

Case Report

Familial epidermal nevi: case report and literature review

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Received March 3, 2016; Accepted June 7, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: Epidermal nevi (EN) are a kind of benign skin hamartomas arising from the overproduction of keratinocytes. EN tends to distribute along the lines of Blascho mirroring lines of ectodermal embryologic development. Sporadic EN is common, but familial EN is rare. We report here a new family with five members presenting two variants of EN.

Keywords: Hamartoma, inflammatory linear verrucous epidermal nevus, keratinocyte, mosaicism, verrucous nevus

Introduction

Epidermal nevi (EN) are nests of epidermal cells that are noted at birth or within the first year as a thin plaque or linear tan patch often along Blaschko lines [1]. Extensive EN, often in unilateral distribution, is called systematized EN. Histologically, EN is characterized by hyperkeratosis and papillomatosis. EN can have syndromic/nonsyndromic association with other cutaneous/extracutaneous lesions. Treatments of EN include topical tretinoin cream and 5-fluorouracil, topical corticosteroids, laser therapy, cryotherapy, trichloroacetic acid peeling and surgical therapy [2]. Except complete excision, other treatments could hardly prevent recurrence.

According to clinical manifestation, EN can be divided into five types: localized EN, nevus uniuslateris, inflammatory linear verrucous EN (ILVEN), systematized EN, and EN syndrome. ILVEN demonstrates mild chronic inflammation in superficial dermis. EN usually occurs sporadically, and familial occurrence is rarely reported in literatures. Here, we report two cases from a family with a history of ILVEN.

Case report

The family included eleven members who belonged to four generations with blood relationship. Five individuals from three generations in this family suffered from EN, including the propositus (case 1), his mother, his uncle, as well as his elder female cousin and her son (**Figure 1**). Two out the five cases were typical and discussed in details. Case 1, a 22-year-old man, presented with erythematous, linear, verrucous and keratotic lesions following Blaschko's line since early infancy on the buttock and perianal areas, the right upper and lower extremities, as well as submaxilla (**Figure 2A**). The lesions were located around the anus when he was 10 days old, and the lesions were slowly increased in both size and distribution, finally covering the above mentioned areas. Pruritus existed at the lesions all the time. No abnormality was detected in general physical and systemic examinations. Laboratory examinations such as complete blood count, routine urine analysis, serum electrolytes, and liver and kidney function tests were all within normal ranges. Histological examination showed hyperparakeratosis and acanthosis of the epidermis.

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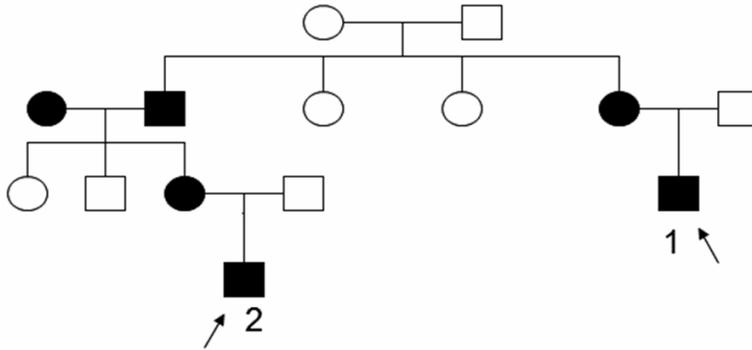


Figure 1. Pedigree pattern of the family. Men are presented by squares, and women by circles. The solid symbols denote EN cases.

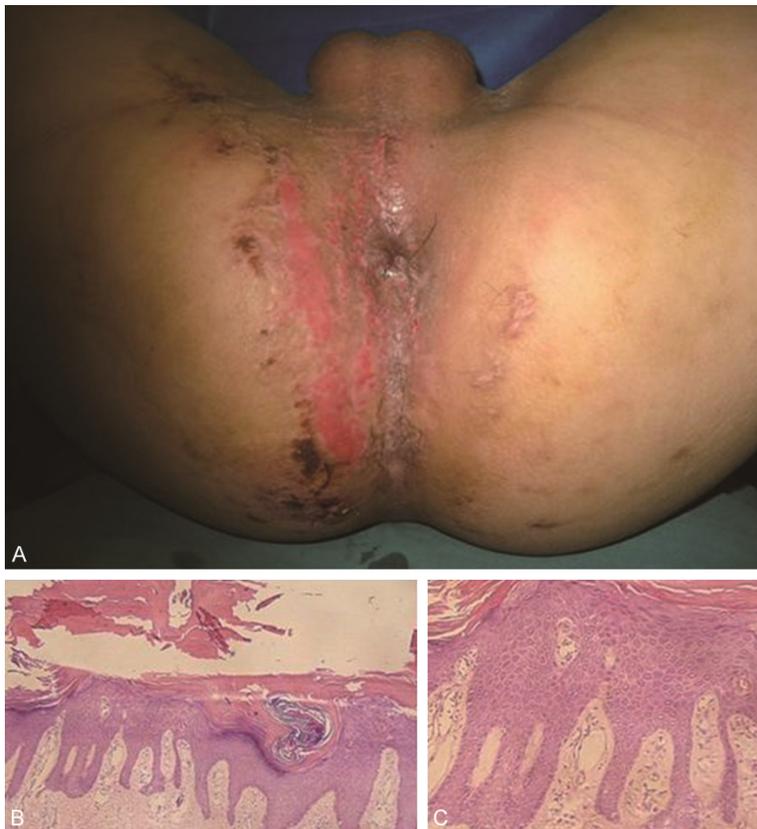


Figure 2. Case 1. (A) Erythematous, keratotic, verrucous and linear lesions following Blaschko's line on the buttock. Hyperkeratosis and acanthosis of the epidermis after hematoxylin and eosin staining observed under magnifications of (B) $\times 40$ and (C) $\times 100$.

The upper dermis showed mild perivascular lymphohistiocytic infiltration with dilated blood vessels (**Figure 2B** and **2C**). Previous treatment included carbon dioxide laser, which removed part of his lesion but resulted in apparent scarring. However, new lesions were not prevented. Case 2, a 2-year-old boy who was the nephew

of case 1, was noticed to have small erythematous soft verrucous papules and plaques arranged in linear pattern in the right buttock (**Figure 3A**), perianal areas and the right underarm at birth. The lesions caused continuous itching. The child had normal developmental milestones. His skin biopsy specimen was similar to that of case 1 and showed hyperplastic and papillomatous epidermis with hyperparakeratosis and lymphocytic infiltration in the upper dermis (**Figure 3B** and **3C**). Based on clinical and histopathological grounds, the two cases were diagnosed to have ILVEN. In addition, the three other cases in the same family were the mother and uncle of case 1, as well as the mother of case 2. All the three cases shared similar clinical changes, but refused skin biopsy. Clinical examination and family history could give presumptive diagnoses of ILVEN for two cases and localized EN for one case (mother of case 1) (**Figure 4**). The mother of case 1 was treated with minor operation, and the other two were both successfully treated with full thickness excision and skin grafting. No recurrence occurred for the three until now.

Discussion

EN is noted at birth or early infancy as verrucous papules that slowly grow and coalesce to form linear verrucous plaques. Only one lesion is presented in the localized variant, which is classically presented as a well-demarcated linear array of verrucous papules or plaques. Nevus uniuslateris is considered as a linear EN that is localized at only one side of the body, along the lines of Blaschko. ILVEN is a unilateral linear epidermal nevus distinguished clinically

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Figure 3. Case 2. (A) Erythematous verrucous papules and plaques arranged in linear pattern on the right buttock. Hyperplastic and papillomatous epidermis with hyperparakeratosis and lymphocytic infiltration in the upper dermis after hematoxylin and eosin staining observed under magnifications of (B) $\times 40$ and (C) $\times 100$.



Figure 4. A limited verrucous tan plaque on the right nasolabial groove. Because of continuous scratching for better appearance, the original lesion was almost invisible.

by its erythema and pruritus, and histopathologically by the presence of inflammation and parakeratosis. In the systematized variant, multiple and extensive linear epidermal nevi are found along Blaschko's lines in widespread and symmetric distribution. Patients with epidermal nevus syndrome usually suffer from systemic manifestations such as abnormalities of the skeletal, ocular, and central nervous systems in addition to systematized or localized epidermal nevi [3].

The linear pattern often follows Blaschko's lines, which are believed to represent patterns of epidermal migration during embryogenesis. This suggests that EN may be caused by a postzygotic mutation of keratinocytes during embryogenesis. Sobey et al. have discovered mosaicism for chromosome 6 in skin fibroblasts of EN lesions [4]. Mutations of keratins 1 and

10 are shown to be responsible for a rare subgroup of EN, the linear epidermolytic hyperkeratosis [5]. Hafner et al. have identified activating FGFR3 mutation in 33% of patients with nonorganoid EN [6]. The mutations are present only in EN, while adjacent normal skin shows wild-type FGFR3 sequence. Therefore, mosaicism of the FGFR3 gene in human skin may cause nonorganoid EN [4]. All these researches suggest that EN is caused by spontaneous somatic mutations during embryogenesis, forming skin mosaicism.

Since EN are supposed to be caused by somatic mutations during embryogenesis, EN should be sporadic and nonhereditary. Paradoxically familial cases of EN have been occasionally described in literatures [7-11]. Moulin G et al. report 2 cases of limited ILVEN from a non-consanguineous family found at early infancy [11]. Hamm H et al. report 2 cases of systemized ILVEN from a non-consanguineous family found at early infancy [10]. Alsaleh QA et al. report 4

cases of systemized ILVEN from a consanguineous family found at early infancy or early childhood [9]. Goldman K et al. report 2 cases of systemized ILVEN from a non-consanguineous family found at adult ages [8]. Mazereeuw-Hautier J et al. report 2 cases of limited ILVEN from a non-consanguineous family found at birth or childhood [7]. Neither autosomal nor X-linked inheritance can explain such a contradictory phenomenon. Mazereeuw-Hautier et al. have put forward two concepts to explain the familial occurrence, paradigmatic inheritance and the retrotransposon theories [7]. According to the first hypothesis, heterozygous individuals who are phenotypically normal carry a mutation through generations. A familial aggregation would only be observed when an event of postzygotic loss of heterozygosity occurring at an early stage of embryogenesis gives rise to a clone of cells that are either homozygous or hemizygous for the mutation. In the latter theory, retrotransposons that are of retroviral origin exist in human genome. They may affect the activity of adjacent genes at an early stage of development, resulting in silencing or activation of gene expression. In animals, retrotransposons may give rise to phenotypic variation in the form of variegated coat patterns reminiscent of Blaschko's line. This concept may also explain why some skin disease occurs usually sporadically and occasionally familiarly. In the family reported herein, both hypotheses are reasonable, but a lot more family cases and further investigations are still needed to explain this uncommon inheritance phenomenon. To summarize, we report familial EN affecting five family members in two generations with two variants: ILVEN and localized EN. Further studies should focus on the genetic background of this family for a better understanding of the familial occurrence of EN.

Acknowledgements

We thank Guodong Song for the clinical pictures and Pathology Department of Jinan Central Hospital for pathological sections. This work was supported by the Affiliated Hospital of Shandong University of Traditional Chinese Medicine.

Disclosure of conflict of interest

None.

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