

# Does Inflammatory Linear Verrucous Epidermal Nevus Represent a Segmental Type 1/Type 2 Mosaic of Psoriasis?

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## Key Words

Inflammatory linear verrucous epidermal nevus (ILVEN) · Linear psoriasis · Postzygotic mutation · Nevoid psoriasis, heritability · Segmental type 1/type 2 mosaic · Epigenetic

## Abstract

**Background:** A 6-year-old girl with a symmetric linear eruption on both of her legs, clinically and histologically resembling inflammatory linear verrucous epidermal nevus (ILVEN) or linear psoriasis (LP), with concomitant psoriasis of the guttata type and a positive family history of psoriasis is presented. The questions as to whether LP actually exists and ILVEN represents a distinct entity are still under debate. **Objective and Methods:** The recent literature concerning case reports of ILVEN and LP is reviewed. **Results:** Case reports of ILVEN and LP can be subdivided into four different groups: (1) ILVEN with or without concomitant psoriasis, only in part reacting to antipsoriatic treatment, (2) ILVEN without concomitant psoriasis, (3) LP with concomitant psoriasis vulgaris, with both groups 2 and 3 reacting successfully to antipsoriatic treatment, and (4) LP without concomitant psoriasis vulgaris and with no family history of psoriasis (very rarely reported). **Conclusion:** It is hypothesized that inflammatory linear verrucous eruption besides nevoid

psoriasis/LP represents a further segmental type 1/type 2 mosaic of psoriasis which, if a (verrucous) epidermal nevus exists, shows a high affinity of occurrence in close context to such a nevus. Heritability is thought to be possible.

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Psoriasis vulgaris, today recognized to be the most prevalent autoimmune disease in man [1], is thought to be caused by genetic and environmental factors. Most molecular genetic examinations propose a polygenic origin [2]. Type I psoriasis is defined by early onset, heritability, high association with human leukocyte antigen (HLA) and a strong tendency to become generalized, while type II psoriasis is characterized by later onset, weak HLA association and a sporadic appearance [3]. Nevoid/linear psoriasis (LP) without further signs of psoriasis is rarely reported [4–6]. Three reports of LP exist occurring in a patient with psoriasis vulgaris [7–9].

Inflammatory linear verrucous epidermal nevus (ILVEN), described in 1971 by Kaidbey and Kurban [10] and Altman and Mehregan [11], always follows the lines of Blaschko. ILVEN, similar to other nevi, is proposed to reflect genetic mosaicism [12]. Cases where there are no clear-cut detectable differences between ILVEN and a possible LP make it difficult to characterize ILVEN as a



**Fig. 1.** Symmetric linear eruption following the lines of Blaschko.

distinct skin disease. The debate is still going on as to whether linear eruptions, clinically and histologically resembling psoriasis, in such cases really do represent LP or if in fact they reflect the coincidental occurrence of ILVEN on a patient with psoriasis vulgaris. Atherton et al. [4] argued that epidermal nevus may, as a result of the postzygotic mutation, provide 'fertile sites' which offer a facilitated development of psoriasiform inflammation. The observation of Al-Enezi et al. [13], who in 2001 reported 2 girls with an ILVEN appearing shortly after birth, followed by the development of juvenile psoriatic arthritis but no other skin signs of psoriasis (with the exception of some nail pitting in one of the girls with a positive family history) supports such considerations.

When presented with a 6-year-old girl with a symmetric rash on both legs, following the lines of Blaschko, clinically and histologically resembling LP or ILVEN, with a positive family history for psoriasis and a guttata type eruption of psoriasis in association with an episode of sore throat, the practicing dermatologist has cause to reflect on pathogenetic considerations.

### Case Report

A 5-year-old girl developed a linear red and scaly plaque on the inner side of her right leg. Topical treatment with a cream containing mometasone (Elocom<sup>®</sup>) almost completely cleared it up, except for some remaining slightly hypopigmented patches. One year later, the rash reappeared as symmetric linear streaks on both legs (fig. 1) together with disseminated tiny red and scaly plaques pre-

dominantly localized on the trunk. This new outbreak was associated with an episode of sore throat. On histological examination, an inflammatory infiltrate of lymphocytes and occasional histiocytes, showing some exocytosis, was present in the upper dermis, just beneath the epidermis, which showed an intact granular layer, orthokeratosis and focal parakeratosis with some neutrophilic granulocytes. Direct immunofluorescence was negative. Histologically, the diagnosis of an initial lesion of psoriasis or a psoriasiform reaction in an epidermal nevus was proposed. Treatment with mometasone on the left leg was again successful whereas tacrolimus 0.03% (Protopic<sup>®</sup>), applied to the right leg, failed to clear it up. Tacalcitol (Curatoderm<sup>®</sup>) was then applied once daily and it was completely cleared up after 8 weeks. The guttata lesions subsided completely within the next few months without any active treatment. Up until this episode, the girl's personal medical history was absolutely uneventful. A thorough inquiry of the family's medical history revealed that the maternal grandfather had suffered from psoriasis vulgaris since his youth.

### Discussion

In addition to environmental triggers like mechanical, chemical or ultraviolet injury, infections, drugs, smoking, psychological stress and others, psoriasis is thought to have a genetic origin [2]. Type I psoriasis is highly HLA associated [3]. In 1994, Tomfohrde et al. [14] reported for the first time a rare family where a single gene localized to the distal end of the long arm of chromosome 17 (17q24-q25) was involved in psoriasis susceptibility. Since then, different linkage of psoriasis susceptibility loci other than HLA and 17q have been reported. None of these loci are X linked. The expression of psoriasis is supposed to be inherited by predominantly polygenic transmission [2]. Most of the predisposing genes may be polymorphisms.

The pathogenesis of ILVEN is still unknown. ILVEN occurs sporadically. Familial cases are extremely rare [15-18]. Therefore ILVEN, similar to other nevi, is thought to be the result of a new and early postzygotic mutation reflecting genetic mosaicism [12]. No molecular genetic knowledge yet exists. In their recent review, Lee and Rogers [19] summarize: ILVEN can be present at birth but more frequently arises in infancy. Neither side is predominant and there is an equal sex distribution. Histopathological reports, if available, document psoriasiform changes.

A thorough study of the recent literature concerning cases which are interpreted by their authors as to represent ILVEN or LP reveals that the findings can be subdivided into four different groups (some representative reports are cited in parentheses):

- first, there are case reports of ILVEN with [13, 20, 21] or without [13, 22] concomitant psoriasis, which only in part react to anti-inflammatory/antipsoriatic treatment like steroids, calcipotriol, dithranol, topical isotretinoin [22] or methotrexate;
- second, there are case reports of ILVEN without concomitant psoriasis [23–25], and
- third, we can find three case reports of LP with concomitant psoriasis vulgaris [7–9], both the second and third group reacting successfully to treatment with antipsoriatics;
- fourth, three case reports of LP without concomitant psoriasis vulgaris (‘nevroid psoriasis’) exist [4–6] without a family history of psoriasis. All these cases histologically and clinically represented typical psoriasis following the lines of Blaschko and reacted exceptionally well to antipsoriatic treatment.

Lipsker et al. [26] demonstrated for the first time that an acquired inflammatory dermatosis in Blaschko-linear distribution does show genetic mosaicism. Furthermore various acquired inflammatory eruptions showing linear arrangement are supposed to reflect mosaicism resulting from clonal ‘predisposed’ cells predetermined during embryogenesis [27, 28]. Various autosomal dominant skin disorders, such as dyskeratosis follicularis, disseminated superficial actinic prokeratosis, pemphigus benignus familiaris and others, may show linear arrangement. In segmental type 1 mosaic, a new and early postzygotic mutation in a so far healthy person gives rise to a clone of cells which in turn can be responsible for the development of a linear phenotype of such a disease. If the mutation is not confined to somatic cells but also includes the germ line, this new mutation may be inherited by the offspring [29]. In a sporadically occurring acantholytic epidermal nevus, the postzygotic mutation may also involve the germ line, and this can cause bullous congenital ichthyosiform erythroderma in the offspring [30]. An example of a functional mosaic of an X-linked dominant, male-lethal trait would be the CHILD nevus that can be transmitted from a mother to her daughter [31].

Linear arrangement of inflammatory skin diseases that usually show an autosomal dominant mode of transmission, if they happen in an already affected person, may be the result of loss of heterozygosity [32], thereby reflecting a segmental type 2 mosaic [29, 33].

In linear inflammatory dermatosis, which represents a segmental type 1 mosaic of an otherwise autosomal dominant inherited skin disease, a mutation in a *single* gene is supposed to be causative. Segmental type 2 mosaic of an otherwise autosomal dominant inherited skin disease

is also supposed (and has been demonstrated [32]) to be the result of loss of heterozygosity in a *single* gene. In psoriasis, which is thought to be of polygenic origin, Happle [34] proposed somatic recombination as an explanation for the occurrence of linear arrangement: in a subject heterozygous for several genes predisposing to psoriasis, LOH occurs in one of these genes during early embryogenesis, giving rise to a clone of cells which is homozygous or hemizygous for this gene, thereby changing from an ordinary additive gene to a major gene predisposing to psoriasis. Together with other predisposing genes and environmental factors LP may develop. This concept could explain the occurrence of LP as a nevroid variant (segmental type 1 mosaic) but also as LP developing in context with psoriasis vulgaris (segmental type 2 mosaic).

Besides acanthosis with elongation of the rete ridges and hyperorthokeratosis, ILVEN shows areas characterized by spongiotic epidermis, absent granular layer and parakeratosis [35]. In other words, ILVEN unites histologically the characteristics of a (verruccous) epidermal nevus with a superimposed subacute eczema [36]. Cases interpreted by their authors as representing ILVEN which do not respond completely to anti-inflammatory/antipsoriatic treatment [13, 20–22] are described as a preexisting (verruccous) epidermal nevus with a sudden onset of a pruritic inflammation. In these cases, it is only the superimposed pruritic inflammation which reacts positively to the treatment. The underlying nevus, as a rule, cannot be treated by antipsoriatics. Cases interpreted by their authors as representing ILVEN and successfully treated by antipsoriatics show a pruritic inflammation from the start [23–25]. In these cases, the anti-inflammatory/antipsoriatic treatment can only be successful because there exists no underlying epidermal nevus. Therefore, today’s findings in the literature concerning ILVEN can be differentiated into ILVEN *with* and ILVEN *without* a (reported) underlying (verruccous) epidermal nevus. But, what is ILVEN without an underlying nevus? It is not a nevus. It is an inflammatory linear verruccous eruption. Why should we not conclude then that analogous to the heritability of acantholytic epidermal nevus [30], this inflammatory linear verruccous eruption is hereditary, and not the nevus? The following new definition could help to abolish confusion: what up to now has been named ILVEN represents an inflammatory linear verruccous eruption, which is clinically and histologically strongly similar to psoriasis [19], can be successfully treated by antipsoriatics and, if a (verruccous) epidermal nevus is existing, shows a high affinity of occurrence in close context with such a nevus [4] – the acronym could be changed to ILVE(N). Therefore one

could hypothesize, that ILVE(N), like nevoid psoriasis/LP, represents a further segmental type 1 mosaic of psoriasis, which, analogous to the proposed explanation for the presence of LP [34], results from an early postzygotic mutation of a gene predisposing to psoriasis. Consequently the occurrence of ILVE(N) in a patient with psoriasis vulgaris could be interpreted as a segmental type 2 mosaic of psoriasis (the 6-year-old girl presented here would be such a case).

Interestingly, except for the few reports of familial ILVEN [15–18] no further comments supporting the possibility for a heritability of ILVEN to the offspring exist. In 2002, Happle [37] hypothesized that a transposable element, which is partly activating and partly silencing a neighboring gene by demethylation or methylation at an early developmental stage, could be responsible for the development of ILVEN. But up to now there is nothing yet known about the role of epigenetics in autosomal genes predisposing to inflammatory skin diseases like psoriasis.

However, only a thorough follow-up of patients with ILVE(N) and their offspring, and also the results of further molecular genetic investigations, will help to confirm or to reject such hypothetical considerations.

## Conclusion

Understanding the genetic background of linear variants of inherited disorders (which are otherwise an autosomal dominant trait) and knowledge of genomic and functional mosaicism allow us to hypothesize that a polygenic inflammatory disease like psoriasis may show clinical variants which reflect so-called segmental type 1 or type 2 mosaics. Like nevoid psoriasis/LP, ILVE(N) may represent a segmental type 1 or type 2 variant of psoriasis caused by an early postzygotic genetic or even epigenetic event.

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