CASE REPORT

Dyschromatosis universalis hereditaria: a familial case with ultrastructural skin investigation

Yi-Ying Chin¹,²,³, Gwo-Shing Chen¹,³, Stephen Chu-Sung Hu¹,³, Cheng-Che E. Lan¹,²,³,*

¹ Department of Dermatology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
² Department of Dermatology, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan
³ Department of Dermatology, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

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A B S T R A C T

Dyschromatosis universalis hereditaria (DUH) is a rare disease that is inherited both in autosomal dominant and autosomal recessive patterns. It is characterized by appearance of pinpoint to pea-sized hypo- and hyper-pigmented macules distributed in a reticulated pattern over the trunk and limbs within the first few years of life. Although the pathogenesis is still not clear, some authors proposed that decreased melanosome synthesis rate may underlie this disorder. We describe a 56-year-old female and her 24-year-old son with generalized symmetrically distributed hypo- and hyper-pigmented macules. After clinical, histological and ultrastructural examination, we proposed defect in melanosome transfer from melanocytes to keratinocytes may underlie the pathogenesis of DUH.

Introduction

The dyschromatoses are a group of rare genodermatoses characterized by the presence of asymptomatic hyper-pigmented macules admixed with variably sized hypo-pigmented macules. There are two classic forms of dyschromatoses: dyschromatosis universalis hereditaria (DUH) and dyschromatosis symmetrica hereditaria (DSH, which is also known as acropigmentation symmetrica of Dohi). In recent years, with the development of genetic analysis, ADAR1 or DSRAD gene mutations have been found in DSH but not in DUH, and therefore these two diseases are now regarded as two different entities.¹ Although the first reported case² and most subsequently reported cases of DUH were of Japanese origin, sporadic cases have been reported from all over the world.³⁻⁵ Herein, we report a Taiwanese mother and her son with DUH.

Case presentation

Patient 1 was a 56-year-old Taiwanese woman who presented with generalized symmetrically distributed hypo- and hyper-pigmented macules. The skin lesions appeared in infancy and progressed with time. Patient 2 was her 24-year-old son with a history of similar skin lesions which appeared before one year of age. Physical examinations of the skin of both patients revealed disseminated hyper- and hypo-pigmented macules of varying size ranging from 2 mm to 30 mm involving almost the entire body in a symmetrical pattern, which were more prominent on the extremities with relative sparing of the palms, soles and face (Figure 1). The individual skin lesion was mottled in appearance. Hair, nails, teeth and the oral mucosa appeared normal. Both patients had normal mental and developmental milestones. They reported no extensive sun exposure, history of photosensitivity, or systemic illness prior to the onset of the lesions. The mother was married to a non-consanguineous male with no similar skin lesions. None of the mother’s siblings or her parents had similar skin lesions. The family pedigree is shown in Figure 2.

We performed skin biopsies on the hypo- and hyper-pigmented lesions of both patients. The specimens were sent for hematoxylin and eosin (H&E) stain and transmission electron microscopy (TEM) study. The H&E stained specimens taken from the hyper-pigmented macules of both patients revealed increased melanin deposition in the basal layers of the epidermis (Figure 3A). No conspicuous melanin incontinence was found. There was no acanthosis or hyperkeratosis of the epidermis and the dermis was unremarkable. The hypo-pigmented lesions were also biopsied which showed decreased melanin deposition in the basal layers of the epidermis (Figure 3B). Melanocytes were present in the basal layers of both hyperpigmented and hypopigmented areas.

* Corresponding author. Cheng-Che E. Lan, Department of Dermatology, Kaohsiung Medical University Hospital, No. 100, Tzyou 1st Road, Kaohsiung 807, Taiwan. Tel.: +886 7 3121101 6104; fax: +886 7 3216580.
E-mail address: laneric@gmail.com (C.-C.E. Lan).
Ultrastructural examination via TEM revealed that the melanocyte number was similar in both the hyper- and hypo-pigmented lesions (approximately 10–15 basal keratinocytes: one melanocyte) (Figure 4A and 4B). The melanosomes numbers were similar in the melanocytes of both hypo- and hyper-pigmented lesions, and melanosomes of all stages were found in the melanocytes of both lesions (Figure 4D–G). However, there were very few melanosomes noted in the adjacent keratinocytes of the hypo-pigmented lesion. In contrast, the keratinocytes of the hyper-pigmented lesions contained numerous fully melanized melanosomes which were aggregated to form melanosome complexes (Figure 4C). Most of the melanosomes were smaller than 0.5 μm.

Discussion

In this report, we described two cases of DUH and their ultrastructural skin findings. In our patients, we found there was no obvious difference in melanocyte numbers between the hyper- and hypo-pigmented lesions and the melanosome numbers in the melanocytes of both lesions were also similar. However, decreased melanosome numbers in the adjacent keratinocytes of the hypo-pigmented lesions were noted. In contrast, numerous fully melanized melanosomes were aggregated to form melanosome complexes in the keratinocytes of the hyper-pigmented lesions. According to the above findings, we proposed defect in melanosome transfer from melanocytes to keratinocytes may underlie the pathogenesis of DUH.

Autosomal dominant inheritance pattern was seen in our patients. Most of the previously reported DUH cases were also inherited in autosomal dominant pattern though some were autosomal recessive and sporadic cases were noted.

The clinical diagnosis of DUH in these two cases was made based on the distribution of the skin lesions and the history of the patients. Other pigmentary disorders which should be considered in the differential diagnosis were reviewed and compared in Table 1.

The typical DUH skin lesions were characterized by the appearance of pinpoint to pea-sized hypo- and hyper-pigmented macules distributed in a reticulated pattern over the trunk and limbs which often appeared within the first few years of life. Though mucosa and palmoplantar areas were frequently spared, some cases had oral mucosa and tongue involvement with mottled pigmentation. Abnormalities of hair and nails have also been described. Associated abnormalities were rarely seen though cases with tuberous sclerosis, photosensitivity and neurosensory hearing defect, small stature and high-tone deafness, and X-linked ocular albinism had been reported. Compared to previously reported cases, the skin lesions of our patients are more prominent at extremities and less skin lesions are found on the trunk region. There are no associated abnormalities noted.

The histopathology of DUH specimens usually show normal epidermis with no acanthosis or parakeratosis. The hyperpigmented lesions reveal an increase in melanin content of the basal layer and melanin incontinence is sometimes seen. The hypo-
pigmented lesions show relatively decreased melanin deposition at the basal layer. In contrast to some reports, there was no conspicuous melanin incontinence in the hyper-pigmented lesion in our cases.

The etiology and pathogenesis of DUH is not clearly established. Cutaneous pigmentation depends on the number of melanocyte, the melanogenic activity within the melanocytes, the proportion of mature melanosomes and/or their transfer and distribution within the keratinocytes. Yang and Wong reported a DUH case with “giant pigment granules” in keratinocytes, melanocytes and dermal phagocytes among the hyperpigmented lesion, but those findings were not seen in our cases. Our findings also differed from Kim et al., who found no melanosomes in the melanocytes and keratinocytes of the hypo-pigmented lesions. Our finding is consistent with Nuber et al., who also found similar melanocyte numbers in both hypo- and hyper-pigmented lesions. Besides, the melanosome numbers in the melanocytes were also similar in both hypo- and hyper-pigmented lesions. In addition, Nuber et al. reported positive DOPA reaction is similar (which indicates tyrosinase activity) under TEM in melanocytes of both hyper- and hypo-pigmented skin lesions. According to our findings and the finding of Nuber et al, we propose the difference in transfer and distribution of melanosomes within the epidermal melanin units may underlie the pathogenesis of DUH.

The distinct clinical and morphologic patterns between the juxtaposed hypo- and hypopigmented macules suggest the possibility of different genotypes in the same individual which indicates cutaneous mosaicism. But the typical distribution of DUH skin lesions does not fit the patterns of clinical involvement of cutaneous mosaicism, such as lines of Blaschko, a checkerboard pattern, a phylloid pattern, a patchy pattern without midline separation, or a lateralization pattern.

Figure 3 Skin biopsy specimen taken from patient 1. (A) Hyper-pigmented lesion showed increased melanin deposition in the basal layer of the epidermis, no conspicuous melanin incontinence was seen (H&E, 100×). (B) Decreased melanin deposition at the basal layer of the hypo-pigmented lesion (H&E, 100×).

Figure 4 (A) Electron micrograph showed melanosomes in the melanocyte (black arrow) and keratinocytes of the hyper-pigmented lesion (TEM, 4000×). (B) melanocyte (white arrow) of the hypopigmented lesion, only few melanosomes are found in the adjacent keratinocytes (TEM, 4000×). (C) The melanosomes in the keratinocytes of the hyperpigmented lesion aggregate to form melanosome complex (red arrow) (TEM, 25000×). (D) Different stages of melanosomes are found in the melanocyte of the hypopigmented lesion (TEM, 30000×). (E) Close view of different staged melanosomes. (K: keratinocyte; I: stage I melanosome; III: stage III melanosome; IV: stage IV melanosome).
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<th>Table 1 Differential Diagnosis of Dyschromatosis Universalis Hereditaria.5,8–10</th>
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<td>Inheritance</td>
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<tr>
<td>Dyschromatosis universalis hereditaria</td>
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<td>Dyschromatosis symmetrica hereditaria</td>
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<td>Dyskeratosis congenita</td>
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<td>Xeroderma pigmentosum</td>
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<td>Generalized Dowling–DeGos disease</td>
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<td>Chronic arsenic toxicity</td>
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AD = autosomal dominant; AR = autosomal recessive.
In summary, we report these two cases of DUH and their ultrastructural skin findings. Our results indicated that defects in melanosome transfer to keratinocytes may underlie this disorder. Further functional studies are needed to clarify the pathoetiology.

References