoma, basal cell carcinoma, trichilemmal cyst and epidermoid cyst. Although it has recently been reported that somatic mutation of BRAF gene is implicated in MN quite frequently, their pathogenic mechanisms, especially the association with other cutaneous tumors, are still elusive. Despite the high frequency of both tumors, however, collision tumors of SK and MN are extremely rare that only a few case reports have been documented so far.

Hereby, we report five cases of simultaneous occurrence of SK and MN in 14-year-old female, 36-year-old female, 39-year-old female, 58-year-old male, and 62-year-old male patients. Additional molecular tests for BRAF mutation (V600E) on micro-dissected tissue of the 58-year-old man revealed positivity on the MN and negativity on the SK. Although these results cannot give direct evidence that both tumors have different pathogenic mechanisms, it seems to be more relevant that these collision tumors may occur by chance.

Key words: seborrheic keratosis; intradermal nevus; skin neoplasms**Cite this article:**

Chong Y, Song D-H, Jang K-T, Park KH, Lee EJ. Concurrent Occurrence of Seborrheic Keratosis and Melanocytic Nevus in the Same Lesion. *Our Dermatol Online*. 2014; 5(2): 179-182.

Introduction

Seborrheic keratosis (SK) is one of the most common benign epithelial tumors of the skin. Despite its frequency, many aspects of SK, especially its pathogenetic mechanism, remain elusive. Not a small number of cutaneous malignant tumors such as basal cell carcinoma, squamous cell carcinoma and melanoma have been documented to be found with SK [1]. Benign tumors that have very occasionally been documented include cutaneous ganglioneuroma, sebaceoma, eccrine poroma and trichilemmoma [1]. However, whether these combined tumors and SK share the same pathogenic mechanism is unclear. Likewise, melanocytic nevus (MN) is another very common disease, showing anecdotal association with other cutaneous tumors such as trichoepithelioma, syringoma, basal cell

carcinoma, trichilemmal cyst and epidermoid cyst [1]. Although it has recently been reported that somatic mutation of *BRAF* gene is implicated in MN quite frequently, their pathogenic mechanisms, especially the association with other cutaneous tumors, are still elusive [2].

Considering the frequency of these two tumors, there have been surprisingly few additional reports of the cases in the literature that SK and MN are combined in the same lesion [3-9]. Some of the cases even showed additional concurrent occurrence of other tumors such as basal cell carcinoma, which suggests the hypothesis that multipotential differentiation capacity of the follicular germ may explain the coexistence of these tumors [6,8].

Here we report additional four cases of simultaneously occurring SK and MN in the same lesion. Moreover, the mutation analyses of *BRAF* gene were performed on the separately micro-dissected tissue from MN and SK in one of the cases.

Case Report

A 58-year-old Korean man presented with a dark pigmented lesion on his posterior neck that has been slowly growing for last few years. On physical examination, the size and shape was recorded as 0.6 - 0.5 cm-sized, ovoid brown pigmented papule with focal area of dense pigmentation (Fig. 1A). Two additional pigmented papules were found on the lower part of the neck and inguinal area.

On microscopic finding, epidermal layer of the lesion showed monotonous proliferation of basaloid cells with a variable degree of squamoid differentiation. Hyperkeratosis, acanthosis, focal parakeratosis and multiple pseudohorn cysts were characteristically noted, which made the lesion easily identified as SK (Fig. 2A). Underneath the epidermal lesion, relatively well-circumscribed small nests of bland pigmented melanocytes were found (Fig. 2B). The cytologic atypia of the melanocytes was minimal, consistent with intradermal MN. Additionally excised lesions on the cheek and inguinal area were diagnosed as SK after histologic evaluation.

A second case was a 39-year-old Caucasian woman with a similar pigmented tumor on her right forearm. On physical examination, it measured 1.0 - 0.9 cm and showed a brown-black warty plaque with a rather greasy texture. The microscopic findings revealed SK overlapping MN of intradermal type (Fig. 2B).

A third case was a 62-year-old Korean man with a pigmented lesion on his face. It measured 1.2 - 1.0 cm and showed a brown warty plaque with greasy surface and focal area of black

pigmentation. Microscopically, it was diagnosed as MN of intradermal type juxtaposed with SK (Fig. 2C).

A fourth case was a 36-year-old Korean woman with a 1.0 - 0.7 cm-sized, mulberry-shaped, pigmented lesion on her abdomen. It reveals a brown warty appearance with greasy surface (Fig. 1B). Microscopically, it was SK overlapping MN of intradermal type (Fig. 2D).

Finally, a 14-year-old Korean woman presented with a 0.9 - 0.8 cm sized, pigmented lesion on her back. It was SK overlapping MN of compound type.

As an ancillary test, peptide nucleic acid clamp real-time polymerase chain reaction (RT-PCR) for *BRAF* mutation (V600E) were performed on DNAs separately collected from MN and SK in the first case by micro-dissection (PNA Clamp *BRAF* mutation detection kit, Panagene Ltd., Daejeon, Korea), according to the manufacturer's instruction. Genomic DNAs were extracted from the micro-dissected, formalin-fixed, paraffin-embedded tissue of MN and SK using Maxwell® 16 FFPE Plus LEV DNA purification kit (Promega Co., WI, USA) with Maxwell® 16 Research System (Promega Co., WI, USA). Extracted DNAs were quantified by NanoDrop LITE spectrophotometer (Thermo Fisher Scientific Inc., MA, USA) and diluted properly. About 10 ng/ul of DNA was used as a template DNA in each PCR. RT-PCR was performed with CFX 96™ Real time system (Bio-Rad, CA, USA) and analyzed with PNA Clamp™ analyzer Kor v.4.0.6 for Bio-Rad (Bio-Rad, CA, USA). Tests with threshold cycle (Ct) of 22 to 30 were considered to be appropriate to use. The cut-off value of delta-Ct values, referred to as the difference between Cts of control and samples, were 2.0 to determine the presence of mutant DNA.

Interestingly, *BRAF*^{V600E} mutation was found only in MN in the first case while the mutation was not detected in SK.

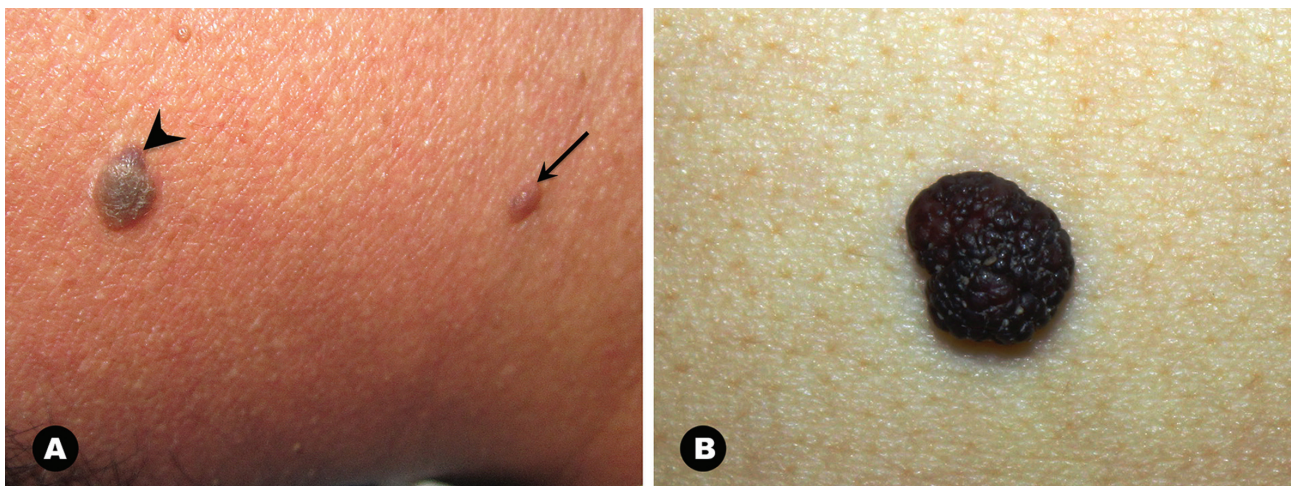


Figure 1. Gross finding of the concurrent seborrheic keratosis and melanocytic nevus of a 58-year-old male patient (Case 1) and a 36-year-old female patient (Case 4). (A), A 0.6 - 0.5 cm-sized, oval brown pigmented papule with superficial scale is noted on the posterior side of the neck of the first patient. Focal area of slightly dense pigmentation is seen within the lesion (Arrowhead). Another papular lesion, pathologically confirmed as seborrheic keratosis later, is also noted in the lower part of the neck (Arrow). (B), A mulberry-shaped, black pigmented, polypoid mass, measuring 1.0 - 0.7 cm, is found on the abdomen of a 36-year old female patient. It seems to be hard to define two components in this lesion grossly.

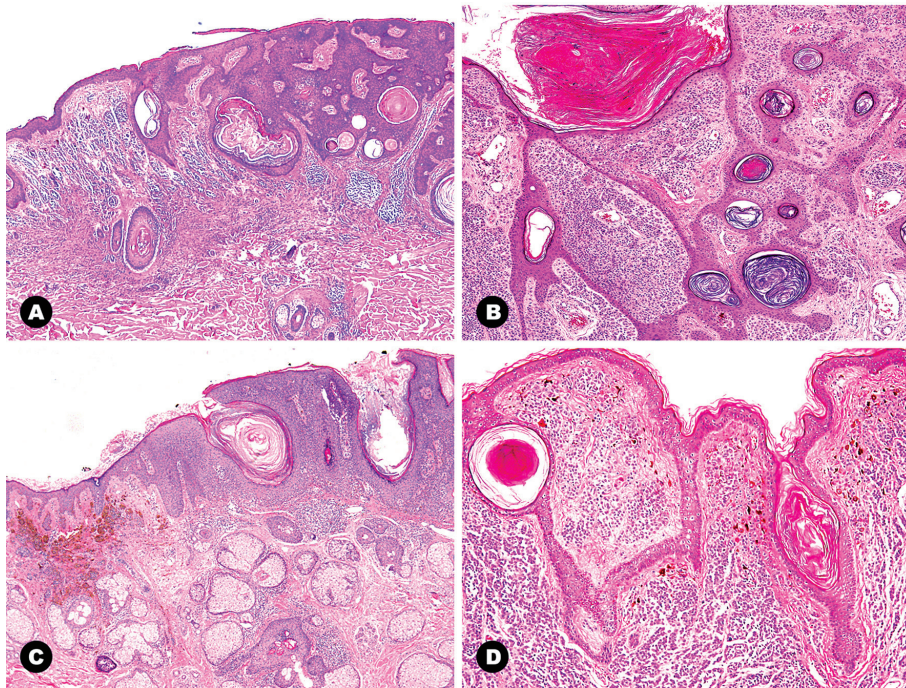


Figure 2. Microscopic finding of concurrent seborrheic keratosis (SK) and melanocytic nevus (MN) (H&E stain). (A), Intradermal nevus is located just beneath the SK in Case 1 ($\times 40$). (B), Compound type nevus is found beneath the SK in Case 2 ($\times 100$). (C), Intradermal nevus is found juxtaposed to the SK in Case 3 ($\times 40$). (D), Intradermal nevus is found beneath the SK in Case 4 ($\times 100$).

Discussion

Combined SK and MN in the same lesion was first described by Requena et al. [3] in 1989 and another case of compound nevus and SK followed by Wagner et al. [4]. In 1994, Boyd and Rapini [5], in a retrospective study of 40,000 cutaneous biopsies, reported 14 cases of MN juxtaposed with SK. Three additional reports, in total less than 20 cases, have been reported since then [6-8]. The clinicopathological findings of the cases

are summarized in Table I.

Although the number of reported cases is limited and the clinicopathologic information of the 14 cases in Boyd and Rapini's report [5] is lacking, there seems to be no predominant clinicopathologic features among the cases. Both male and female patients can be affected, the age of the patients widely varies from 14 up to 82, and all parts of the skin, especially exposed sites to sunlight, can be involved as seen in usual SK.

Year	Authors	No. of Cases	Age (yrs) / Sex	Site	Size (mm)	Type of nevus	Intertumoral positioning	Other associated tumors
1989	Requena et al. [2]	1	45/Male	Face (cheek)	Unspecified	Junctional	Overlapped	
1991	Wagner [4]	1	36/Female	Ankle		Compound	Overlapped	
1994	Boyd et al. [5]	14	Unspecified	Unspecified	Unspecified	Unspecified	Juxtaposed	Unspecified
2001	Betti et al. [6]	1	54/Male	Back	30	Junctional and compound	Overlapped	Basal cell carcinoma
2003	Kim et al. [7]	1	82/Male	Face (canthus)	5	Intradermal	Overlapped	
2005	de Giorgi et al. [8]	1	38/Female	Hip	13	Compound	Juxtaposed	Basal cell carcinoma
2008	Gonzalez-Vela et al. [9]	1	39/Female	Back (scapular)	13	Intradermal	Overlapped	
2013	Present case 1	1	58/Male	Neck	6	Intradermal	Overlapped	
	Present case 2	1	39/Female	Arm	10	Compound	Overlapped	
	Present case 3	1	62/Male	Face	12	Intradermal	Juxtaposed	
	Present case 4	1	36/Female	Abdomen	10	Intradermal	Overlapped	
	Present case 5	1	14/Female	Back (upper)	9	Compound	Overlapped	

Table I. Summary of the 8 reports with collision tumor of seborrheic keratosis and melanocytic nevus.

Intradermal, junctional and compound types of MN can be involved with SK either in overlying or juxtaposed manner. Additional remarkable clinicopathological findings were not otherwise described.

Among 25 cases including present three cases, 2 cases were accompanying basal cell carcinoma in part of the lesions [6,8]. One of them, reported by Betti et al. [6] in 2001, revealed a junctional nevus and separately-found compound nevus underneath a part of the SK while another part of the SK showed complexes of a typical superficial basal cell carcinoma arising within. The authors carefully suggested the possibility of involvement of the multipotential follicular germ in the pathogenic mechanisms of SK and accompanying basal cell carcinoma in this case. Furthermore, giving the examples of several cutaneous tumors associated with melanocytic lesions, the authors suggested the idea that nevi might interact with stromal elements to induce epithelial growths. However, they concluded their case as a chance association because of its rarity in comparison with the frequency of SK and MN. De Giorgi et al. [8], in the other report, focused on the dermoscopic features and did not mention about the pathogenic mechanism of this collision tumor.

In this report, we found the *BRAF* mutation status of SK and MN in one of these collision tumors differs from each other, suggesting the possibility of independent pathogenic mechanisms of each component. Although this finding might be not enough to explain the different pathogeneses of these tumors, juxtaposed presentation in some of the reported cases and relatively low frequency of these collision tumors favor the coincidental occurrence of these tumors. Taking into account that the most commonly associated tumors to SK was MN and vice versa in Boyd and Rapini's retrospective study [5], it seems to have more persuasive power. Because of relatively low clinical significance of SK and MN, both dermatologists and

pathologists may not notice these collision tumors frequently. With an extension of this idea, it seems to be more relevant to take UV exposure for the common pathogenic trigger in both tumors as in usual SK and MN. For a clearer explanation, additional cases and more studies on the known pathogenic causes of SK and MN, such as *BRAF* mutation are required.

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