

# Superimposed Segmental Manifestation of Both Rare and Common Cutaneous Disorders: A New Paradigm

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**Abstract.** In autosomal dominant skin disorders, a superimposed mosaic involvement arranged in a linear or otherwise segmental pattern is sometimes noted. Molecular proof of such “type 2 segmental manifestation” has so far been provided in Hailey-Hailey disease and Cowden syndrome. A similar superimposed segmental involvement can be found in numerous common disorders with a polygenic background, such as psoriasis, lichen planus, or vitiligo. In polygenic diseases, however, we can never recognize with certainty a “type 1 segmental manifestation”, which is why we should use more neutral terms in the form of “isolated” versus “superimposed” segmental involvement. In the near future, the new paradigm of superimposed segmental manifestation may hopefully help elucidate the molecular basis of both monogenic and polygenic skin disorders.

**Key words:** autosomal dominant skin disorders, type 2 segmental manifestation, loss of heterozygosity, polygenic skin disorders, isolated versus superimposed segmental manifestation.

## MANIFESTACIÓN SEGMENTARIA SOBREIMPUESTA EN ENFERMEDADES CUTÁNEAS RARAS Y FRECUENTES: UN NUEVO PARADIGMA

**Resumen.** En los trastornos cutáneos autosómicos dominantes a veces se aprecia un mosaicismo sobreimpuesto con una disposición en patrón lineal o segmentario. La prueba molecular de ese tipo de «manifestación segmentaria tipo 2» la han proporcionado la enfermedad de Hailey-Hailey y el síndrome de Cowden. En numerosos trastornos frecuentes con una herencia poligénica como la psoriasis, el liquen plano o el vitíligo, se puede encontrar una afectación segmentaria sobreimpuesta similar.

Sin embargo, en las enfermedades poligénicas nunca podemos reconocer con certeza una «manifestación segmentaria tipo 1», por lo que utilizamos términos más neutrales, como afectación segmentaria «aislada» frente a «sobreimpuesta».

En un futuro próximo el nuevo paradigma de manifestación segmentaria sobreimpuesta ayudará, en el mejor de los casos, a esclarecer la base molecular de los trastornos cutáneos monogénicos y poligénicos.

**Palabras clave:** trastornos cutáneos autosómicos dominantes, manifestación segmentaria tipo 2, pérdida de heterocigosis, trastornos cutáneos poligénicos, manifestación segmentaria aislada frente a sobreimpuesta.

In this review, a general perspective of superimposed segmental manifestation of skin disorders is presented. With regard to this new concept, rare monogenic and common polygenic disorders have some things in common, but there are also major differences that will be explained in the following paragraphs.

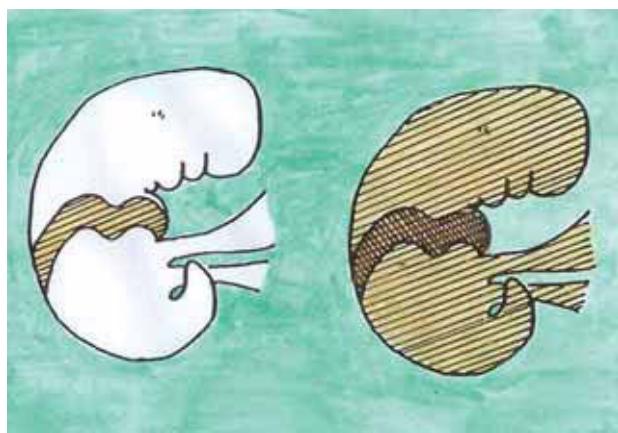
It is well known that autosomal dominant skin disorders may sometimes occur in a segmental form reflecting

mosicism. Until the end of the past century, the erroneous concept prevailed that all of these mosaic manifestations resulted from postzygotic new mutations occurring at an early developmental stage in an otherwise healthy embryo. Today it is clear that this view was too simplistic.

## Superimposed Segmental Manifestation of Rare, Monogenic Skin Disorders

In 1973, when preparing my “Habilitationsschrift” on the Gorlin syndrome, I came across some case reports on adnexal skin tumors showing a strikingly pronounced segmental involvement<sup>1,2</sup>. Subsequently I found some reports on segmental cutaneous leiomyomatosis in patients whose

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**Figure 1.** Two different types of segmental manifestation of autosomal dominant skin disorders. Type 1 (left) reflects heterozygosity resulting from an early postzygotic new mutation in an otherwise healthy embryo. Type 2 (right) originates from early loss of the corresponding wild-type allele in a heterozygous embryo.



**Figure 2.** Type 2 segmental leiomyomatosis in a 42-year-old man<sup>9</sup> (reprinted with permission). The segmental lesions were present since infancy, whereas bilateral, less pronounced, nonsegmental leiomyomas developed later on his arms and legs.

family members had the ordinary, nonsegmental phenotype<sup>3,4</sup>. Such cases puzzled me because the segmental lesions tended to be far more pronounced than the nonsegmental tumors. Apparently, this was not compatible with the generally held belief that such cases reflected a simple mosaic manifestation originating from a postzygotic new mutation.

In 1991, I proposed to explain cases of linear porokeratosis coexisting with disseminated superficial actinic porokeratosis (DSAP), or associated with a family history of DSAP, by a somatic recombination resulting in loss of heterozygosity<sup>5</sup>. In 1993 I mentioned in a review that the lesions of pronounced segmental leiomyomatosis may likewise reflect early LOH<sup>6</sup>, but still I did not take the opportunity to deduce from these clinical examples a new concept that would be of significance for genetics and general medicine.

## Delineation of a General Rule

Some years later I got the idea that such cases exemplified a general, and rather simple, rule of dichotomy<sup>7,8</sup> (fig. 1). The well-known type 1 reflected a postzygotic new mutation occurring at an early developmental stage in an otherwise healthy embryo. By contrast, a type 2 segmental involvement resulted from early loss of the corresponding wild-type allele occurring in a heterozygous embryo<sup>7</sup>. Pertinent clinical examples comprised DSAP, cutaneous leiomyomatosis, epidermolytic hyperkeratosis of Brocq, Darier disease, neurofibromatosis 1, multiple syringomas, and Hailey-Hailey disease<sup>8</sup>. A typical case of type 2 segmental leiomyomatosis is shown in figure 2<sup>9</sup>. This patient developed, in addition, some nonsegmental leiomyomas on all of his limbs [personal communication Dr. Francisco Camacho, Sevilla, June 1995]. Today, the number of examples of a possible type 2 segmental involvement includes 20 different autosomal dominant skin disorders (table 1).

## Molecular Proof of the Concept

In a patient with linear Hailey-Hailey disease being superimposed on symmetrical, nonsegmental lesions, Poblete-Gutiérrez et al<sup>23</sup> provided molecular evidence that the segmental disorder originated from loss of the corresponding wild-type allele. The linear disorder had been present since the age of 3 months, whereas nonsegmental lesions appeared 24 years of age. Several family members of this patient had nonsegmental Hailey-Hailey disease.

In 2007, Happle<sup>17</sup> identified type 2 segmental Cowden disease in a case that had been mistaken as an example of "Proteus syndrome"<sup>26</sup>. The 3-year-old boy belonged to a family with Cowden disease and had a *PTEN* germ-line

mutation. He had a unilateral, systematized epidermal nevus showing loss of the corresponding wild-type allele. Similar, previously published cases of "Proteus" or "Proteus-like syndrome"<sup>27,28</sup> could be reclassified in the same way<sup>17</sup>. The associated 'linear Cowden nevus' differs from all other epidermal nevi so far known<sup>29</sup>. Hence, in this particular disorder I provided further molecular proof of the new genetic concept without doing any molecular analysis myself.

## Historical Cases Revisited and Explained by the New Concept

A classical report of a type 2 segmental involvement was published in 1893 by Vittorio Mibelli<sup>30</sup>. His patient had a type of porokeratosis that is today called the "plaque type of Mibelli" and known to be inherited as an autosomal dominant trait. Apparently, nobody had so far worried about the fact that Mibelli's 21-year old patient had a pronounced segmental involvement of his right forearm and hand (fig. 3A), whereas disseminated plaques were noted on both hands (fig. 3B), the face and the neck. The linear disorder had appeared at the age of 2 years, whereas the nonlinear, disseminated plaques were first noted at the age of 7 years. Moreover, a brother and a sister as well as the father were affected with nonsegmental plaques of porokeratosis. Hence, Mibelli's publication can be taken as the earliest report known so far documenting a type 2 segmental manifestation of an autosomal dominant skin disorder<sup>24</sup>.

Another historical case was found to be an example of type 2 segmental acanthosis nigricans<sup>25</sup>. A male patient with coexistent segmental and nonsegmental acanthosis nigricans was repeatedly described by Hellen Ollendorff Curth in articles that appeared during the years 1936 through 1976<sup>31-35</sup>. Nonsegmental acanthosis nigricans developed at the age of 10 years and disappeared almost completely after puberty, whereas a pronounced, strictly unilateral manifestation in the form of a large "acanthotiform nevus" had been noted at birth and remained unchanged during a follow-up period of 40 years<sup>35</sup>. In a biopsy specimen obtained from the segmental lesion, the epidermal proliferation was "more marked" when compared to that of the nonsegmental disorder "but was much of the same character"<sup>31</sup>. Curth was unable to explain this unusual case, but today it can be taken as a typical example of type 2 segmental acanthosis nigricans.

## Additional Possible Examples of Type 2 segmental Involvement

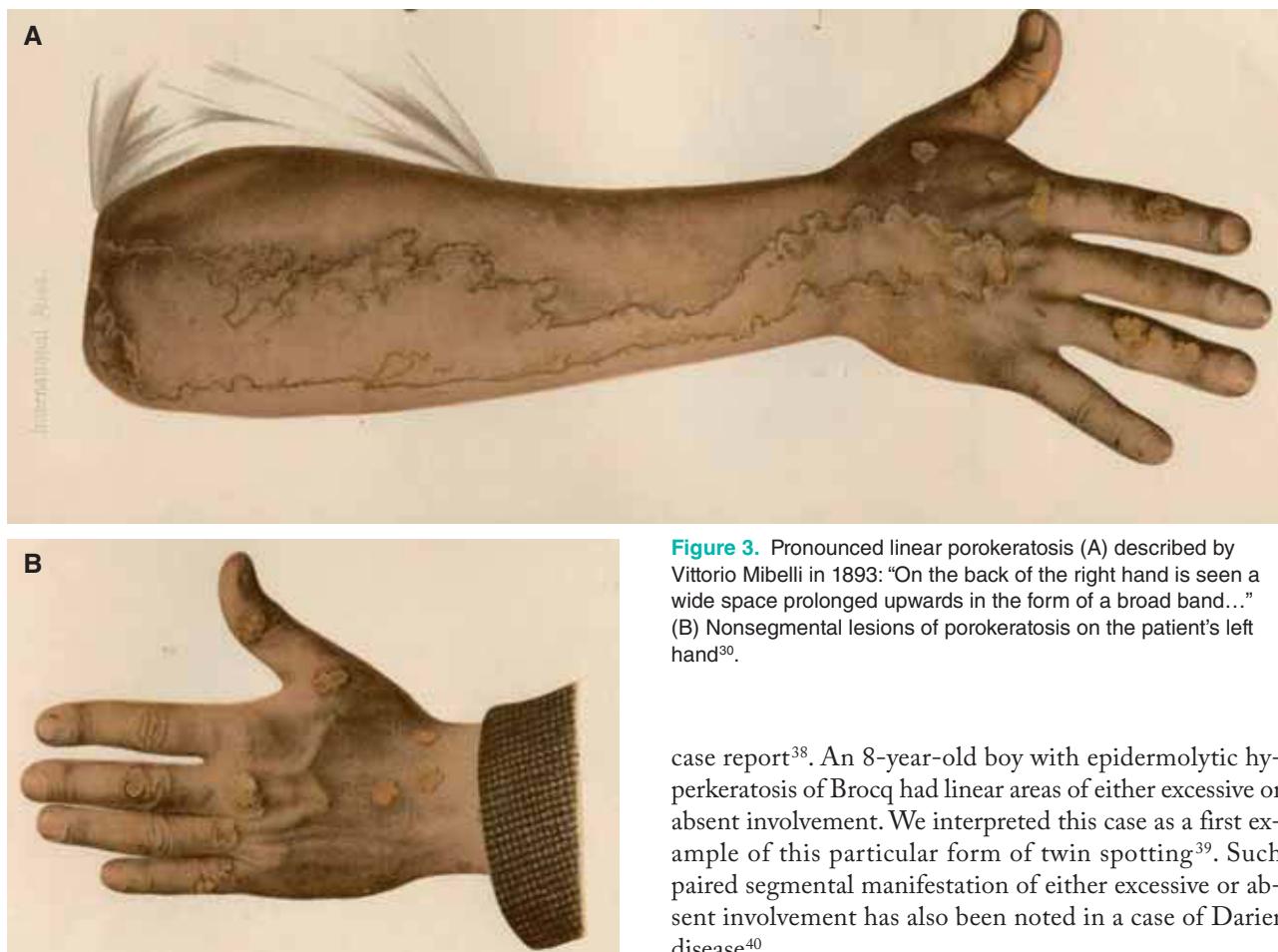
Wright and Ryan<sup>36</sup> described "multiple familial eccrine spiradenoma with cylindroma" present in three consecu-

**Table 1.** Presently known examples of type 2 segmental manifestation of autosomal skin disorders

|   |
|---|
| Neurofibromatosis 1 <sup>8,10</sup>                           |
| Tuberous sclerosis <sup>11,12</sup>                           |
| Cutaneous leiomyomatosis <sup>7,8</sup>                       |
| Glomangiomatosis <sup>12-14</sup>                             |
| Buschke-Ollendorff syndrome <sup>15,16</sup>                  |
| Cowden disease <sup>17</sup>                                  |
| Multiple eccrine syringoma <sup>8</sup>                       |
| Multiple trichoepithelioma <sup>14,18</sup>                   |
| Multiple spiradenoma (present review)                         |
| Multiple basaloid follicular hamartoma                        |
| Nonsyndromic hereditary basal cell carcinoma <sup>12,19</sup> |
| Darier disease <sup>8,20,21</sup>                             |
| Hailey-Hailey disease <sup>8,22,23</sup>                      |
| Epidermolytic hyperkeratosis of Brocq <sup>7,8</sup>          |
| KID syndrome <sup>12,14</sup>                                 |
| Disseminated superficial actinic porokeratosis <sup>7,8</sup> |
| Plaque-type porokeratosis of Mibelli <sup>24</sup>            |
| Autosomal dominant dyskeratosis congenita <sup>12</sup>       |
| Acanthosis nigricans <sup>25</sup>                            |
| Ehler-Danlos syndrome type III (present review)               |

tive generations. A female individual of the youngest generation (case 5) had a "linear arrangement of subcutaneous nodules overlying the left mastoid" with onset in childhood. Histopathologically, these nodules were exclusively eccrine spiradenomas, whereas the nonsegmental tumors of the other family members were found to be either eccrine spiradenomas or cylindromas, with onset in adulthood in 3 out of 4 cases. Remarkably, pain was reported as being "marked" in case 5, whereas in the other cases pain was described as "present in some lesions". Hence, this report can be taken as an example of type 2 segmental eccrine spiradenomatosis.

In a 25-year-old woman with Ehlers-Danlos syndrome type III, a disease inherited as an autosomal dominant trait, Sidwell et al<sup>37</sup> described a large connective tissue nevus (collagenoma) involving the left side of her back and the left arm. This lesion had been present since childhood. Interestingly, the authors stated that "there have been no published reports to our knowledge of collagen naevi associated with Ehlers-Danlos syndrome, though several such cases have been observed by one of us (F. M. Pope).



**Figure 3.** Pronounced linear porokeratosis (A) described by Vittorio Mibelli in 1893: "On the back of the right hand is seen a wide space prolonged upwards in the form of a broad band..." (B) Nonsegmental lesions of porokeratosis on the patient's left hand<sup>30</sup>.

case report<sup>38</sup>. An 8-year-old boy with epidermolytic hyperkeratosis of Brocq had linear areas of either excessive or absent involvement. We interpreted this case as a first example of this particular form of twin spotting<sup>39</sup>. Such paired segmental manifestation of either excessive or absent involvement has also been noted in a case of Darier disease<sup>40</sup>.

### Open Questions

Future clinical and molecular research may answer the question whether the type 1 segmental manifestation occurs more frequently when compared to the type 2, or whether it's the other way around. In some disorders such as cutaneous leiomyomatosis or neurofibromatosis 1, it is my impression that the most frequently occurring segmental manifestation is the type 2<sup>12,41</sup>.

On the other hand, why do different genodermatoses strikingly differ with regard to the frequency of type 2 segmental manifestation? In some disorders such as glomangiomatosis, leiomyomatosis, DSAP and neurofibromatosis 1, the proneness to develop such superimposed segmental involvement appears to be extremely high<sup>12</sup> and may even give rise to familial occurrence of this particular form of mosaicism<sup>42-44</sup>. Conversely, in autosomal dominant ichthyosis vulgaris such mosaic manifestation appears to be extremely rare or even absent. Most likely, this discrepancy can be explained by the fact that different regions of the human genome show a different proneness to mitotic recombination<sup>45</sup>.

A common abnormality of collagen production may account for the development of both disorders in the same patient." Possibly, such cases can be categorized as a type 2 segmental manifestation of Ehlers-Danlos syndrome type III.

### What Happens to the Wild-Type Daughter Cell Resulting From Somatic Recombination?

One day, when we discussed this concept within our working group, Dr. Arne König asked me this question. Somatic recombination gives rise to two different homozygous cells, one of them carrying two wild-type alleles. Hence, why shouldn't we find a segmental area of healthy skin in vicinity to the type 2 segmental involvement? For obvious reasons, it seems virtually impossible to recognize such healthy segment of skin in a disorder like glomangiomatosis, but what about other autosomal dominant cutaneous traits? Some years later, when sitting in the library of the National Skin Centre in Singapore, I found a remarkable

Because the type 2 segmental involvement can today be taken as a well-established concept, the question arises whether it may be justified to assume this particular form of mosaicism also in cases of early pronounced segmental manifestation of a monogenic disorder even when nonsegmental lesions are not noted in the patient and his family<sup>46-48</sup>.

In order to solve such problems, we have to patiently wait until the concept of type 2 segmental involvement of autosomal dominant disorders is accepted by the majority of clinical dermatologists. Until now we are far from this goal. Many authors still ignore this concept when reporting characteristic cases of a type 2 segmental manifestation, for example in leiomyomatosis<sup>49-52</sup>, glomangiomatosis<sup>53-55</sup>, neurofibromatosis 1<sup>56,57</sup>, multiple trichopithelioma<sup>18,58</sup>, Buschke-Ollendorff syndrome<sup>59</sup>, DSAP<sup>60,61</sup>, or Hailey-Hailey disease<sup>62</sup>.

## Superimposed Segmental Manifestation of Common, Polygenic Skin Disorders

Common skin disorders with a polygenic background such as psoriasis or lichen planus may sometimes occur in a pronounced form arranged in a linear, checkerboard, or otherwise segmental distribution. These pronounced and conspicuous lesions are often associated with a less severe, nonsegmental involvement. Such cases can be best explained as a superimposed segmental manifestation<sup>63</sup>. In contrast to the monogenic traits, however, it is not appropriate in polygenic disorders to distinguish between a "type 1" and "type 2 segmental manifestation".

## Why not "Type 2 Segmental Manifestation"?

In polygenic diseases such as psoriasis or atopic dermatitis, we can never recognize with certainty a "type 1" segmental involvement because we can never exclude the possibility that additional nonsegmental lesions will appear later in life. Therefore, it seems appropriate to use less specific terms in the form of "isolated" versus "superimposed" segmental manifestation<sup>63</sup>. This terminology implies that an isolated segmental involvement may later transform into a superimposed one.

Another difference between monogenic and polygenic disorders lies in the fact that cases of a type 2 segmental manifestation of monogenic traits can plausibly be explained by LOH, whereas in polygenic disorders showing a superimposed segmental involvement the possibility of a postzygotic mutation giving rise to heterozygosity at an additional predisposing gene locus should likewise be considered.

**Table 2.** Presently known examples of polygenic disorders showing a superimposed segmental involvement\*

|                               |
|-------------------------------|
| Psoriasis                     |
| Pustular psoriasis            |
| Atopic dermatitis             |
| Chronic prurigo <sup>64</sup> |
| Lichen planus                 |
| Lichen nitidus <sup>65</sup>  |
| Granuloma annulare            |
| Vitiligo                      |
| Systemic lupus erythematosus  |
| Dermatomyositis <sup>66</sup> |
| Pemphigus vulgaris            |
| Graft-versus-host reaction    |
| Erythema multiforme           |
| Drug eruption                 |

\*Disorders without a reference number are reviewed in Happle R<sup>63</sup>.

A list of polygenic skin disorders showing a superimposed segmental involvement is presented in table 2. It should be borne in mind that the segmental lesions do not always follow Blaschko's lines. For example, segmental vitiligo is arranged in a flag-like pattern that is so far difficult to classify.

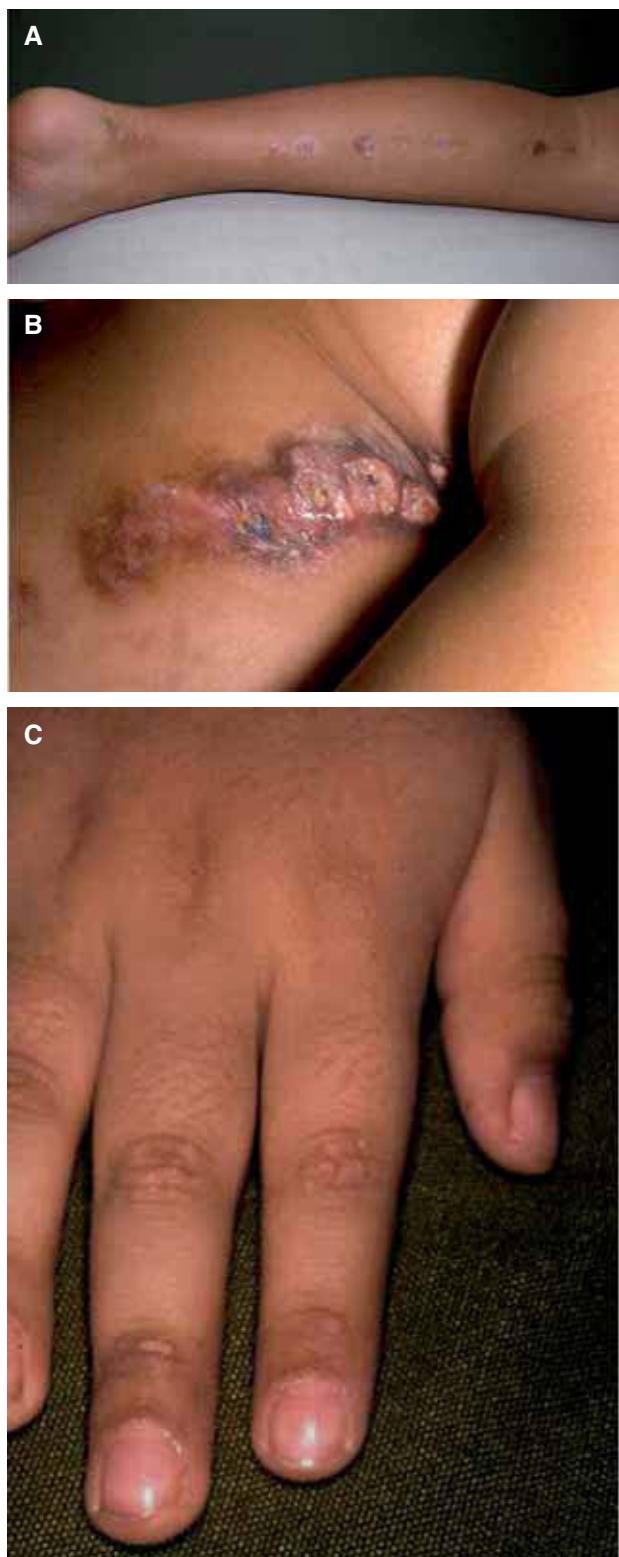
## Recently Reported Examples of Polygenic Skin Disorders Showing a Superimposed Segmental Involvement

Boccaletti et al<sup>67</sup> reported on a 6-year-old boy with disseminated lichen nitidus who had, in addition, pronounced linear lesions of the same disorder involving his left hand (fig. 4). This case has been interpreted as an example of superimposed linear lichen nitidus<sup>65</sup>.

Boente et al<sup>66</sup> described an 8-year-old boy with a 5-year-history of a linear atrophic disorder involving his left thigh to the heel (fig. 5A). The segmental area was indurated and partly ulcerated and repeatedly showed calcium extrusions (fig. 5B). Shortly after the onset of the linear disease the boy intermittently developed a nonsegmental periorbital and malar rash, and typical Gottron papules appeared on his finger joints (fig. 5C). Arthralgia, proximal weakness and malaise were likewise noted, but blood findings were found to be normal. During the bilateral rashes the linear lesions worsened. The authors cate-



**Figure 4.** Superimposed linear lichen nitidus in a 6-year-old boy. A. Pronounced linear involvement of left hand. B. Less severe, nonsegmental lesions of lichen nitidus involving the trunk. C. Biopsy from a linear palmar lesion showing typical features of lichen nitidus (HE,  $\times 100$ )<sup>67</sup>. Reprinted with permission from European Journal of Pediatric Dermatology.



**Figure 5.** Superimposed linear dermatomyositis in an 8-year-old boy. A. Linear arrangement of indurated, atrophic lesions. B. close-up of linear lesion showing calcium extrusion. C. Gottron papules showing a symmetrical distribution<sup>66</sup>. Reprinted with permission from *Dermatology* (Karger, Basel, Switzerland).

gorized this disorder as a further example of superimposed segmental manifestation of a polygenic disorder. This view has been supported by Lipsker and Lenormand who described a similar case<sup>68</sup>.

Kawachi et al<sup>64</sup> reported on a 75-year-old man with a 20-year history of chronic prurigo predominantly involving his arms, and a 3-year history of a pruritic linear eruption running from his left buttock to the lower leg. The linear lesion persisted for at least 6 years. Histopathological examination showed a subacute spongiotic dermatitis, which is why the authors assumed that the linear dermatitis was superimposed on the patient's chronic prurigo.

## Clinical and theoretical significance of superimposed segmental involvement of polygenic skin diseases

The concept of superimposed segmental manifestation of polygenic skin disorders can explain why "mixed" cases may occur, why the segmental involvement is usually present rather early in life or may even be noted at birth, and why these lesions are particularly resistant to therapeutic approaches.

In polygenic skin diseases, a superimposed segmental manifestation tells us something about the primary role of the skin in the pathogenesis of a given disorder. For example, psoriasis cannot simply be caused by the action of T cells, macrophages and neutrophils, because the arrangement of superimposed linear psoriasis heralds an etiologic factor inherent in the keratinocytes.

## Future aspects of the paradigm of superimposed segmental manifestation

In both monogenic and polygenic skin disorders, the concept of superimposed segmental manifestation may turn out to be of importance for molecular research because it offers the opportunity to compare DNA samples obtained from segmental and nonsegmental skin areas by application of presently available molecular methods such as the chip technique.

### Conflict of interests

Author has no conflict of interests to declare.

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