

ULTRASTRUCTURE OF SKIN IN PRIMARY SYSTEMIC AMYLOIDOSIS

Takasi Kobayasi and Gustav Asboe-Hansen

Department of Dermatology, University of Copenhagen, Rigshospital, Copenhagen, Denmark

Abstract. Amyloid masses were found in the dermis of two brothers suffering from primary amyloidosis. The masses consisted of fibrils, composed in turn of twin hollow filaments of amyloid. An amyloid filament appeared as a 3 nm thick lucent core with a 2 nm thick wall. Occasionally 4-6 filaments were packed together in one fibril. The twin filaments were slightly twisted, with a twisting angle of 2.5 degrees and a coiling pitch of 1 160 nm. Wavy shapes of amyloid fibrils were also seen in elastic fibres. Amyloid fibrils were found in elastic fibres, under the basal lamina of the epidermis, sweat gland epithelium and Schwann cells; also around perineural cells, perivascular cells and, in one of the brothers, in collagen fibril bundles. No amyloid fibrils were found under the endothelial basal lamina. It would appear that amyloid fibrils are pathological fibrils belonging to the elastic fibre-basal lamina system.

Key words: Primary amyloidosis; Ultrastructure; Amyloid fibrils; Elastic fibre

Spleen, kidney and liver of primary systemic amyloidosis have been studied by electron microscopy and amyloid masses found to consist of characteristic fibrils (9). Similar amyloid masses have also been noticed in the dermis of lichen amyloidosus (4, 5, 8) and nodular amyloidosis (2). This study revealed amyloid masses in the skin of the familial type of primary systemic amyloidosis.

MATERIALS AND METHODS

Two brothers, 72 and 67 years of age, had suffered from neurological symptoms over the last 30 years. Both showed macroglossia. The younger brother had discrete small yellowish papules on the trunk, while the elder had no eruptions. Neither had Bence-Jones' protein in the urine.

Biopsy specimens were taken from the eruptions of the younger patient and from normal skin on the leg of the elder brother. The specimens were fixed in a 6% glutaraldehyde solution of 0.1% cacodylate buffer with 7.5% sucrose. After osmification and dehydration, the specimens were embedded in Epon 812 and sectioned with an ultramicrotome. Ultrathin sections were stained with

uranyl acetate and lead citrate. A Siemens electron microscope (Elmiskop 1A) was operated at 80 kV for observation.

OBSERVATION

In both patients, amyloid masses were found in the interfibrillar spaces of the corium, as well as under the basal lamina of the epidermis, sweat glands and Schwann cells of the peripheral nerves. The younger brother showed a greater accumulation of amyloid in these areas than did his brother and, in addition, amyloid was demonstrated in collagen fibril bundles, in the walls of the larger vessels and around perineural cells.

Amyloid masses consisted of fibrils arranged in random directions (Fig. 1 A, B). The individual amyloid fibrils were straight, without branchings and were composed of twin hollow filaments showing a slight helix with a twisting angle of 2.5 degrees and a coiling pitch of 1 160 nm. The surface of the fibrils showed transverse bandings with repeating units of 10 nm. The cut-surfaces of the twin hollow filaments revealed two lucent cores, each 3 nm across, and with 2 nm thick walls. Occasionally two and three twin filaments were packed together (Figs. 1 A, 8).

Amyloid masses in the interfibrillar spaces of the dermis contained fragments of elastic fibre matrix (Fig. 2), some of which had dense rims (Fig. 3). Other masses contained numerous amyloid fibrils radiating from the inside of elastic fibres where numerous amyloid fibrils were densely packed (Fig. 4). The wavy fibrils were also found within the elastic fibres. An amorphous material covered the amyloid masses and elastic fibres (Fig. 3). Some elastic fibres showed densely packed, straight amyloid fibrils in the matrix, whereas no amyloid fibrils appeared outside the elastic fibres (Fig. 2).

In the papillary layer, amyloid masses joined the epidermal basal lamina which was thickened and multi-layered or thin and single, with occasional interruptions (Fig. 5 A, B). The former changes were found under well-preserved basal cells, the latter under disintegrated basal cells. The masses contained a few normal collagen fibrils and anchoring fibrils, but no elastic fibrils could be seen.

In peripheral nerves, the amyloid fibrils were usually found close to the basal lamina of Schwann cells (Fig. 6) though the Schwann cells and the axons themselves were normal. In the younger patient, amyloid fibrils were also found between the perineural collagen fibrils and under the basal lamina of the perineural cells.

In collagen fibril bundles, thick and twisted collagen

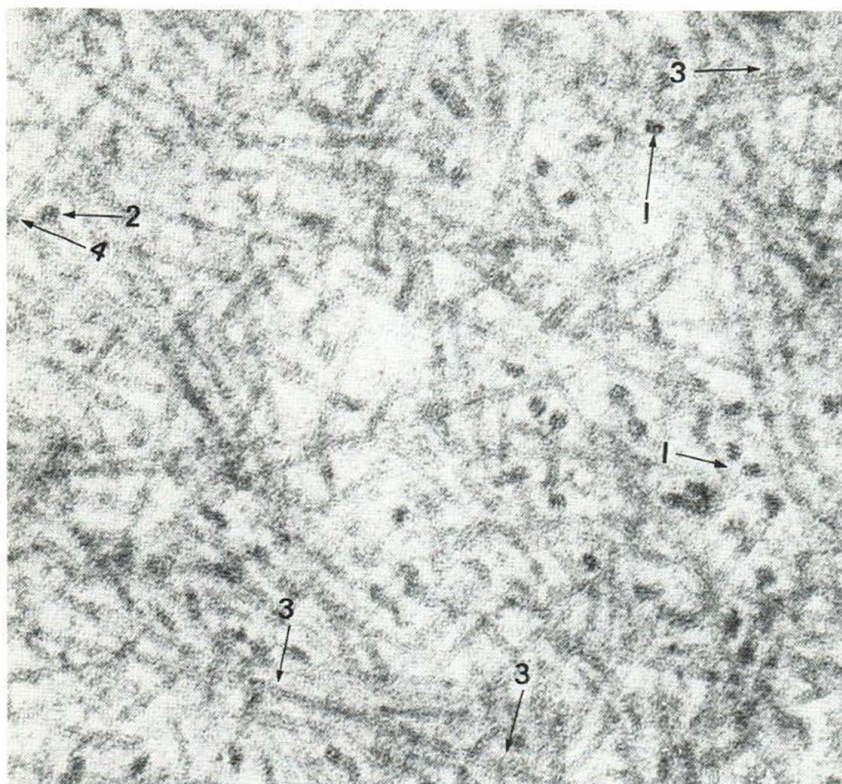


Fig. 1 A. Mass of straight amyloid fibrils. Arrow 1 indicates a pair of hollow fibrils of amyloid cut at different angles. Arrow 2 shows the cut-surface of four filaments and arrow 4 four filaments in longitudinal section. Arrow 3 indicates twisting of amyloid fibril with cross bandings. $\times 180000$.

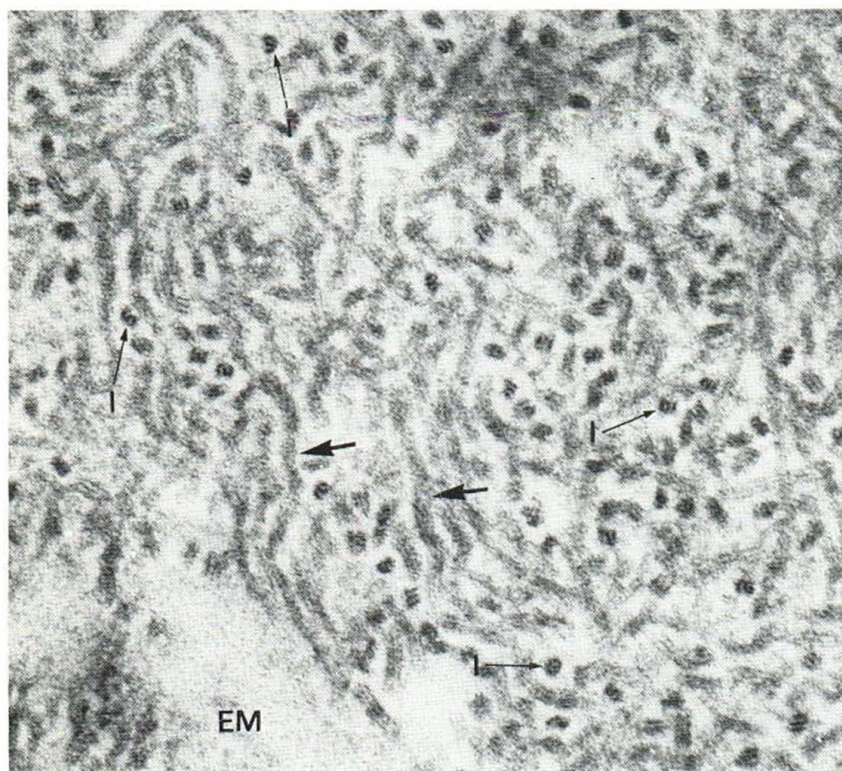


Fig. 1 B. Wavy amyloid fibrils (thick arrows) and cutsurfaces of twin hollow fibrils as seen in Fig 1 A are demonstrated. Elastic fibre matrix (EM). $\times 180\ 000$.



Fig. 2. An amyloid mass with amyloid fibrils and elastic fibre matrix (EM). At the lower left corner, an elastic

fibre is seen, containing wavy amyloid fibrils (arrows) in its matrix. $\times 25\,500$.

fibrils intermingled with normal ones (Fig. 7). They showed irregular and bizarre cut-surfaces and were partly split into smaller collagen fibrils. Amyloid fibrils were seen among the collagen fibrils, always in continuation with the amyloid masses of the interfibrous spaces.

The vascular walls showed amyloid fibrils on the elastic fibres, on the basal lamina of smooth muscle cells and on the outside of the perivascular cells, while the endothelial basal lamina showed no amyloid.

Mast cells and fibroblasts of the corium showed no amyloid fibrils in their cytoplasm. Mast cells contained

mature granules and showed no evidence of degranulation. Fibroblasts contained well-developed granular endoplasmic reticulum with a thready material in their dilated cisternae.

DISCUSSION

Previous authors have described the fibrils of amyloid as being rigid, non-branched with a diameter of 300–1000 nm (4, 5, 8). Using negatively

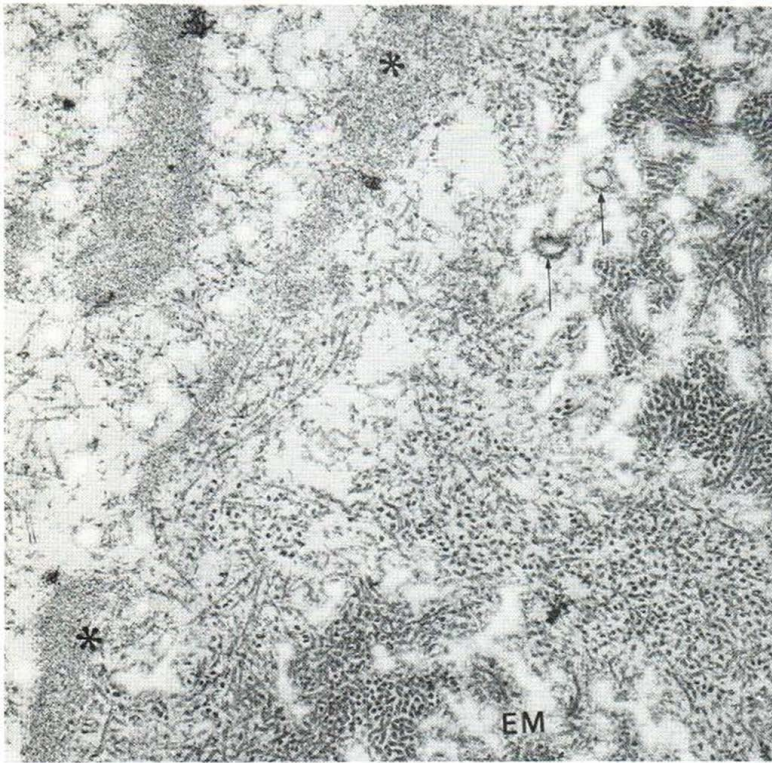


Fig. 3. An elastic fibre is replaced by amyloid fibrils in most of its areas. *EM*: Fragments of elastic fibre matrix. *Arrows*: Debris of the matrix with dense rim. A brim of amorphous material encircles amyloid masses (*asterisks*). $\times 42\,000$.

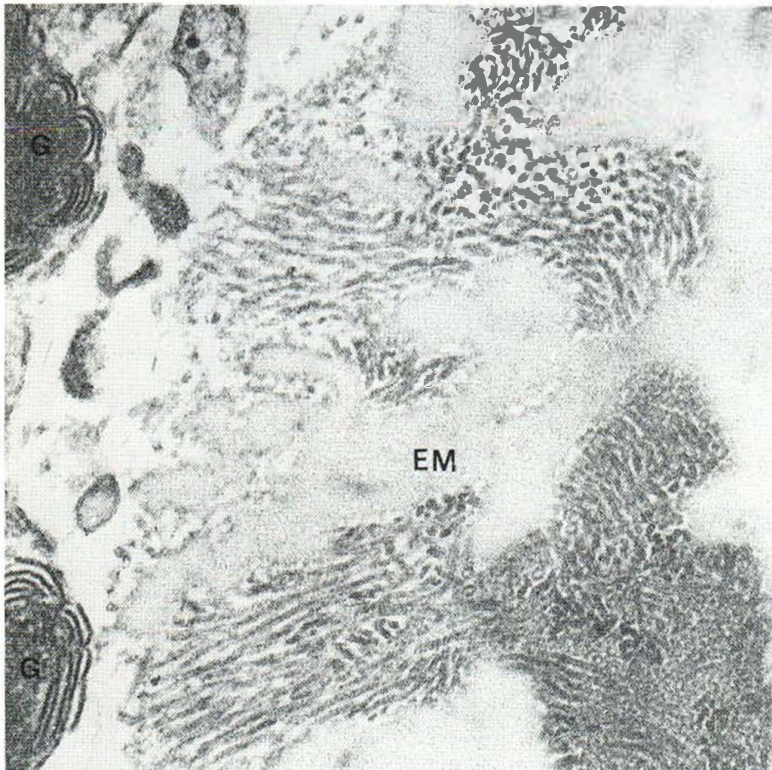


Fig. 4. Amyloid fibrils radiate from the elastic matrix (*EM*). *G*: Mature mast cell granules. $\times 84\,000$.

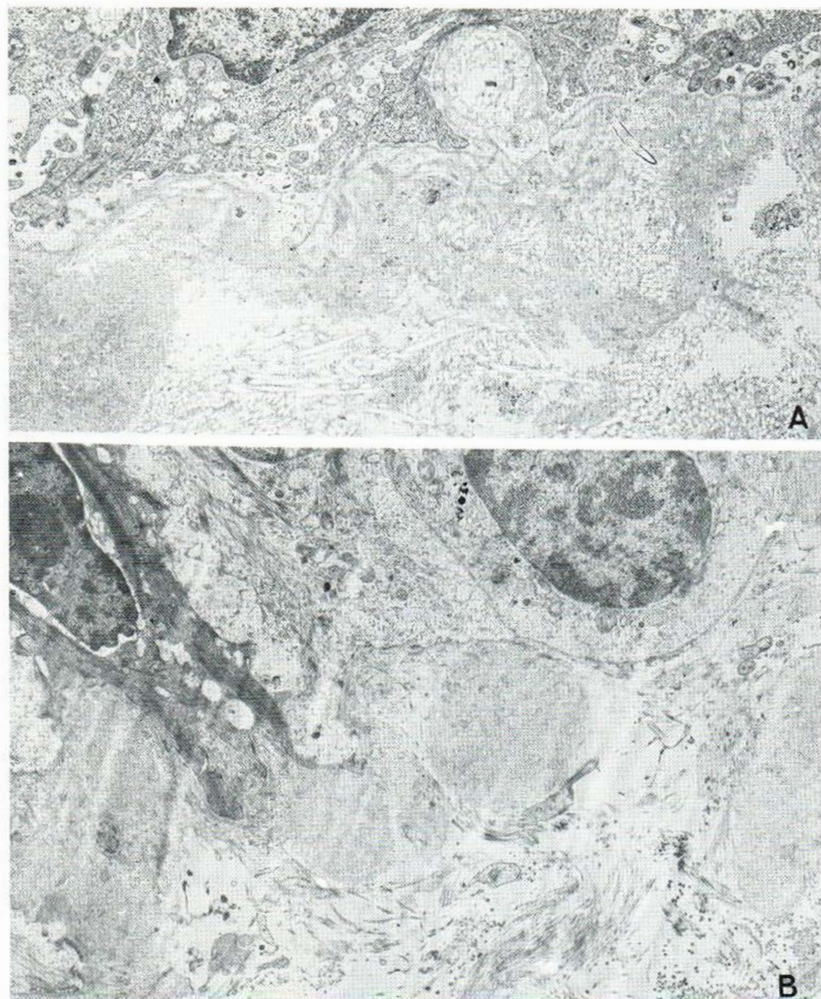


Fig. 5. Amyloid masses in the dermo-epidermal junction. (A) Amyloid masses under a multi-layered basal lamina. Basal epidermal cells are not degenerated. $\times 4500$. (B) Amyloid masses under edematous basal cells. No multiplication of the basal lamina is seen. $\times 4500$.

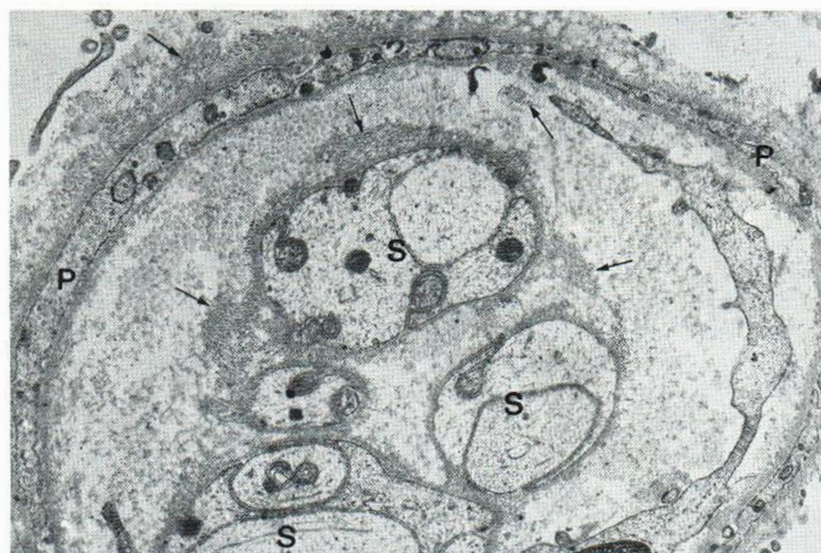


Fig. 6. A peripheral nerve with amyloid fibrils (arrows). S: Schwann cells. P: Perineurial cells. $\times 6750$.

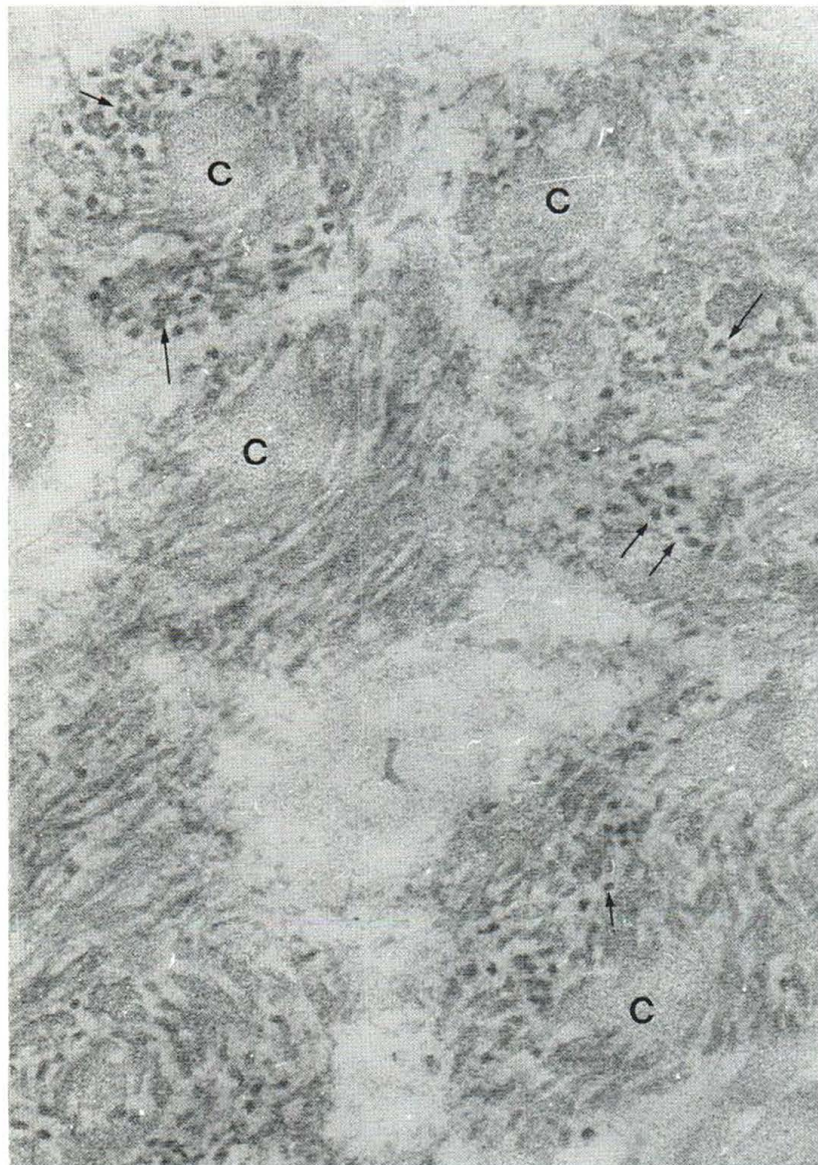


Fig. 7. Bizarre cut-surfaces of collagen fibrils (C) with amyloid fibrils (arrows). = 102 000.

stained material from amyloid of spleen, Shirahama & Cohen (9) found that amyloid fibrils consist of several closely packed, 7.5 nm thick amyloid filaments. The thickness of an individual amyloid fibril depends upon the numbers of amyloid filaments contained. The present findings showed that the amyloid fibrils are usually composed of one pair of filaments. The details of an amyloid fibril are illustrated in Fig. 8. The amyloid filaments have been reported to consist of five or six pentagonally arranged protofibrils, 2.5–3.5 nm across (9). The

present study failed to demonstrate this fine structure in ultrathin sections. The hollow filaments of amyloid seen in this study are identical with the amyloid filaments of Shirahama & Cohen (9). The transverse bands of the amyloid filaments have not been described previously.

In lichen amyloidosis, amyloid fibrils appear in large masses, the origin of which remains unknown (4, 5, 8). In nodular amyloidosis, elastic fibre matrix has previously been found in the centre of the amyloid masses (2), as in the present inves-

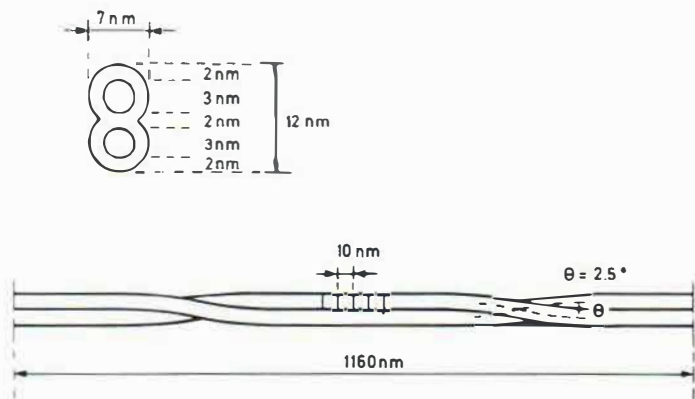


Fig. 8. Amyloid fibrils, schematic.

tigation. Our findings strongly suggest that amyloid fibrils develop in the elastic fibre matrix. The dermal aspect of the basal lamina of the epidermis and Schwann cells is the second area having this affinity. The third is the area around perineural, perivascular and smooth muscle cells. Since elastic fibre matrix, elastic fibrils and basal lamina form one continuous structure (7), it is now deduced from these studies that this is the tissue material where amyloid fibrils develop. In parenchymatous organs such as liver, spleen and kidney, no such relationship between amyloid fibrils and connective-tissue components has been demonstrated.

Twisted collagen fibrils have been found in the dermis of connective tissue nevi (3), pseudoxanthoma elasticum skin (1) and the shagreen patch of tuberous sclerosis syndrome (6). No twisted collagen fibrils have been found in lichen amyloidosis (4, 5, 8) or nodular amyloidosis (2). Apparently, twisted collagen fibrils do not belong to the unique tissue alterations of amyloidosis.

Cells which produce or phagocytose amyloid have been found by light-microscopy. The present study has not demonstrated any cells containing amyloid fibrils.

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G. Asboe-Hansen, M.D.
Department of Dermatology
Rigshospitalet, Blegdamsvej 9
DK-2100 Copenhagen Ø
Denmark