European Journal of Dermatology

Clinical Report

ejd180219R1

Congenital nevi with hypomelanosis and fine scales

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Running head: Congenital nevi with hypomelanosis and fine scales

Word count: 1185

Number of figures: 2

Number of tables: 0

Number of references: 14

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Abstract

Background: Nevus is a hamartoma or malformation of one or more skin components, resulting in aberrant differentiation of the cell lineage(s) mostly during developmental stages. Although multiple lineages may be involved in a nevus, the combination of melanocyte and keratinocyte abnormalities has been rarely discussed. **Patients and Methods:** We introduce two cases of congenital nevi with hypomelanosis and superficial fine scales. Skin specimens of the patients were analyzed through immunohistochemistry and electron microscopy. **Results:** Morphological and immunohistochemical studies indicated aberrant epidermal differentiation in the lesional skin specimens. Electron microscopy showed defective melanosome maturation in the melanocytes of the nevi samples. **Conclusion:** These results demonstrate that both epidermal and melanocytic lineages can concomitantly contribute to the formation of a nevus lesion.

Keywords: epidermal nevus, nevus depigmentosus, melanosome, epidermal differentiation, keratin, filaggrin

Developmental cells undergo migration, differentiation and proliferation to build organs that fully function in the body. Once genetic or epigenetic changes occur in a cell lineage, the behavior of its progeny cells can be altered. If the abnormal cells remain in the tissue after development without being eliminated from cell-cell competition but behave in a benign manner, the area that contains the cells is called a hamartoma or malformation. A nevus is a skin hamartoma or malformation, and it can originate from one cell lineage (e.g., a melanocytic nevus) or multiple cell lineages (e.g., an organoid nevus). Among the many kinds of nevi, epidermal nevi and nevus depigmentosus often show features that are reminiscent of their development due to their distribution along Blaschko's lines. The pathomechanism of epidermal nevus is explained by postzygotic somatic mutations of *HRAS*, *FGFR3* or other genes in the epidermal keratinocyte lineage [1]. In contrast to epidermal nevus, nevus depigmentosus affects the melanocyte lineage [2, 3] and might be caused by mosaic *mTOR* mutations [4]. These two examples of congenital nevi are associated with postzygotic genetic/epigenetic alterations in one cellular source. However, nevi with hypopigmentation and abnormal keratinization have not been well-described. Here we present two cases of congenital nevi with hypomelanosis and fine scales on the skin surface.

Patients and Results

Case 1

A 5-year-old Japanese girl born to non-consanguineous parents was referred to us with congenital, asymptomatic, hypopigmented streaks on the right leg. Her parents had no pigment anomalies. The patient had no developmental delay or mental retardation. A physical examination revealed asymptomatic, hypopigmented streaks on the right leg along the Blaschko's lines (**Fig. 1a, 1b**). The lesion was pruritic and harbored fine scales on its surface. Dermoscopic examination without gel revealed swollen, scaly ridges with a significantly irregular arrangement (**Fig. 1c**). A biopsy specimen was obtained from a scaly lesion inside a streak. Haematoxylin and eosin staining showed acanthosis in the epidermis and superficial perivascular dermatitis in the upper dermis (**Fig. 1d, 1e**). Keratin and filaggrin expressions were examined, as described previously [5]. Keratin 14 (K14) was detected in the basal layer and the lower-to-middle spinous layer (**Fig. 1f**). Both keratin 1 (K1) and keratin 10 (K10) were detected in the middle-to--upper spinous layer, granular layer, and horny layer (**Fig. 1g, 1h**). Filaggrin/profilaggrin was present only in the granular layer (**Fig. 1i**). Electron

microscopic examination revealed melanocytes with immature melanosomes (**Fig. 1j**). High magnification showed abundant stage 1 and stage 2 melanosomes, and scant stage 3 and stage 4 melanosomes in melanocytes (**Fig. 1k**).

Case 2

A 22-year-old Japanese woman was referred to us due to hypopigmented macules on the left shoulder. She was born to non-consanguineous parents and her parents have no pigmentary anomalies. She had been otherwise healthy, without any developmental defects. Her medical history was unremarkable. The hypopigmented lesions were present on her shoulder at birth. She had noticed the pigmented area within the lesions 1 year prior to the referral. Examination found five scaly, well-demarcated, hypopigmented macules of 6cm in maximum diameter on the shoulder (**Fig. 2a, 2b**). The lesions were distributed not in a Blaschko-linear manner but in a phylloid pattern. Blackish dots were seen within each lesion, which is consistent with previous reports of lentiginous formation in nevus depigmentosus [6-9]. Biopsy specimens from hypopigmented areas showed mild hyperkeratosis and acanthosis (**Fig. 2c**) compared with non-lesional skin (**Fig. 2d**). K1, K10 and K14 labeling were broader in the lesional epidermis

than in the non-lesional area (**Fig. 2e-j**), reflecting acanthosis in histopathology. In lesional skin, filaggrin was expressed in several epidermal layers beneath the stratum corneum; in non-lesional epidermis, it was expressed in only one layer (**Fig. 2k, 2l**). Electron microscopy revealed immature melanosomes in melanocytes of the lesional skin (**Fig. 2m**), while non-lesional epidermis had melanocytes with mature melanosomes (**Fig. 2n**).

Discussion

We have described congenital nevi with characteristics of hypomelanosis and fine scales on the surface. The immunohistochemical studies confirmed the alteration of epidermal structure in both cases. In these cases, ultrastructural analysis revealed immature melanosomes in the melanocytes of the lesional skin samples.

The provisional clinical diagnoses of the two cases were linear epidermal nevus (or inflammatory linear epidermal verrucous nevus; Case 1) and nevus depigmentosus (Case 2). Epidermal nevus commonly varies from pale brown macules to brownish verrucous or hyperkeratotic lesions with or without a prominent inflammatory component. Aberrant keratin expression has been shown

in nevi of epidermal and appendageal lineages, i.e., (i) porokeratotic eccrine ostial and dermal duct nevus (PEODDN) caused by somatic mutations in the *GJB2* gene encoding the gap junction protein connexin-26, and (ii) congenital hemidysplasia with ichthyosiform erythroderma and limb defect (CHILD) syndrome, an X-linked dominant disorder of lipid metabolism with disturbed cholesterol biosynthesis [10, 11]. In contrast, nevus depigmentosus is characterized by congenital or early-onset leukoderma, persistency throughout life, normal texture and sensation, and skin-colored border [12], and its diagnosis relies on clinical manifestations and histopathology [2, 3]. However, neither of our two cases could be classified as a typical epidermal nevus or nevus depigmentosus, because each lesion showed abnormalities in both keratinocytes and melanocytes.

One possible reason for these manifestations is the sharing of postzygotic somatic mutations between epidermal keratinocytes and melanocytes in a given lesion, which could generate abnormalities in both cells. Another explanation is that postzygotic somatic mutations in either the keratinocyte lineage or the melanocyte lineage may affect the behavior of the other cells. In accordance with this notion, the ultrastructural morphology of not only keratinocytes but also

melanocytes has been reported to be altered in epidermal nevus [13]. The limitation of our study is that we have not determined whether the former or the latter explanation is more likely. Methodological advances, including single-cell sequencing technologies, may help to uncover the genetic alterations in a single keratinocyte and/or a neighboring melanocyte in a nevus in future studies.

In closing, we propose that abnormalities of keratinocyte proliferation/differentiation and immature melanosomes in melanocytes can occur simultaneously in a congenital nevus lesion. Our study suggests that more cellular sources may be involved in the formation of a nevus than are currently recognized.

Acknowledgements

We thank Prof. Tamio Suzuki and Prof. Ichiro Katayama for their valuable comments on Case 2.

Funding statement: None

Conflicts of interest: None declared

Figure 1

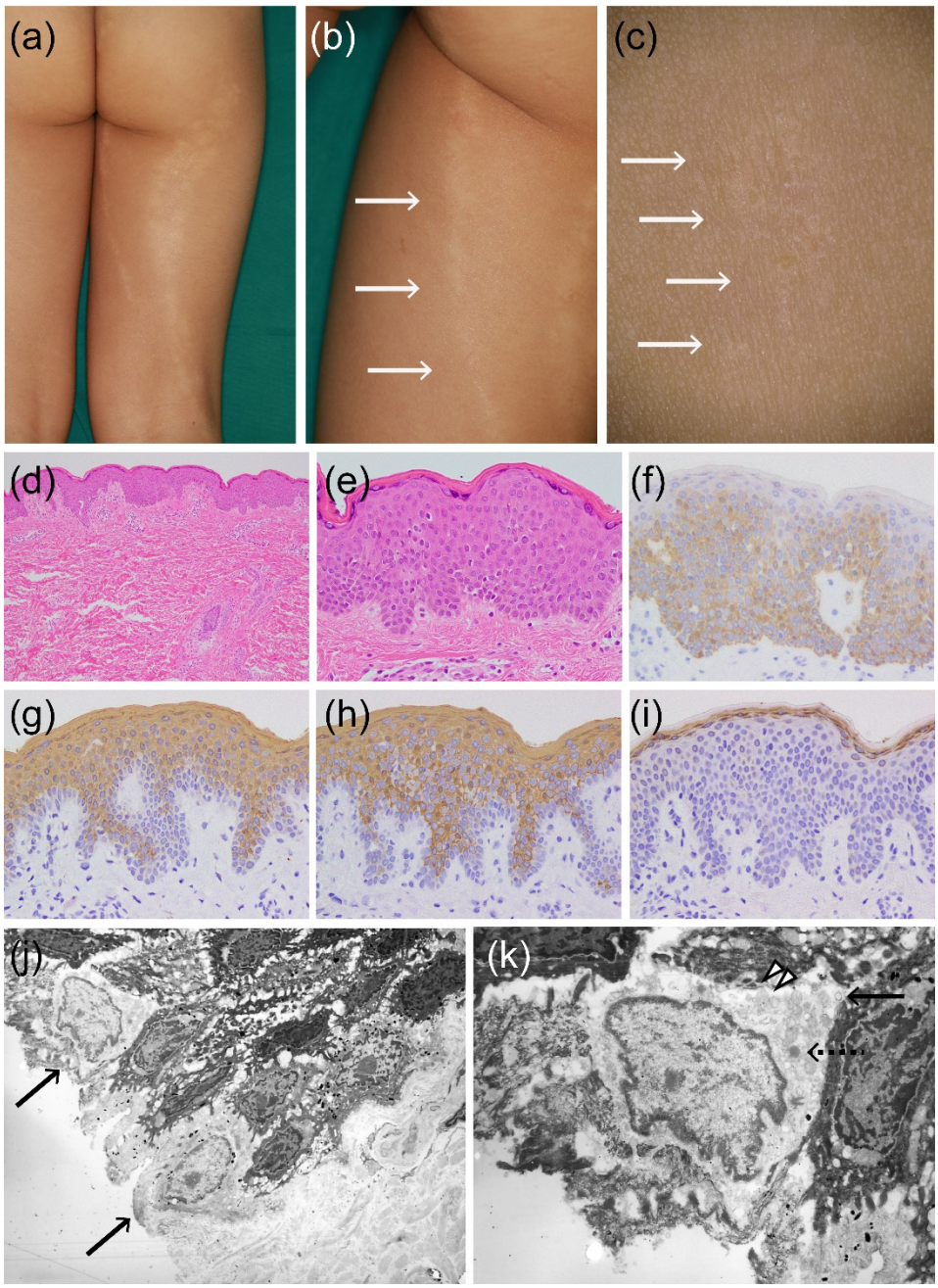

Figure 1. Clinical manifestations, histological and ultrastructural analyses for Case 1.

(**a-b**) Clinical manifestations. Hypopigmented streaks on the right dorsal thigh (**a**). Fine scales attached to the streaks (arrows) (**b**).

(**c**) Dermoscopic observation. Scaly, swollen ridges with a slightly irregular arrangement (arrows).

(**d-e**) Histological observation (haematoxylin and eosin staining). Original magnification x40 (**d**) and x400 (**e**).

(**f-i**) Immunohistochemical studies. K1 (**f**), K10 (**g**), K14 (**h**) and filaggrin (**i**) (original magnification x400).

(**j-k**) Electron microscopy studies. Melanocytes with immature melanosomes (arrows) (original magnification x2,000) (**j**). Abundant stage 1 (arrow) and stage 2 (arrowheads) melanosomes, and scarce stage 3 (dotted arrow) and stage 4 melanosomes in a melanocyte (original magnification x5,000) (**k**).

Revised Figure 2

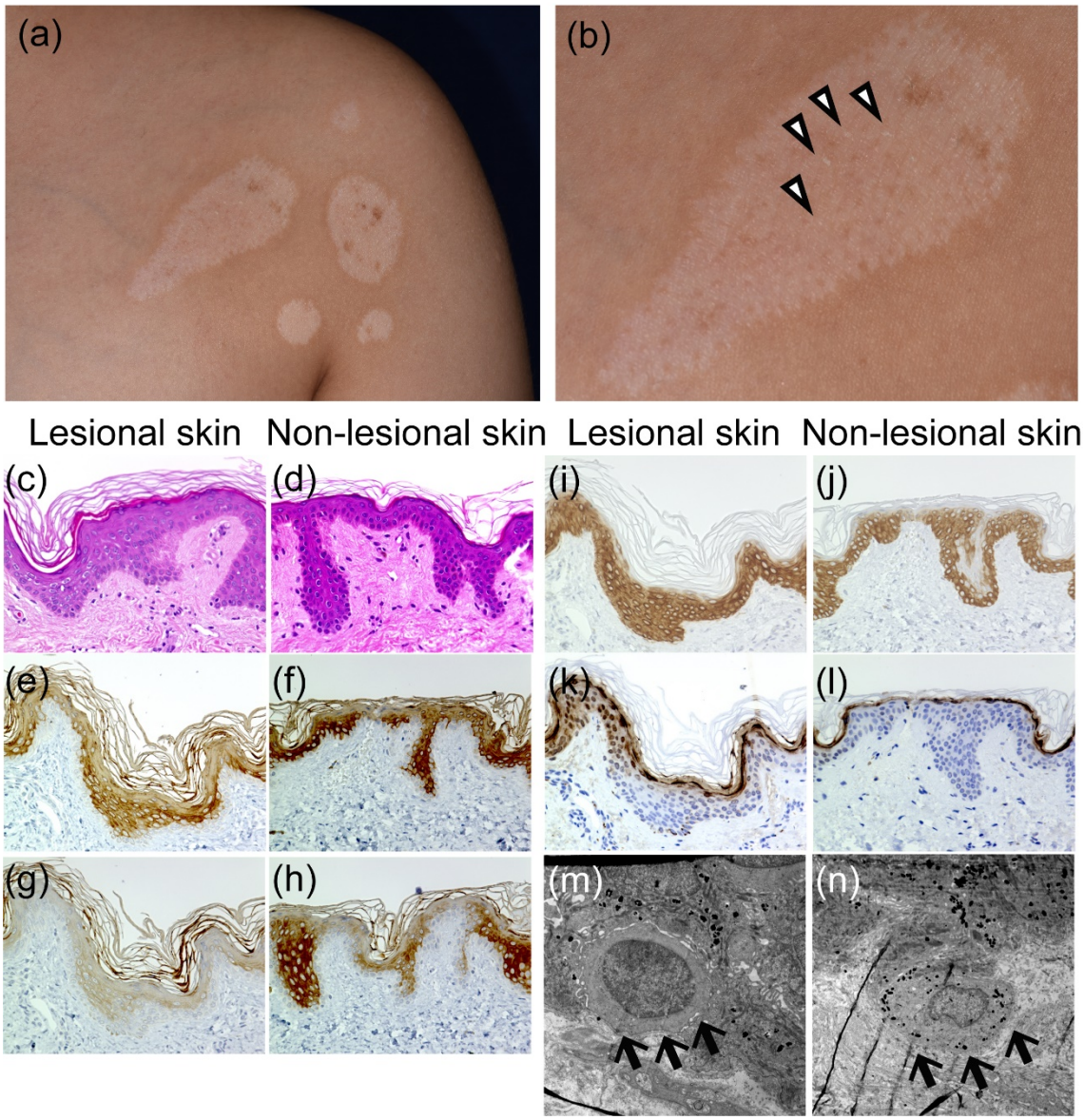

Figure 2. Clinical manifestations, histological and ultrastructural analyses for Case 2.

(**a-b**) Clinical manifestations. Round hypopigmented macules on the left shoulder (**a**). Fine scales on the macule (arrowheads) (**b**).

(**c-d**) Histological observation. Acanthosis and hyperkeratosis in the epidermis of

the lesional skin (**c**). Non-lesional skin (**d**) (Haematoxylin and eosin staining. Original magnification x400).

(**e-l**) Immunohistochemical studies on lesional skin (**e, g, i, k**) and non-lesional skin (**f, h, j, l**). K1 (**e, f**), K10 (**g, h**), K14 (**i, j**) and filaggrin (**k, l**). (original magnification x400).

(**m-n**) Electron microscopy studies on melanocytes of the lesional epidermis (**m**) and the non-lesional epidermis (**n**) (arrows; original magnification x5,000).

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