Case Report

Epidermolysis Bullosa Simplex-Dowling–Meara Mimicking Epidermolysis Bullosa Simplex with Mottled Pigmentation

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Abstract

Epidermolysis bullosa simplex-Dowling–Meara (EBS-DM) variant is an autosomal dominant blistering genodermatosis due to mutations in genes coding for keratin 5 (K5) or keratin 14 (K14), specifically at the rod domain. Postinflammatory dyspigmentation can arise at sites of blistering, sometimes in a reticulate or mottled configuration. This mimics EBS with mottled pigmentation (EBS-MP), usually due to mutation in the head domain of K5, for which the pigmentation is not preceded by blisters. We report a case of an adult Malay male with recurrent blisters and mottled hyperpigmentation over his trunk and limbs, consistent with EBS-DM clinically, and confirmed on genetic mutation sequencing. Different K5 or K14 mutations, by altering keratinocyte adhesion and interfering with melanin pigment transport, can lead to variable phenotypes of skin fragility and/or hyperpigmentation, possibly modulated by other genetic or environmental factors.

Keywords: Epidermolysis bullosa simplex with mottled pigmentation, epidermolysis bullosa simplex-Dowling–Meara, mottled hyperpigmentation

Introduction

Epidermolysis bullosa simplex-Dowling–Meara (EBS-DM) is an autosomal dominant blistering genodermatosis due to mutations in genes coding for keratin 5 (K5) or keratin 14 (K14), specifically at the rod domain. Clinical manifestations include generalized herpetiform blistering, progressive palmoplantar keratoderma, nail dystrophy, and frequent mucosal involvement. Postinflammatory hyper- and hypopigmentation is common and can sometimes be reticulate or mottled. A differential diagnosis will be EBS with mottled pigmentation (EBS-MP). We report a case of an adult Malay male with EBS-DM and prominent mottled hyperpigmentation, confirmed on genetic mutation sequencing. We compare this case with EBS-MP and other causes of reticulate hyperpigmentation due to K5 or K14 mutations.

Case Report

A 29-year-old Malay male presented with recurrent blisters over frictional sites of his trunk and limbs since birth. There was less blistering with time but he would still develop new blisters when his skin was rubbed. The blisters would resolve, leaving dark brown patches. He had thickened palms and soles since young. There was no family history of note. On examination, there were extensive dark brown macules and patches distributed over his trunk [Figure 1] and limbs, with some arranged in a mottled, reticulate pattern, especially over his thighs. A cluster of dried-up scale-crust was noted over the right thigh [Figure 2], and a coalescent group of tense vesicles was noted over the left mid-back [Figure 3]. Diffuse palmoplantar keratoderma was present. Longitudinal melanonychia was present over the fingernails. Dental malalignment was seen. A fresh blister was induced over the patient's right forearm using a pencil eraser, and biopsy was taken from blister edge for immunofluorescence mapping, which revealed slightly ragged K5 and K14 staining at the basal keratinocytes. Blood was sent for sequencing of the K5 and K14 genes. Heterozygous mutation in K14 (14 p.R125C) was found. This was consistent with EBS-DM.

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Discussion

EBS-DM is an autosomal dominant blistering genodermatosis due to mutations in genes coding for K5 or K14, leading to their decrease at the basal keratinocytes, with skin fragility. The point mutations occur at the rod domain (Pfendner and Bruckner, 2016).[1] Clinical manifestations include generalized herpetiform blistering, progressive palmoplantar keratoderma, nail dystrophy, and frequent mucosal involvement (Pfendner and Bruckner, 2016).[1] Blistering tends to improve with age. Postinflammatory hyper- and hypopigmentation is common and can sometimes be reticulate or mottled.[2] EBS-MP was a differential in this patient [Table 1]. Blistering in EBS-MP, however, tends to be mild and localized over the distal extremities.[3] Herpetiform blisters are not a feature. Of note, the pigmentation of EBS-MP is not preceded by blisters and most commonly involves the trunk. Focal palmoplantar keratoderma may be seen. The mutation most commonly seen in EBS-MP is the p.Pro25 Leu mutation in the head domain of K5.[3]

Histologically, a biopsy from an area of hyperpigmentation for both EBS-DM and EBS-MP shows focal hyperpigmentation of the basal cells and pigmentary incontinence without an inflammatory infiltrate.[2,4] Ultrastructural analysis of pigmented areas demonstrates mature melanosomes within the basal keratinocytes that could be interpreted as consistent with postinflammatory hyperpigmentation.[2,5] Round and whisk-like tonofilament clumps in the basal keratinocytes can be seen in EBS-DM, while in EBS-MP, sparse round tonofilament clumps can be seen.[2]

In our patient, his hyperpigmentation only appeared over sites of previous blistering, consistent with postinflammatory changes. Grouped herpetiform blisters were seen with confluent

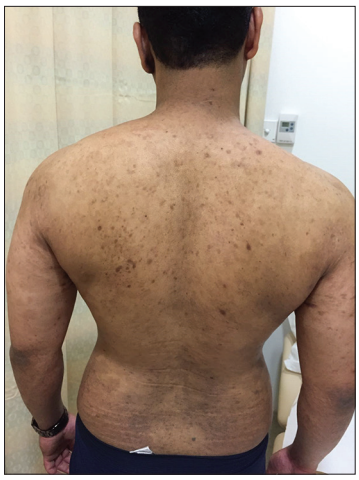

Figure 1: Mottled postinflammatory hyperpigmented macules and patches distributed over the posterior trunk and proximal upper limbs

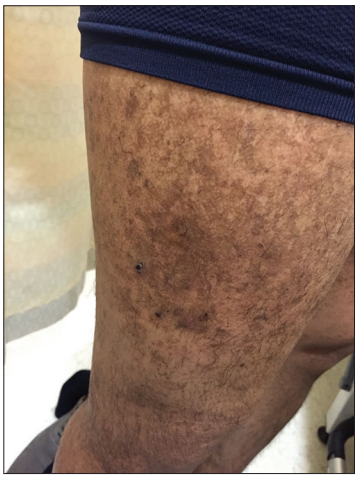

Figure 2: Discrete to confluent postinflammatory hyperpigmented macules and patches, some in reticulate configuration, distributed over the right thigh. Cluster of dried-up scale-crust seen over the mid-lateral aspect of the right thigh

Table 1: Clinical features of different reticulate pigmentation disorders due to keratin mutations

	Pigmentation	Blistering	Other clinical features	Genetic mutation
EBS-DM	Postinflammatory hyper- and hypopigmentation can occur at sites of the previous blistering; can be reticulate or mottled	Generalized, herpetiform at birth; improves with age	Progressive confluent palmoplantar keratoderma, nail dystrophy, and frequent mucosal involvement	Rod domain in K5 or K14 gene
EBS-MP	Mottled hyper- or hypopigmentation; not preceded by blisters; most commonly involves the trunk	Mild and localized over the distal extremities; no herpetiform blisters	Focal palmoplantar keratoderma may be seen	Head domain in K5 gene (most common)
DDD	Reticulate hyperpigmentation in the intertriginous areas	Nil	Comedonal lesions over the back, neck, and pitted perioral scars	Loss-of-function mutation in K5 gene
DPR	Reticulate hyperpigmentation trunk, neck, proximal limbs; persists throughout life	Acral blistering sometimes observed	Poorly developed dermatoglyphics, hypohidrosis, and heat intolerance (common to both DPR and NFJS); diffuse alopecia	Mutation of dominant gene coding for K14
NFJS	Reticulate hyperpigmentation of trunk, neck, possibly peri-orbital/peri-oral; can fade after puberty	Acral blistering sometimes observed	Poorly developed dermatoglyphics, hypohidrosis, and heat intolerance (common to both DPR and NFJS); palmoplantar keratoderma, nail dystrophy, and enamel defects	Mutation of dominant gene coding for K14

EBS-DM: Epidermolysis bullosa simplex-Dowling–Meara, EBS-MP: Epidermolysis bullosa simplex with mottled pigmentation, DDD: Dowling–Degos disease, DPR: Dermatopathia pigmentosa reticularis, NFJS: Naegeli–Franceschetti–Jadassohn syndrome

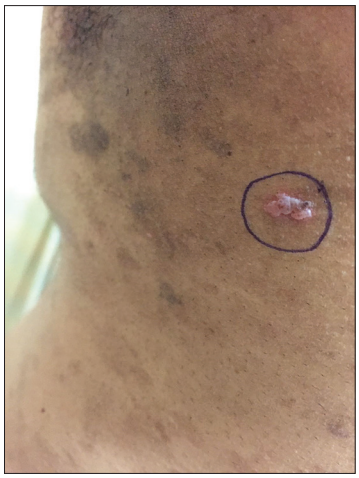

Figure 3: Coalescent group of tense vesicles noted over the left mid-back

palmoplantar keratoderma, consistent with EBS-DM. The heterozygous mutation in K14 (14 p.R125C) is well-described in EBS-DM, occurring at the highly conserved boundary region of the central alpha-helical rod domain (Pfendner and Bruckner, 2016).[1]

Other causes of reticulate pigmentation due to underlying keratin mutations include Dowling–Degos disease (DDD), dermatopathia pigmentosa reticularis (DPR), and Naegeli–Franceschetti–Jadassohn syndrome (NFJS) [Table 1]. DDD is an autosomal dominant disorder associated with loss-of-function mutation in K5 gene, typically occurring in adults.[6] Patients can present with reticulate hyperpigmentation in the intertriginous areas, associated with comedonal lesions over the back, neck, and pitted perioral scars. DPR and NFJS are both allelic autosomal dominant ectodermal dysplasias, associated with mutations in K14 gene.[7] Both present with reticulate hyperpigmentation, poorly developed dermatoglyphics, hypohidrosis, heat intolerance, and sometimes, acral blistering. Palmoplantar keratoderma, nail dystrophy, and enamel defects are common in NFJS, whereas diffuse alopecia is only seen in DPR. In DPR, hyperpigmentation persists throughout life, while in some cases of NFJS, hyperpigmentation fades after puberty.[7]

K5/K14 mutations can alter keratinocyte organization and adhesion leading to skin fragility. These mutations can also result in hyperpigmentation, possibly due to aberrant melanosome uptake by keratinocytes and longevity of melanin granules in basal keratinocytes.[6] K5 has been shown to interact with components of microtubule-dependent motors, which are involved in melanin pigment transport.[6,8] The relationship between these genetic mutations and the variable phenotypes is unclear and may be modulated by other genes or environmental factors.

Our patient was given genetic counseling and referred to a local EB support group. At last review, he was coping well.

Conclusion

EBS-DM can present with marked postinflammatory hyperpigmentation that mimics EBS-MP. A history of preceding blisters where hyperpigmentation is seen and the presence of herpetiform blisters are useful to differentiate EBS-DM from EBS-MP clinically. Genetic mutation sequencing shows point mutations in the rod domain for K5 or K14 in EBS-DM while the mutation most commonly seen in EBS-MP is the p.Pro25 Leu mutation in the head domain of K5. Of note, K5 or K14 mutations can lead to skin fragility, hyperpigmentation, or both.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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