

## Vascular Changes in Morphea

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Vascular changes in morphea were studied in skin biopsies from 14 patients. Small vessels with pericytes present the changes in three different patterns. The first was the endothelial cells in a stimulated condition and thickened vascular wall with infiltrating macrophages and mast cells. The second was characterized by thick basal lamina of pericytes and the third by activated pericytes with infiltrating lymphocytes and plasma cells. Otherwise, all patterns showed altered endothelial cells and infiltrating macrophages and mast cells similar to the first pattern. The first pattern was mostly found in uninvolved skin. The second and the third were found in the inflammatory and sclerotic areas. It seems, therefore, that activated pericytes are the most essential changes in vessels of morphea. Probably, muscular vessels are simply involved in the fibrotic process. *Key words: Vessels; Pericytes; Scleroderma.* (Received September 10, 1984.)

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Vascular changes in scleroderma, both of the generalized and localized types, include damage of vascular endothelial cells, multiple layers of vascular basal lamina and perivascular cell infiltrates consisting of mast cells, lymphocytes, plasma cells, macrophages and fibroblast-like cells (1, 2, 3, 4, 5). In a previous paper, the authors demonstrated that the fibroblast-like cells in morphea represented myofibroblasts originating from activated perineural cells in the lesions (6). Pericytes of small vessels are of a nature similar to those of perineurium. This study deals with the description of vascular pericytes in morphea.

### MATERIAL AND METHODS

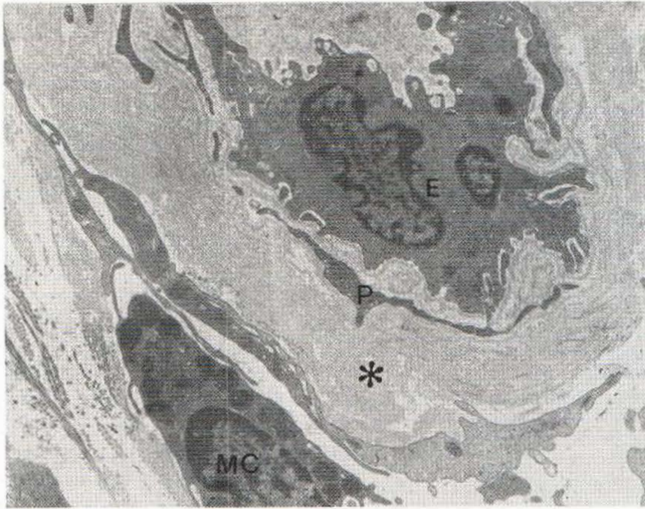
Fourteen patients, one male and 13 females, aged between 16 and 74 years, were studied. Ten of the patients showed single or a few plaques or morphea, while 4 presented multiple plaques. In 8 patients the plaques studied were located on the trunk, in 5 on the lower extremities, and in one on an arm. Seven patients showed a distinct inflammatory zone or lilac ring in the periphery of the plaques. The duration of the plaques ranged between one month and 10 years (average 3.4 years). The skin biopsies were removed using a 3 mm manual punch within the sclerotic areas of the plaques, in the lilac rings and from the uninvolved skin of a symmetrical area (10 cases) or near the plaques (4 cases). The skin specimens were fixed in 6% glutaraldehyde solution of 0.05 M cacodylate buffer, pH 7.3, with 7.5% sucrose. The specimens were osmicated, dehydrated and embedded in epon. Ultrathin sections were cut by Reichert ultramicrotomes OM 2 or Ultracut, and stained with uranyl acetate and lead citrate. For observation, a JEOL electron microscope 100CX was operated at 80 kV.

### RESULTS

Small vessels with pericytes (Table I, Figs. 1-4) exhibit three different patterns of the changes.

#### *First pattern* (Fig. 1)

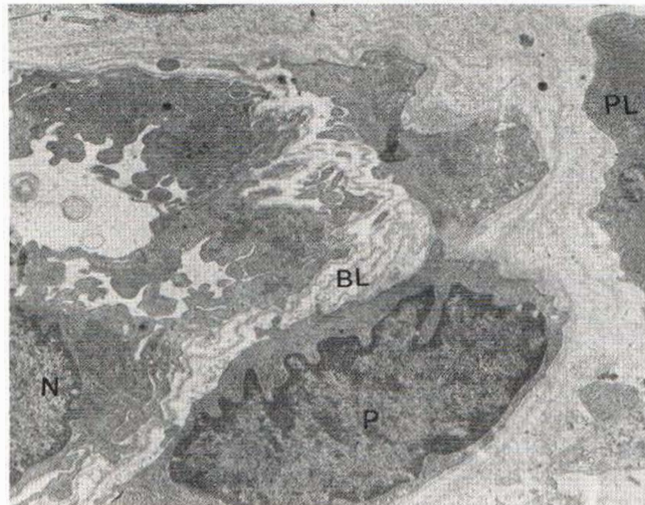
Endothelial cells show irregular luminal surfaces with cytoplasmic protrusions. The cytoplasm contains filaments, vacuoles and a few ribosomes as well as a few mitochondria.



*Fig. 1.* A vessel with a thick wall. Luminal surface of the endothelial cells is irregular with cytoplasmic protrusions. The wall (\*) consists of multiple layers of basal lamina, thread-like material and collagen fibrils. Pericytes (P). Endothelial cells (E). Mast cell (MC).  $\times 10350$ .



*Fig. 2.* A vessel shows thick basal lamina of endothelial cell (E) and pericyte (P). Macrophage (M).  $\times 10350$ .



*Fig. 3.* A vessel shows large endothelial cells with irregular luminal surfaces, large nuclei with rough chromatin granules (N), a wavy fragmented basal lamina (BL) and a pericyte with numerous ribosomes and a nucleus (P). Plasma cell (PL).  $\times 10350$ .

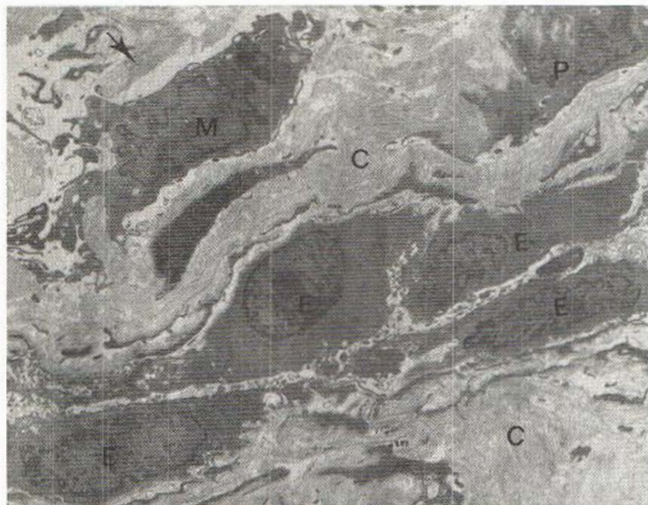


Fig. 4. A vessel with hypertrophic endothelial cells (E) and pericytes (P). Macrophage (M). Thin collagen fibrils (C). Filamentous aggregates of collagen (arrow).  $\times 4140$ .

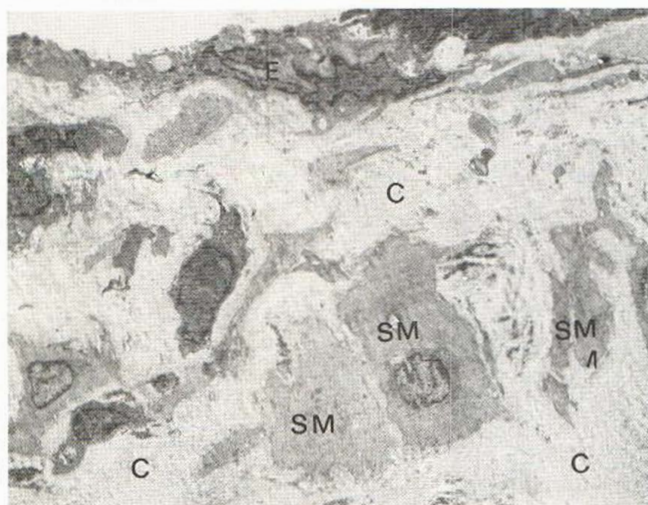


Fig. 5. A vessel with smooth muscle cells (SM). Endothelial cells are flat (E). Smooth muscle cells are separated by collagen fibril bundles (C).  $\times 4140$ .

Nuclei are invaginated with thick layers of peripheral chromatin aggregates. The vascular wall is thickened and consists of multiple layers of basal lamina, collagen fibrils and thready material. Slender cytoplasm of pericytes is inserted between basal laminae. Mast cells and histiocytes are seen around the vessels.

#### Second pattern (Fig. 2)

The structures of the endothelial cells and the pericytes resemble the first pattern. The basal laminae of the endothelial cells and of the outer surfaces of the pericytes are thickened.

#### Third pattern (Fig. 3 and 4)

The endothelial cells are large with numerous rounded protrusions of cytoplasm. The cells contain endoplasmic reticula, ribosomes and mitochondria. The nuclei are large with invaginations. Chromatin granules are rough and spreading over the nuclei. Endothelial

basal lamina is wavy, fragmented and multiple layered. Pericytes are also hypertrophic with cytoplasmic and nuclear substructures similar to the endothelial cells. Multiple layers of basal lamina are seen on the cell surfaces. Plasma cells, lymphocytes, mast cells and histiocytes infiltrate the tissues. Thin collagen fibrils and so-called filamentous aggregates of collagen are seen in the perivascular areas visualizing degradation of collagen fibrils.

Vessels with smooth muscle cells (Fig. 5) show flat endothelial cells with irregular luminal surfaces, intracytoplasmic vacuoles and a few other cell organelles. Under the endothelial cells some vessels show thickened basal lamina around smooth muscle cells like the second pattern described above. Masses of collagen fibrils separate smooth muscle cells. Mast cells, lymphocytes, histiocytes and plasma cells are infiltrating.

## DISCUSSION

Among the patterns of the altered walls of small vessels, the third pattern seems to be the most significant change related to the pathogenesis. The change indicates an active cytoplasmic function of pericytes and cell responses as described previously (1, 6). However, the present study failed to demonstrate basal lamina interruption and dislocation as found in nerves (6). The second pattern indicates increased formation of basal lamina by pericytes. These patterns suggest that the pericyte activation in vessels as well as in nerves is an important pathological process in morphea. The first pattern represents thickened vascular wall with endothelial cells in a stimulated condition. Such endothelial cells seem to be distributed widely in the uninvolved areas of the body as well as in the lesions and in the muscular vessels. Sera of scleroderma patients have been found to contain a factor which is cytotoxic for vascular endothelial cells (7).

A previous report has described endothelial cell damage and destruction (1) while the present study demonstrated no destruction of endothelial cells. The endothelial cell changes seem not to be essential for the development of morphea. Furthermore, the nerve changes in morphea (6) are not simply consequences of endothelial cell changes in the individual vessels. One of the key-points in morphea pathogenesis is probably found in pericyte activation and transformation to fibroblast-like myofibroblasts (6).

Pericytes are known to regulate blood flow in small vessels. However, when the cells are transformed into myofibroblasts, increasing their number of ribosomes and endoplasmic reticula while decreasing their cytoplasmic filaments and desmosomes, the cells inhibit their ordinary blood flow regulation and increase their secretory function. The muscular vessels, probably, do not play an active role for the disease process, since the smooth muscle cells show no cytoplasmic changes of activation.

Table I.

sym. = symmetrical site; sur = surroundings of the lesion. The numbers indicate the biopsies showing the changes. Patterns II and III are mostly found in lilac ring and sclerotic areas, while pattern I is often seen in uninvolved areas

	Pattern of change		
	I	II	III
Uninvolved skin	8 (7 sym., 1 sur.)	4 (3 sym., 1 sur.)	2 (1 sym., 1 sur.)
Lilac ring	1	7	5
Sclerotic area	0	5	2

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