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Patchy Dermal Hypoplasia as a Characteristic Feature of Proteus Syndrome

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Background: The diagnostic criteria of Proteus syndrome include various lesions of localized overgrowth such as digital gigantism, hemihyperplasia with unilateral macrocephaly, epidermal nevus, and mesodermal hamartomas such as lipoma, lymphangioma, hemangioma, or fibroma. Hyperplasia of the plantar dermal tissue may result in a characteristic cerebriform appearance. However, hypoplastic lesions involving various tissues such as subcutaneous fat or muscles also may be observed in this syndrome. This paradoxical phenomenon has so far been underestimated, and the presence of circumscribed lesions of dermal hypoplasia has been entirely ignored.

Observations: We report 4 cases of Proteus syndrome associated with large patches of dermal hypoplasia, resulting in a more prominent appearance of venous vasculature.

Conclusions: Patchy dermal hypoplasia appears to be a characteristic feature within the spectrum of Proteus syndrome. The anomaly should not be confused with partial lipohypoplasia that may likewise be associated with this multisystem birth defect. From a review of the literature, we conclude that patchy dermal hypoplasia may have occurred in several previous cases. In the future, recognition of this cutaneous anomaly may help to establish the diagnosis in otherwise doubtful cases. To explain the coexistence of lesions of dermal hyperplasia and hypoplasia, we propose the genetic concept of "twin spotting." At the gene locus of Proteus syndrome the embryo would carry 1 allele giving rise to dermal overgrowth, whereas the corresponding allele would be responsible for a diminished proliferation of cutaneous fibroblasts. Somatic recombination may result in 2 different populations of cells homozygous for either allele.

Arch Dermatol. 1997;133:77-80

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THE PROTEUS syndrome includes partial gigantism of the fingers or toes, localized overgrowth of other body parts such as macrocephaly, and multiple mesodermal hamartomas such as lipoma, lymphangioma, hemangioma, or fibroma. 

Hyperplasia of the plantar dermal tissue may result in a characteristic cerebriform appearance ("moccasin feet"). The name of the syndrome reflects the protean variability of all of these signs and symptoms. Paradoxically, we herein describe several cases of Proteus syndrome showing widespread patchy lesions of dermal hypoplasia. It is our purpose to draw attention to this neglected cutaneous feature of the syndrome and to explain it by the genetic mechanism of "twin spotting."

REPORT OF CASES

CASE 1

A 6-year-old boy was affected with multiple developmental anomalies that were present since birth. He was the product of a normal pregnancy and delivery. Physical examination showed asymmetrical enlargement of the right cheek, the right ear, the left arm, and the right leg, including macrodactyly of the second and third toes. In addition, clinodactyly of the left fifth finger, malposition of the left third toe, and a cerebriform appearance of the soles were noted. Several brownish streaks of hyperkeratosis, representing an epidermal nevus of the soft, papillomatous type, were present on the right side of his neck and in the right axillary region. Below the left axilla, a subcutaneous lump measuring 8 cm in diameter was noted, suggesting on palpation the presence of a cavernous lymphangioma. A large telangiectatic nevus involved the left side of the lower part of his back and the lateral and ventral aspects of his left leg. On the left lower leg, several varicose veins were noted within the area of the telangiectatic nevus. In addition, small areas of telangiectatic nevus were noted on the upper part of the back, the dorsal aspects of both hands, the right leg, the penis, and the scrotum.

On the left side of the abdomen, several large areas of slight dermal...
hypoplasia with an irregular outline but a sharp midline demarcation were noted (Figure 1). The dermal hypoplasia was more easily discernible on palpation than on inspection. These areas were slightly erythematous and showed a more prominent venous vasculature. In part, there was overlapping with the lesions of the telangiectatic nevus. Similar lesions of widespread dermal hypoplasia involved the inner aspect of the right upper arm, the left groin, and the left thigh. The general health of this boy was otherwise good, as was his mental development.

CASE 2

A 7-year-old boy was affected since birth with a marked facial asymmetry. He had been born at term. His birth weight was 5000 g, his length was 59 cm, and his head circumference measured 38 cm. During infancy, an asymmetrical overgrowth of his left arm and his right leg was noted, and his facial asymmetry became more apparent, largely due to hypoplasia of the left half of his head. His motor and mental milestones were delayed. At age 7 years, an episode of epileptic seizures occurred, and subsequent neurological and angiographic examination revealed megalencephaly, electroencephalogram abnormalities, and marked intracranial phlebectasia on the right side.

On physical examination, short stature (102 cm), macrocephaly (circumference, 55 cm), marked facial asymmetry with hypoplasia of the left side, and asymmetrical overgrowth of the left arm and the right leg were noted. The left half of his tongue was considerably smaller, with a distinct midline demarcation. On his left arm, several small lesions of telangiectatic nevi were present and a linear brownish lesion with a velvety surface was noted, consistent with a diagnosis of epidermal nevus of a soft, papillomatous type. Bilateral hyperplasia of the plantar connective tissue resulted in a cerebriform appearance. In addition, a large well-demarcated area of dermal hypoplasia with venous prominence covered the ventral aspect of the right half of his trunk and his neck (Figure 2) as well as the medial part of his right arm and the lateral aspect of his right leg. On the left side, a similar cutaneous anomaly covered a segmental area comprising the lower part of his thorax and the upper part of his abdomen.

CASE 3

A 10-year-old Turkish girl was affected since birth with a large area of abnormally thin skin involving the right side of her trunk. When this cutaneous area was exposed to coldness, the girl suffered considerable pain, sometimes lasting for days, and the underlying veins became more prominent. Several years ago, the girl underwent surgery on her left foot, but her father was unable to give further details on this operation.

On physical examination, a large area of dermal hypoplasia showing prominent venous vasculature and a sharp midline separation covered the right half of her trunk (Figure 3). This abnormal area was superimposed by an extensive telangiectatic nevus involving the lower part of the thorax and the upper part of the abdomen on the right side. Her left foot had only 4 toes and showed macrodactyly of what was first taken as the second toe. This toe showed a transversal scar and absence of the nail. Moreover, a longitudinal scar was noted on the dorsal aspect of the foot. X-ray films revealed that the second toe had been surgically removed and that the end-phalanx of the remaining enlarged toe had likewise been resected (Figure 4). Hence, the present macrodactyly involved the third toe. On both sides, the plantar connective tissue was increased, resulting in a cerebriform appearance.
CASE 3

Case 3. Patchy dermal hypoplasia with prominent venous vasculature involving the right side of the trunk in a 10-year-old girl. The lesion is partly superimposed by a unilateral telangiectatic nevus.

Case 3. X-ray films of the left and right feet, documenting surgical removal of the entire second ray as well as of the end-phalanx of the enlarged third ray of the left foot (left).

CASE 4

A 7-year-old girl was affected since birth by an enlargement of her left cheek, resulting in marked facial asymmetry. Ultrasound examination showed overgrowth of the subcutaneous fatty tissue between the orbital and mandibular region of the left side. Ophthalmological examination performed at age 5 years showed an abnormally weak convergence reaction but no other abnormalities. Magnetic resonance imaging performed at age 6 years revealed an abnormal enlargement of the left hemisphere, especially of the left occipital lobe. In addition, a large slightly erythematous lesion of dermal hypoplasia with irregular outlines was present on the right side of her trunk (Figure 5). The involved area showed a prominent venous vasculature and a sharp midline demarcation. On palpation, the skin of this area appeared to be slightly thinner than elsewhere on the body.

Careful physical examination did not reveal any other abnormalities. In particular, her extremities, including the digits, were of normal and equal length on both sides. Her mental development appeared likewise to be normal.

COMMENT

In previous reports dealing with Proteus syndrome, various manifestations of overgrowth have been emphasized. Conversely, associated lesions representing hypoplasia or aplasia of tissue have so far generally been neglected. However, a localized absence or decrease of subcutaneous fatty tissue has been reported in several cases of Proteus syndrome. Interestingly, Clark et al. stated that "the importance of lipomatous changes and gigantism has overshadowed the consistent findings of deficient subcutaneous tissue and muscle atrophy in the so-called unaffected regions." Following this line of thought, we would like to emphasize that in previous reports the significance of hyperplastic changes of the dermal connective tissue, including cerebriform plantar lesions, has darkened the paradoxical presence of patchy dermal hypoplasia with prominent veins in the allegedly unaffected areas of skin.

To explain the co-occurrence of dermal hyperplasia and hypoplasia, we propose the genetic mechanism of twin spotting. In plants and animals, twin spots are a well-established phenomenon reflecting somatic recombination. In a developing organism heterozygous for 2 different alleles that are localized on either of a pair of homologous chromosomes, an event of mitotic crossing-over may give rise to 2 different homozygous cells, resulting in a pair of dissimilar mutant patches. The underlying genes may be either allelic or nonallelic. In human skin, the concept of twin spotting has been proposed to explain vascular twin nevi and phacomatosis pigmentovascularis, as well as the paradoxical coexistence of lipomatosis and partial lipohypoplasia observed in Proteus syndrome. Patchy dermal hyperplasia and hypoplasia may originate from a similar mechanism. One allele would account for dermal overgrowth, whereas the corresponding allele would be responsible for a diminished growth of dermal fibroblasts. The 2 alleles balance each other, resulting in a normal dermal tissue. At an early stage of embryogenesis, somatic recombination...
may result in 2 daughter cells homozygous for either allele. One would be a stem cell of circumscribed dermal overgrowth, whereas the other would give rise to patchy dermal hypoplasia.

In patients 1, 2, and 3, a diagnosis of Proteus syndrome could be established with certainty on the basis of other major signs such as macrodactyly, subcutaneous lymphangiomata, epidermal nevus, or cerebriform plantar lesions. In patient 4, however, overgrowth of fatty tissue of the left cheek and ipsilateral megalencephaly were the only additional signs that suggested Proteus syndrome. We propose that the presence of patchy dermal hypoplasia is a further criterion to establish the diagnosis of this phenotype, although in this particular case the absence of clinically recognizable overgrowth of dermal connective tissue makes it difficult to interpret the circumscribed dermal hypoplasia as a twin-spot phenomenon.

In previous reports on Proteus syndrome, several authors have mentioned areas of venous prominence,, which might be taken, at least in some of these cases, as a feature suggestive of the presence of patchy dermal hypoplasia, although some of these authors have interpreted this finding as a sign of partial absence of subcutaneous fatty tissue. On the other hand, the prominent appearance of venous vasculature observed in the areas of patchy dermal hypoplasia should not be confused with the literally prominent and tortuous varicose veins present in telangiectatic nevus as found in Proteus syndrome or Klippel-Trenaunay syndrome.

Patchy dermal hypoplasia as observed in Proteus syndrome can easily be distinguished from other congenital or acquired disorders characterized by a localized absence of dermal tissue. In focal dermal hypoplasia (Goltz syndrome), the lesions are not simply patchy but rather distributed in a pattern following the lines of Blaschko, and they tend to show herniation of fatty tissue. In Dellemann syndrome, the lesions of dermal aplasia usually show a round or oval “punched out” appearance, without any venous prominence. Atrophoderma of the Pasini-Pieri type is a disease showing prominent cutaneous veins, but this is an acquired disorder that is increasing slowly in otherwise healthy patients.

In conclusion, patchy lesions of dermal hypoplasia resulting in a prominent appearance of veins are characteristic of Proteus syndrome, and this cutaneous sign may help to establish the diagnosis in doubtful cases. So far, no data can be given regarding the frequency of this anomaly. Future clinical research on Proteus syndrome should, therefore, pay particular attention to the paradoxical phenomenon of patchy dermal hypoplasia that may or may not be associated with hypoplasia or aplasia of other tissues such as subcutaneous fat or muscles.

Accepted for publication July 22, 1996.
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REFERENCES