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LOCALIZED AMYLOIDOSIS IN BASAL CELL EPITHELIOMAS

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Abstract. Secondary localized amyloidosis has been reported in a variety of epithelial tumors of skin, but it has not been demonstrated previously that this material satisfies the ultrastructural criteria for amyloid. Three basal cell epitheliomas with secondary localized amyloidosis were studied with the electron microscope. In one case a predominance of 60–100 Å filaments indistinguishable from those of primary localized macular and lichenoid amyloidosis was found; in another, tubular filaments of similar dimensions were admixed; and in the third, amorphous substance was predominant. In all instances amyloid was deposited in the stroma of the tumor, forming islands similar to those of dermal collagen; localization was not perivascular. It is postulated that localized cutaneous amyloidosis secondary to basal cell epitheliomas may be induced by dermal fibroblasts under the influence of a product of the tumor cells.

Amyloid deposits in skin may represent a localized process or may be one aspect of a multisystem disease. The localized forms may be primary or secondary (1). Primary localized cutaneous amyloidosis includes lichenoid, macular, and tumefacient types. In secondary localized cutaneous amyloidosis, deposits of amyloid are found in association with another disorder.

Histochemically detectable amyloid has been reported in various epithelial tumors of skin, including basal cell epithelioma (1, 3, 10, 14, 15), seborrheic keratosis (1), Bowen's disease (1), cylindroma (9), and calcifying epithelioma of Malherbe (pilomatrixoma) (4, 11), but it is not known whether such material displays the ultrastructural characteristics of amyloid. The purpose of this investigation was to ascertain whether localized amyloidosis secondary to basal cell epitheliomas satisfies the fine structural criteria for this substance.

MATERIALS AND METHODS

Lesions from 3 patients with localized cutaneous amyloidosis secondary to basal cell epitheliomas were excised under 1% procaine local anesthesia. One part of each specimen was fixed in 10% formalin and processed

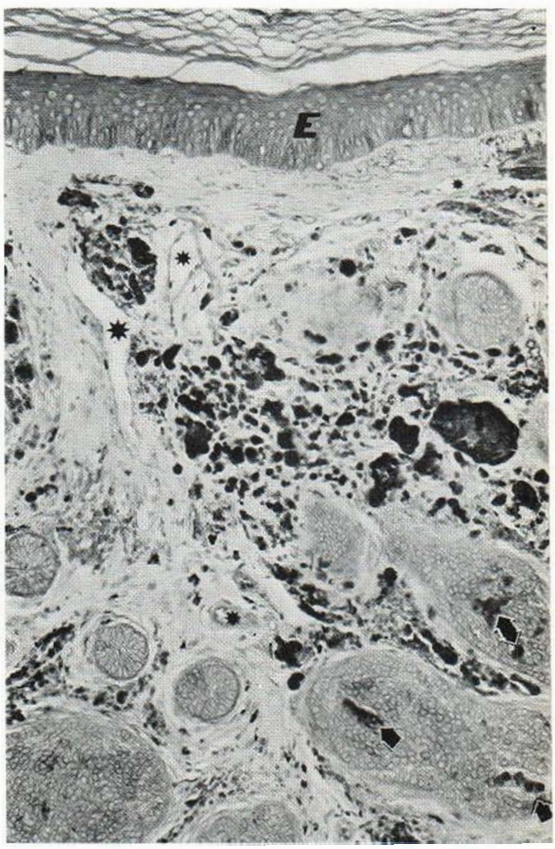


Fig. 1. Amyloid, stained metachromatically with crystal violet, deposited in stroma. Amyloid often absent in perivascular areas (*). Small deposits within invaginated stroma of tumor (*arrows*). *E*, epidermis. Case 1. ×280.

Fig. 2. Multiformed amyloid islands near capillary (*C*) surrounded by fibroblasts (*f*). Multiple basal laminas (*B*) separate deposits from endothelial cells (*E*). Some islands composed of varying ratios of amyloid : collagen (*). *n*, unmyelinated nerve. *Arrow*, half-desmosome-like density in fibroblast. Case 1. × 9 600.

routinely for light microscopy. Paraffin sections were stained with crystal violet and alkaline Congo red; the latter were studied with bright field illumination and polarized light. The other portion was fixed in 5% glutaraldehyde in 0.1 M cacodylate buffer, pH 9.2, for 3 hours, rinsed overnight in the same buffer, and refixed with 1% osmic acid in the same buffer for ½ hour. Specimens were stained with 1% uranyl acetate in 50% ethanol, dehydrated with increasing concentrations of ethanol and propylene oxide and embedded in Araldite. Thin sections, 400–600 Å, were cut in a Porter-Blum MT-2 ultramicrotome, stained with 15% uranyl acetate in

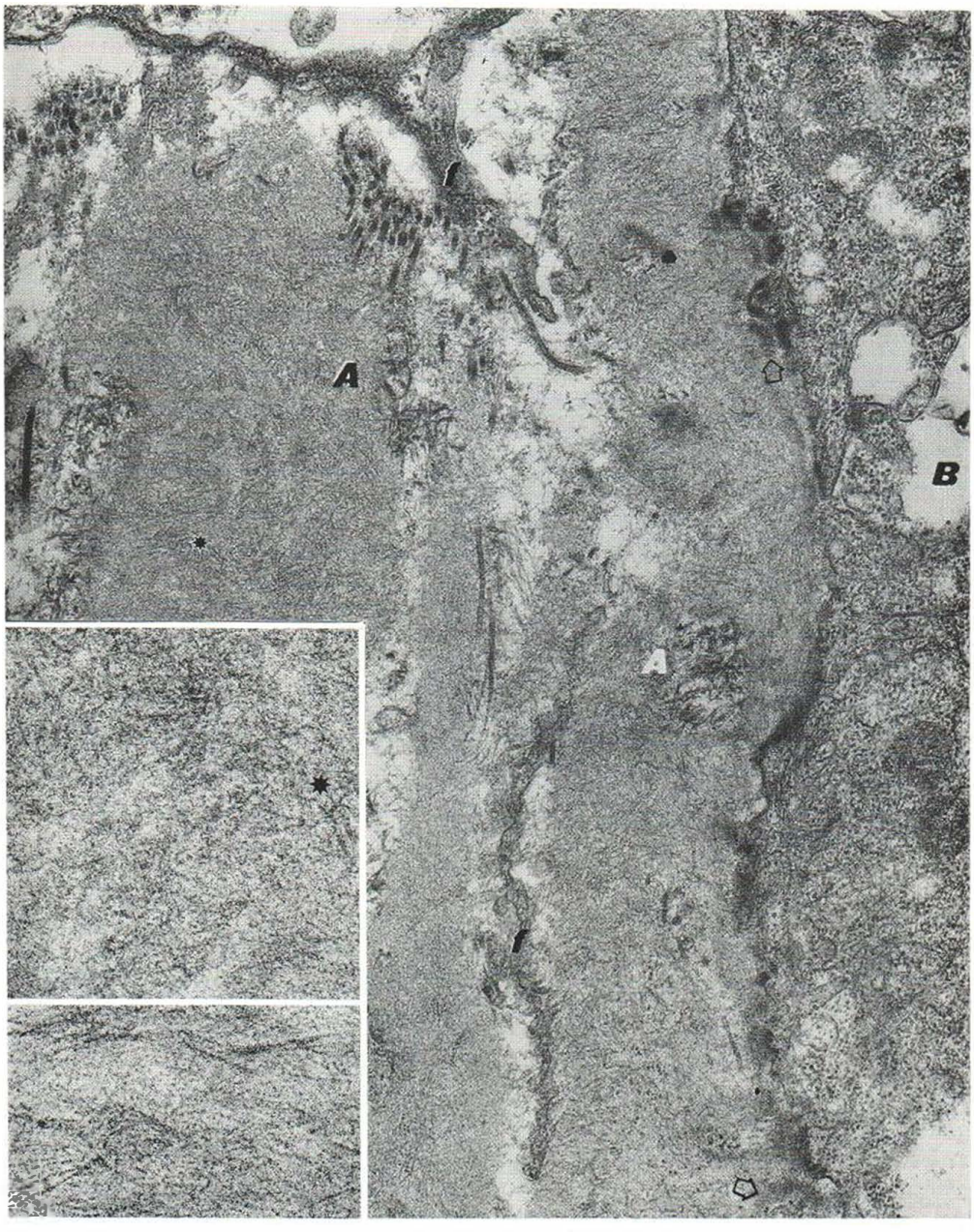


Fig. 3. Amyloid deposition contiguous with basal lamina surrounding periphery of tumor (*B*). Basal lamina irregularly thickened (*arrows*) and in many places obscured. Aggregation of anchoring fibrils (*A*). *f*, process of fibroblast. Case 1. × 30 000. *Upper inset*, enlargement of filaments in main picture; areas marked with * correspond to each other, though rotated nearly 360°. × 87 500. *Lower inset*, filaments in lichen amyloidosus, same magnification (× 70 000).

methanol and Reynolds' lead citrate (12), and observed in a Hitachi HU-11C or HU-12 electron microscope.

For purposes of comparison, several lesions of the lichenoid and macular forms of primary localized cutaneous amyloidosis were also studied. Details of these conditions have been published elsewhere (5, 12).

RESULTS

Basal cell epitheliomas with secondary localized cutaneous amyloidosis occurred on the nose of a woman aged 75, the forehead of a woman aged 84, and the nose of a man aged 55. All patients

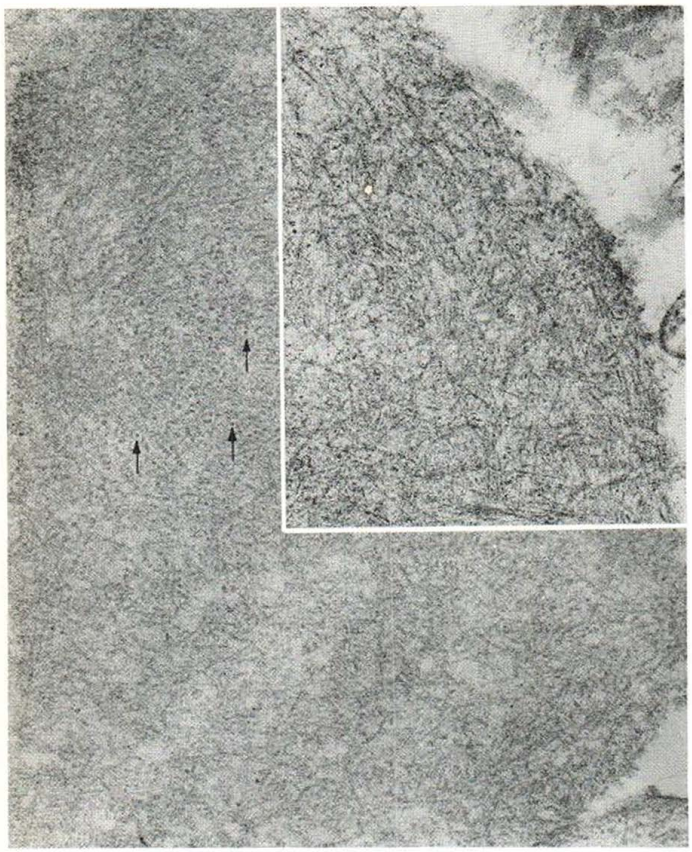


Fig. 4. Tubular filaments predominate; tubular nature evident in cross sections (*arrows*). They measure about 60–100 Å in diameter, similar to filaments in lichen amyloidosus (*inset*). × 38 700. *Inset:* × 62 500.

were white; the lesions were diagnosed clinically as basal cell epitheliomas.

Histologic examination of all lesions disclosed islands of hyperchromatic basaloid cells in the cutis with oval collections of pink amorphous material in the stroma. The latter displayed red metachromasia with crystal violet (Fig. 1); it stained red-orange with alkaline Congo red and showed green birefringence with polarized light. Amyloid was not found in the deeper and lateral portions of the cutis that were free of tumor.

Electron microscopic examination of the first case showed deposits of amyloid separated from endothelial cells by multilayered perivascular basal lamina (Fig. 2). Amyloid deposits resembled collagen islands (Fig. 2); in many islands, collagen and amyloid were admixed (Fig. 2). Some amyloid deposits were contiguous with the basal lamina at the periphery of the tumor (Fig. 3); most were surrounded by fibroblasts. Half-desmosome-like dense plaques were sometimes produced on the plasma membranes of these fibroblasts (Fig. 2). Amorphous substance was increased in the amyloid deposits connected to the basal lamina, but filamentous components were also present (Fig. 3).

Solid and sometimes tubular 60–100 Å filaments were seen. Tubular profiles were best visualized in cross section (Fig. 4). Compared with the amyloid filaments from lesions of lichenoid and macular amyloidosis, solid filaments were similar in their dimensions and in their straight, nonbranching morphologic characteristics (insets of Figs. 3, 4). Tubular filaments were not found in macular and lichenoid amyloidosis (insets of Figs. 3, 4).

Electron microscopic study in the second case also showed variably shaped islands of amyloid (Fig. 5) within the stroma of the tumor. The amyloid was composed mainly of moderately electron-dense amorphous material (Fig. 6 A) with a small number of filaments similar to those in lichen amyloidosus (Fig. 6 B). Degeneration of

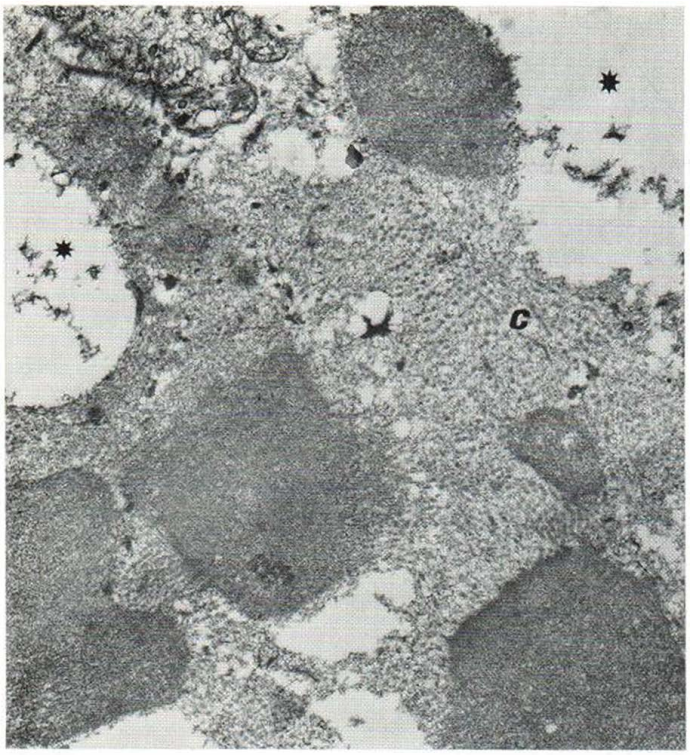


Fig. 5. Several islands of predominantly amorphous material; collagen fibrils (*C*) diminished and degenerated, leaving spaces (*). Case 2. × 11 800.

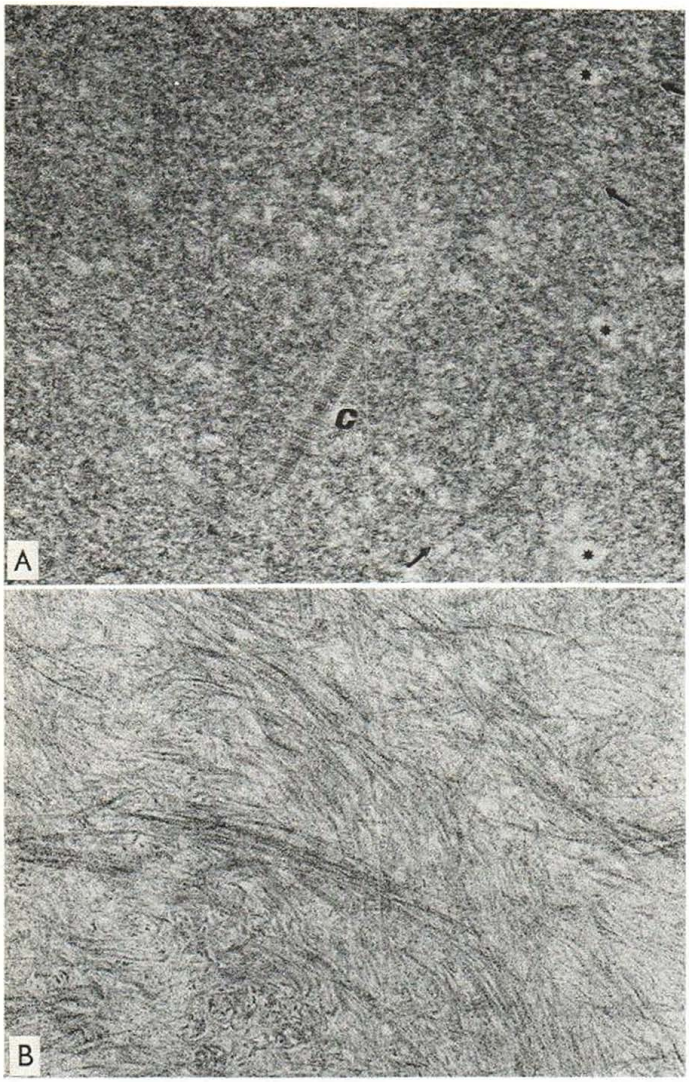
collagen was remarkable in many places and empty spaces half-filled with smudgy material were seen (Fig. 5).

Electron microscopy in the third case revealed islands of amyloid with various ratios of collagen-amyloid admixture in empty spaces between tumor groups (Fig. 7). Amyloid islands were often in contact with the basal lamina of the tumor. Increased numbers of anchoring fibrils abutted upon the basal lamina which often became irregularly widened (Fig. 9). Mast cells were frequently encountered in the stroma (Fig. 7). Straight, nonbranching filaments measuring 60–100 Å (Fig. 8) were seen most often at high magnification; these appeared identical with those of macular and lichenoid amyloidosis (Fig. 8, inset)

COMMENT

Localized amyloidosis secondary to basal cell epitheliomas satisfies the fine structural criteria for this substance. Histochemically identifiable amyloid in basal cell epitheliomas was found to consist of filaments (including the tubular variety) and amorphous substances deposited in the stroma. Filaments with the morphologic characteristics of human cutaneous (2, 5) and systemic experimental (13) amyloid were found either as pure accumulations or admixed with less characteristic material. Varying proportions of amorphous substance can be found in cutaneous amyloid, but its predominance is rather rare. The amorphous material of medium electron-density found in case 2 resembles the major component of the colloid in colloid milium (6) and the hyalin of lipoid proteinosis (7).

The deposition of amyloid in collagen-like islands and its admixture with collagen may indicate that it is produced in a similar fashion. In previous studies on primary localized cutaneous amyloidosis (2, 5, 8), local production of amyloid by dermal fibroblasts was suggested by the deposition of amyloid in close spatial relation with active fibroblasts which often contained intracellular amyloid. This was further supported by the sparing of perivascular spaces; neoformation of amyloid and discharge of intracellular amyloid precursor into the extracellular spaces in granulating wounds following biopsy of amyloid lesions;



Figs. 6 A, B. Enlargement of amorphous island in Fig. 5. Poorly defined short filaments (*arrows*) similar to those in lichen amyloidosus (*B*). Compared with intact collagen fibril (*C*), round spaces (*) seem to represent degenerated collagen fibrils. Case 2. (A and B) × 48 700.

and the good general health and normal serum globulin profiles in these patients.

Epithelial tumors such as basal cell epithelioma, but apparently not mesodermal tumors, have been associated with amyloid deposition. The limitation of amyloid deposits to the stroma of the tumor suggests the possibility of a pathogenetic contribution by tumor cells.

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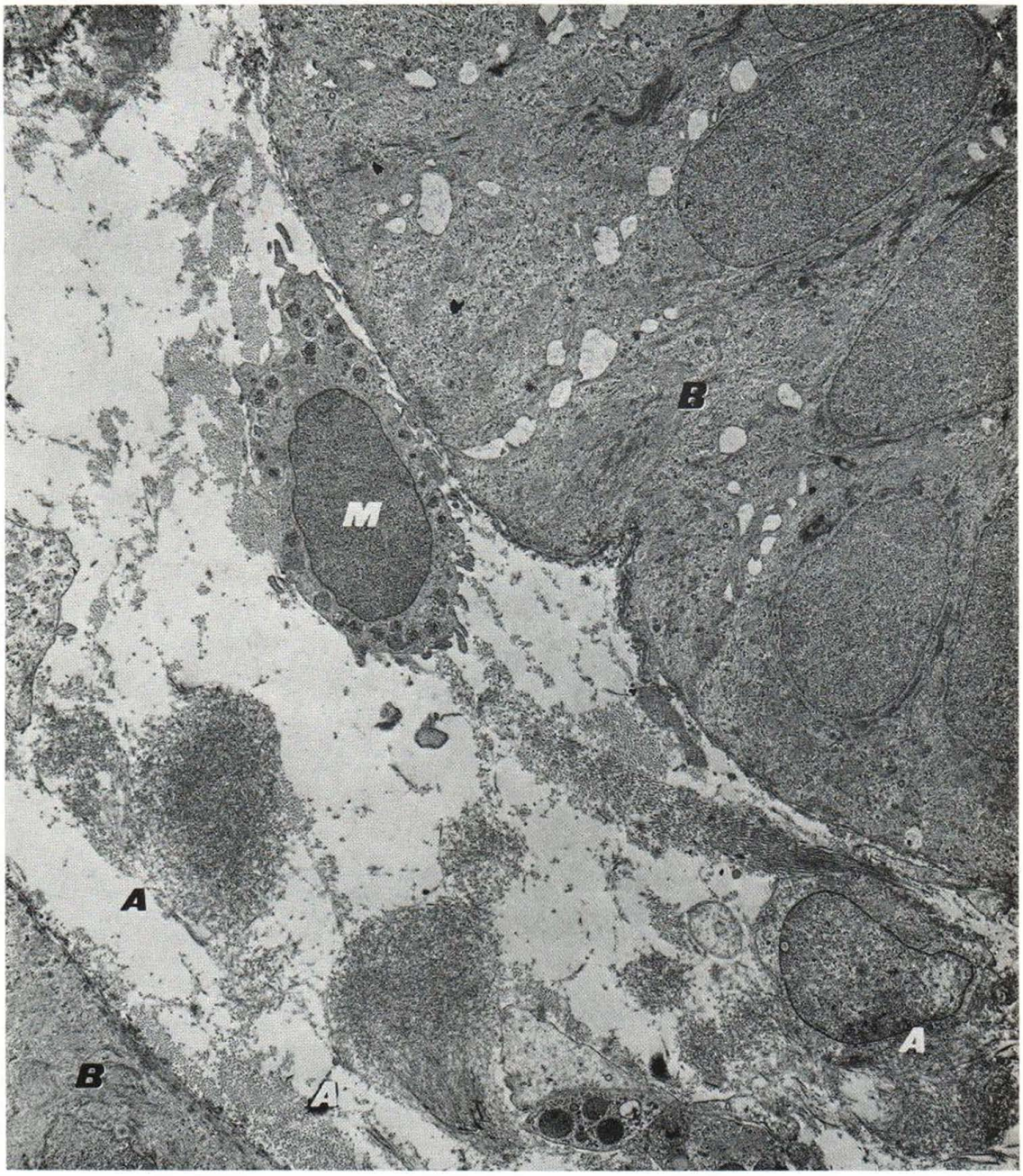

Fig. 7. Coliagenous stroma largely dissolved between two tumor islands (*B*). Amyloid islands (*A*) and mast cell (*M*) in space. Case 3. × 5 800.

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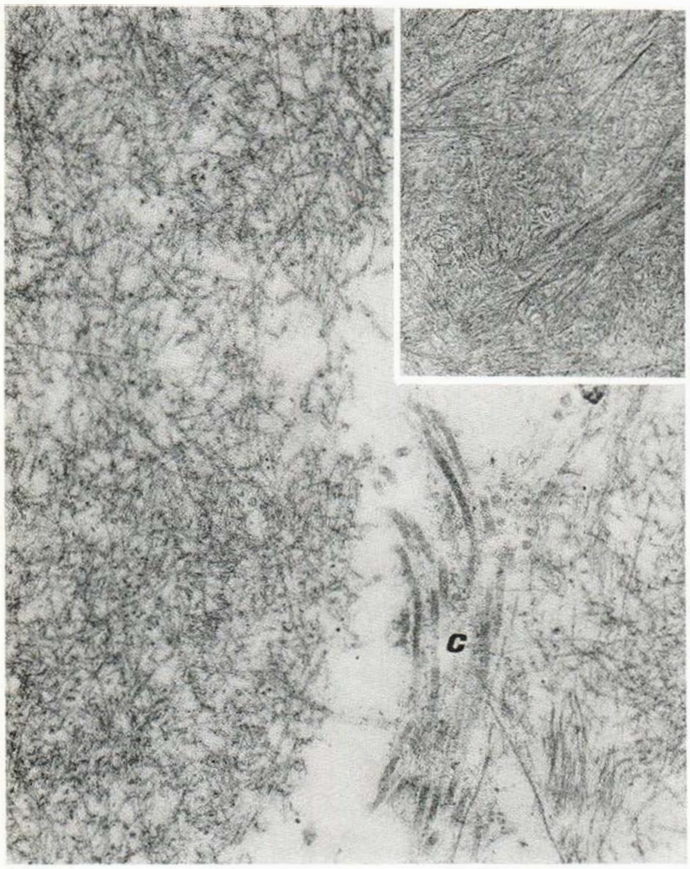

Fig. 8. Amyloid island composed mainly of filaments similar to those in lichen amyloidosus (*inset*). *C*, collagen. Case 3. ×90 000.

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Addendum

After the submission of the manuscript, we found that Sügemi published a paper (1) in which he described histochemically detectable amyloid in the stroma of tumors of epithelial origin; namely, basal cell epithelioma, fibroepithelioma premalignum (Pinkus) and mammary gland carcinoma. Amyloid in these tumors was "adsorbed" to elastic fibers in varying degree, as demonstrated by specific decrease or disappearance of histochemical amyloid by elastase digestion. It may be presumed that the varying amounts of electron-dense amorphous substance admixed in amyloid islands (Fig. 5) represent elastin-like substance.

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Fig. 9. Amyloid island contiguous with thick basal lamina (*arrows*) surrounding periphery of tumor (*B*). Many anchoring fibrils (*) about upon basal lamina. Case 3. × 26 500.