

LOCAL PANATROPHY WITH LINEAR DISTRIBUTION: A CLINICAL, ULTRASTRUCTURAL AND BIOCHEMICAL STUDY

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Abstract. A young female with local panatropy of the right-side extremities affecting all mesodermal layers—dermis, subcutaneous tissue, muscles, and bone—is described. The atrophies were strictly linear.

Ultrastructurally, collagen fibrils of the reticular dermis from the atrophic area consisted of two types, a large population of fibrils with decreased diameter and round cut-surface, and a small population with increased diameter and a "flower-like" cut-surface.

Collagen analysis revealed a reduced hydroxyproline concentration and content per mm² skin in atrophic area as compared with the perilesional and regional control. Urinary excretion of hydroxyproline was normal. Glycosaminoglycan analysis showed a less reduced content of hexosamine and uronic acid in the atrophic area per mm² skin, but no differences in the concentrations. Consistently, the gel/fibre ratio (uronic acid/hydroxyproline) was found slightly elevated in atrophic skin. The proportions of the individual glycosaminoglycans heparin, dermatan sulphate, hyaluronic acid and chondroitin sulphates were not affected.

It is concluded that reduced collagen and ultrastructural changes of collagen fibrils are significant features in local panatropy. The significance of local foetal factors affecting the somatic mesoderm is discussed.

Key words: Panatropy; Collagen; Glycosaminoglycans

In 1902 Campbell presented a case of local panatropy with primary atrophy of skin, underlying soft parts and bone with anisomelia (6). This called attention to one further case of local panatropy observed by Gowers in 1885, and re-examined by Barnes at the end of 1902 (1, 10). At a further re-examination in 1931 the atrophies had changed only slightly in the direction of recovery (2). In none of the original cases was the distribution of the atrophies recognized as being linear. To our knowledge no case has been assessed with modern investigative techniques.

MATERIALS AND METHODS

The patient is a 16-year-old female not predisposed to either cutaneous or to genetic diseases. At about the age

of 6 years, linear thinning of the skin of the right-side extremities developed over a period of a few months. The cutaneous atrophies remained stationary during the subsequent years, with no subjective symptoms. Sclerotic and inflammatory changes were never observed. Initially, she had remittant effusions on her right knee.

Physical examination showed linear dermal atrophy along the axis of the right arm and leg, with a punctate and cribriform appearance and a slight brownish pigmentation (Figs. 1, 2). In the right axilla and right proximal femur, two brown patches were found at the offspring of the linear atrophy. There was underlying atrophy of the subcutaneous tissue and muscles, with a slight right-sided wasting on neurological examination, though the deep tendon reflexes were normal. The muscular atrophy had resulted in hallux valgus and pes planus of the right foot (Fig. 3). Furthermore, there was anisomelia with 1.8 cm shortening of the right arm and 2.5 cm shortening of the right leg, with secondary pelvic declination and lumbar scoliosis (she was complaining of low-back pain). Joints were normal, with no sign of arthritis. Because of the clinical findings the diagnosis was concluded to be local panatropy.

Routine blood status including rheumatological tests (sedimentation rate, nuclear antibodies, rheumatoid factor, Waaler-Rose test) was normal.

Leukocyte chromosomes were 46XX, with no structural abnormalities.

Radiological examinations of chest, oesophagus, spine, extremity skeleton and joints were all normal, except for the anisomelia and scoliosis.

Scanning of the skeleton with technetium and scanning of the distal radius with photonabsorptiometry did not indicate any osseous disease.

Electromyography of atrophic muscles of her right arm was normal, as also were the muscular enzymes lactic acid dehydrogenase, creatine kinase and aldolase.

Skin biopsies for the different examinations were taken from her right upper arm under local anaesthesia of surrounding subcutaneous tissue with 1% lidocaine using a conventional manual punch. Biopsies were obtained from central parts of the atrophic area, with control biopsies from normal-looking skin of the perilesional area and regional control from the same side.

Histology

Skin samples taken as 4 mm punch biopsies were fixed in 4% phosphate-buffered formaldehyde, and processed routinely. The sections were stained with haematoxylin-

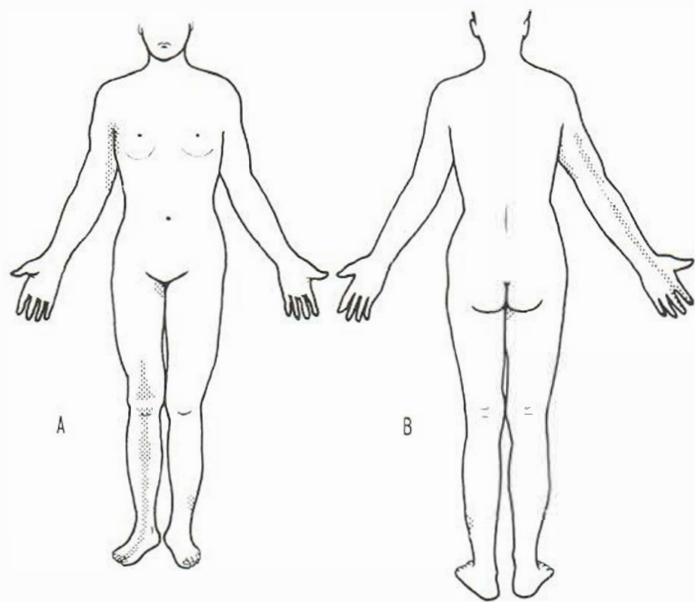


Fig. 1. Distribution chart of the lesions in the case of local panatrophphy with linear distribution presented.

eosin, van Gieson Hansen, PAS, orcein, toluidine blue, and examined with a conventional light microscope.

Electron microscopy

Skin samples taken as 2 mm punch biopsies were fixed in 6% glutaraldehyde or 0.2 mol cacodylate buffer, pH 7.3, with 7.5% sucrose, post-osmicated, dehydrated and embedded in Epon 812. Ultrathin sections were stained with uranyl acetate and lead citrate. For microscopy a Jeol 100 CX electron microscope was used.

Collagen analysis

The content of the collagen-specific amino acid hydroxyproline (Hyp) was measured in skin and urine.

Skin samples taken as 4 mm punch biopsies were extracted with acetone and ether and dried under vacuum. The dried and defatted skin (DDS) was hydrolysed in 6 N HCl for 18 hours at 118°C. The hydrolysate was evaporated

to dryness at 60°C at 50 mbar. The Hyp content of the hydrolysate was measured in an autoanalyser apparatus *ad modum* Blumenkrantz & Asboe-Hansen (5). Hyp was oxidized with chloramine-T, and the resulting pyrrole derivative reacted with *p*-dimethylaminobenzaldehyde. The extinction of the reaction mixture was measured at 555 nm.

A 24-hour urine, sampled while the patient was on a collagen-free diet, was analysed for polypeptide-bound Hyp and for total Hyp. Polypeptides were precipitated from 1 ml urine by adding 5 ml acetone. The precipitate was hydrolysed with 6 N HCl and analysed for Hyp. Total Hyp was determined on 1 ml urine hydrolysed with 1 ml 12 N HCl. The ratio of polypeptide-bound Hyp to total Hyp was calculated.

Glycosaminoglycan analysis

The glycosaminoglycans (GAG) were extracted as sodium salts from dried, defatted skin biopsies after digestion with

Table 1. Local panatrophphy—analyses of collagen and glycosaminoglycans in atrophic skin from upper arm compared with perilesional and regional controls

		Atrophic area	Perilesional control	Regional control
Defatted dried biopsy	mg	3.45	5.75	4.39
Hydroxyproline	nmol/mg	520	640	549
	nmol/mm ²	142	292	190
Uronic acid	nmol/mg	7.9	8.0	7.4
	nmol/mm ²	2.2	3.7	2.6
Hexosamine	nmol/mg	8.5	8.6	8.3
	nmol/mm ²	2.3	3.9	2.9
Ratio uronic acid/Hyp		15.2 × 10 ⁻³	12.5 × 10 ⁻³	13.5 × 10 ⁻³

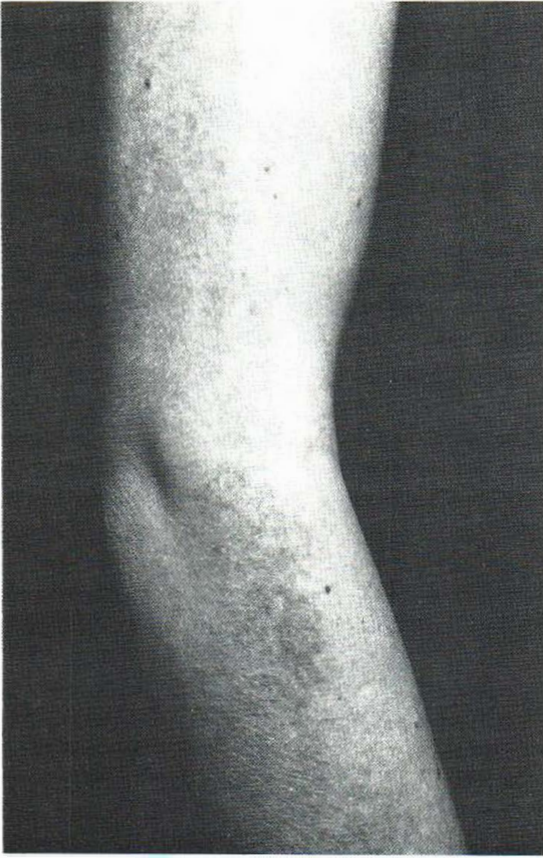


Fig. 2. Atrophic skin changes of right elbow region.

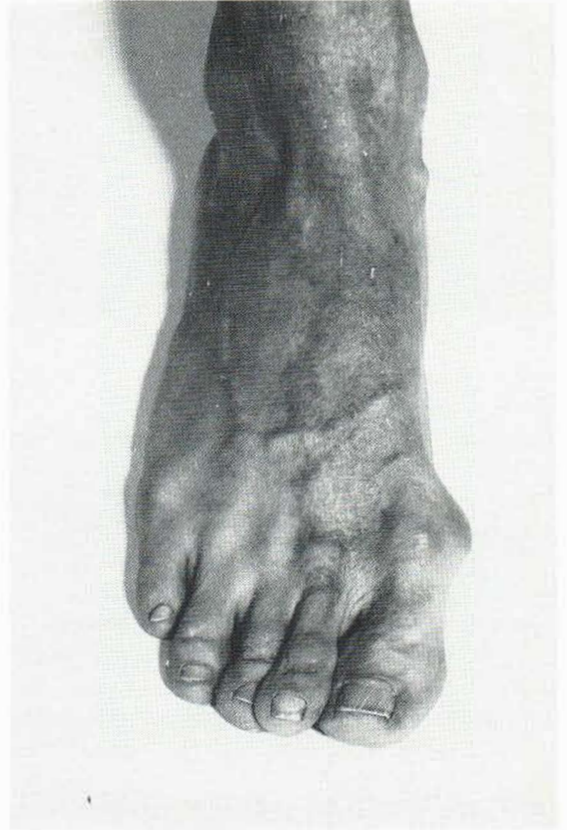


Fig. 3. Atrophic skin changes, hallux valgus, and pes planus of the right foot.

pronase by precipitation with ethanol and cetyltrimethylammonium-bromide, and dried after three washings with ethanol saturated with sodium chloride.

The uronic acid content of the isolated GAG was determined by the meta-hydroxydiphenyl method described by Blumenkrantz & Asboe-Hansen (3).

The total hexosamine content of the GAG was determined after hydrolysis with HCl and evaporation to dryness. The method of Blumenkrantz & Asboe-Hansen giving equal chromogen for glucosamine and galactosamine in an autoanalyser apparatus was used (4).

Electrophoresis of GAG on cellulose acetate plates was performed by a modified method of Cappelletti et al. enabling the separation of heparin, heparan sulphate, dermatan sulphate, hyaluronic acid and chondroitin sulphate 4 and 6 in one monodimensional run (7). After staining with Alcian blue the relative contents of the various GAG were evaluated by optical scanning.

RESULTS

Histology

The epidermis was normal. The dermis was slightly decreased in thickness in clinically atrophic area.

Collagen, glycosaminoglycans, and small capillaries showed no abnormalities, and there were no signs of inflammatory activity. No deposits of immunoglobulins or complement were demonstrated (S. Ullman, M.D.).

Electron microscopy

Collagen fibrils of the reticular dermis from atrophic area consisted of two types (Figs. 4, 5), viz. a large population of fibrils with decreased diameter and round cut-surface, and a small population of fibrils with increased diameter and an irregular cut-surface—'flower-like' because of twisting of the pathologic fibrils (8). Collagen fibrils of the reticular dermis from the perilesional area and control area showed a uni-modal distribution of fibril diameter as in healthy adult skin, and the cut-surface was round and regular.

Collagen analysis

Skin from the atrophic area showed reduced Hyp concentration and content per mm² skin surface,

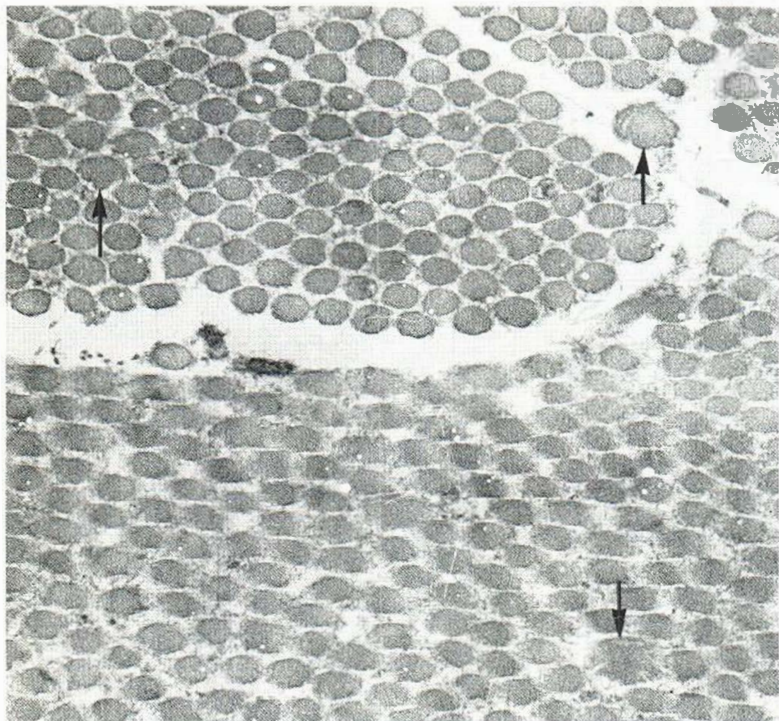


Fig. 4. Collagen fibrils in the reticular dermis. The fibrils with irregular cut-surface are indicated by arrows. $\times 40\ 200$.

consistent with the clinical signs of local dermal atrophy (Table I). Urinary excretion of Hyp ($=428\ \mu\text{mol}/24\ \text{h}$) and ratio of polypeptide-bound Hyp to total Hyp (50%) were normal for the age.

Glycosaminoglycan analysis

In skin biopsies from the atrophic area, a reduced content of uronic acid and hexosamine per mm^2

skin was found, as compared with normal skin and especially the perilesional area (Table I). The reduction in GAG concentration was insignificant. As a result there was only a slight increase in the gel/fibre ratio (uronic acid/Hyp) in the atrophic area.

The isolated GAG represented 5% heparin, 37% dermatan sulphate, 43% hyaluronic acid and 15% chondroitin sulphates. No difference was found between the atrophic and control areas.

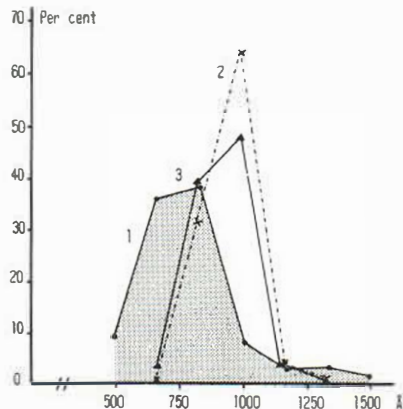


Fig. 5. Diameter of collagen fibrils in the reticular dermis. 1. Atrophic areas ($n=1\ 174$, mean= $783\ \text{Å}$, SD= $190\ \text{Å}$). 2. Perilesional control ($n=759$, mean= $950\ \text{Å}$, SD= $93\ \text{Å}$). 3. Regional control ($n=660$, mean= $930\ \text{Å}$, SD= $122\ \text{Å}$).

DISCUSSION

The case reported presented primary atrophy of all mesodermal layers, i.e. dermis, subcutaneous tissue, muscle and bone. The linear distribution of the lesions along the extremity axis with pigmented patches at the extremity roots suggests that the lesions originate in a clone of abnormal mesodermal cells, which are drawn out with the extremity bud as the extremities grow out in early foetal life. In the original cases presented by Campbell, Barnes and Gowers, distribution charts showed that the lesions of the extremities were, in fact, distributed like isles on a line, while the lesions on the trunk had a segmental or symmetrical distribution (1, 2, 6, 10). These original cases, as well as later reports

and our own case, follow the main principles of the lines of Blaschko (12, 13, 14).

The punctate and cribriform appearance of the atrophy in our case seem comparable to the certainly much more pronounced skin atrophy in the "focal dermal hypoplasia syndrome" (9). Fibroblasts cultured from cutaneous lesions of the "focal dermal hypoplasia syndrome" have exhibited strikingly abnormal growth characteristics (17).

In our case, collagen fibrils were abnormal, with a "flower-like" cut-surface visualized on electron microscopy. Twisted dermal collagen fibrils have been found in pseudoxanthoma elasticum by Danielsen (8), and subsequently identical fibrils have been described in other hereditary and constitutional disorders, such as Ehlers-Danlos syndrome, connective tissue naevi, and primary amyloidosis. Our finding may therefore indicate that hereditary or constitutional factors are involved in local panatropy.

Another ultrastructural finding in our case was a bimodal distribution of the collagen fibril diameter. In scleroderma, local as well as systemic, there are also pathologic populations of collagen fibrils with both decreased and increased diameter (15, 16). Clinically, it is often difficult to distinguish between local panatropy and localized scleroderma in the involutionary state (11).

Biochemical analyses of collagen and glycosaminoglycans showed, consistent with the ultrastructural findings, reduced connective tissue macromolecules in atrophic skin.

Altogether, our case indicates that a reduction in dermal collagen and structural changes of collagen fibres are significant features in local panatropy.

REFERENCES

1. Barnes, S.: Report on Sir William Gowers' case of local panatropy. *Trans Clin Soc Lond* 36: 164, 1903.
2. — Gowers' case of local panatropy. *Br J Dermatol* 51: 377, 1939.
3. Blumenkrantz, N. & Asboe-Hansen, G.: New method for quantitative determination of uronic acids. *Anal Biochem* 54: 484, 1973.
4. — An assay for total hexosamine and differential assay for glucosamine and galactosamine. *Clin Biochem* 9: 269, 1976.
5. — Methods for analysis of connective-tissue macromolecules by determination of certain constituents. *Methods Biochem Anal* 24: 39, 1977.
6. Campbell, H.: Case of extensive wasting of the type of facial hemiatrophy. *Trans Clin Soc Lond* 36: 229, 1903.
7. Cappelletti, R., Del Rosso, M. & Chiarugi, V. P.: A new electrophoretic method for the complete separation of all known animal glycosaminoglycans in a monodimensional run. *Anal Biochem* 99: 311, 1979.
8. Danielsen, L.: Morphological changes in pseudoxanthoma elasticum and senile skin (Thesis). Copenhagen, 1979.
9. Goltz, R. W., Henderson, R. R., Hitch, J. M. & Ott, J. E.: Focal dermal hypoplasia syndrome. *Arch Dermatol* 101: 1, 1970.
10. Gowers, W. R.: Case of local panatropy. *Trans Clin Soc Lond* 36: 240, 1903.
11. Jablonska, S.: Scleroderma and Pseudoscleroderma. Polish Medical Publishers, Warsaw, 1975.
12. Jackson, R.: The lines of Blaschko: A review and reconsideration. *Br J Dermatol* 95: 349, 1976.
13. Jaeger, H.: Atrophie cutanée segmentaire paravertébrale. *Dermatologica* 110: 384, 1955.
14. Klüken, N. & Geib, K.-H.: Kasuistischer Beitrag zur Panatrophia cutis localisata. *Hautarzt* 16: 422, 1965.
15. Kobayasi, T. & Asboe-Hansen, G.: Ultrastructure of generalized scleroderma. *Acta Dermatovener (Stockholm)* 52: 81, 1972.
16. — Ultrastructural changes in the inflammatory zone of localized scleroderma. *Acta Dermatovener (Stockholm)* 54: 105, 1974.
17. Uitto, J., Bauer, E. A., Santa-Cruz, D. J., Loewinger, R. J. & Eisen, A. Z.: Focal dermal hypoplasia: Abnormal growth characteristics of skin fibroblasts in culture. *J Invest Dermatol* 75: 170, 1980.

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