Lamina Densa Malformation Involved in Histogenesis of Primary Localized Cutaneous Amyloidosis

Yuji Horiguchi, Jo-David Fine, Irene M. Leigh, Tatsuhiro Yoshiki, Masamichi Ueda, and Sadao Imamura

Department of Dermatology (YH, SI), Department of Urology (TY), and Institute for Virus Research (MU), Kyoto University, Kyoto, Japan; Department of Dermatology (J-DF), University of North Carolina, Chapel Hill, North Carolina, U.S.A.; and Experimental Dermatology Laboratory (IML), London Hospital, London, U.K.

Skin lesions of lichenoid amyloidosis and macular amyloidosis were immunohistochemically investigated using five monoclonal antibodies against basement membrane zone (BMZ) components. A hemidesmosomal component did not contribute to amyloid deposits, but components of the lamina densa and anchoring fibrils were associated with amyloid deposits in the uppermost dermis. Immunoelectron microscopy revealed that these BMZ components were not only aggregated in the BMZ and dermis, but were also involved in the individual amyloid islets. The lamina densa was disrupted in the interface areas just above the amyloid deposits, where cytoplasm of the basal cells directly faced the aggregate of amyloid filaments. Aggregates of some BMZ components were continuous to the amyloid islets from the lamina densa area. These findings suggest that a lamina densa malformation is involved in amyloid production in the interface of the BMZ, and support the secretion theory rather than the fibrillar body theory of amyloidogenesis in these types of primary localized cutaneous amyloidosis. *J Invest Dermatol 99:12–18, 1992*

Amyloid is a generic term that defines an amorphous homogeneous eosinophilic material that shows characteristic green birefringence on Congo-red staining when viewed under polarized light [1]. Electron microscopy demonstrates that amyloid bodies are composed of 7.5 to 10 nm thick, straight, nonbranching fibrils, aggregated in an irregular, loose meshwork [2]. Although amyloid deposits in different clinicopathologic types of amyloidosis have histologically and morphologically identical properties, it has become apparent that there are several distinguishable mechanisms in the accumulation of amyloid substance in the tissues of amyloidoses.

A partly degraded monoclonal immunoglobulin-light chain produced by the plasma cells is the source of amyloid substance in primary systemic and myeloma-associated amyloidoses [1,3]. Amyloid substance in secondary systemic amyloidosis and familial amyloid polyneuropathy is considered to originate from an acute phase-reaction plasma apolipoprotein [4] and prealbumin [5], respectively. On the other hand, it is probable that in localized amyloidosis, the amyloid deposits originate from proteins synthesized in the tissues associated with such deposition. For example, amyloid in calcitonin-producing medullary carcinoma of the thyroid is thought to be derived from procalcitonin, the precursor of calcitonin [6]. The islet amyloid polypeptide, the putative precursor of the amyloid deposits in the islets of Langerhans in the diabetic pancreas, is produced in the secretory granules of islet β-cells [7].

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Reprint requests to: Dr. Yuji Horiguchi, Department of Dermatology, Faculty of Medicine, Kyoto University, Sakyoku, Kyoto, 606 Japan.

Abbreviations:

BMZ: basement membrane zone
DAB: diaminobenzidine
LA: lichenoid amyloidosis
MA: macular amyloidosis
PBS: phosphate-buffered saline
PLCA: primary localized cutaneous amyloidosis

In primary localized cutaneous amyloidosis (PLCA), which includes lichenoid amyloidosis (LA), macular amyloidosis (MA), biphasic amyloidosis (combined type of lichenoid and macular eruptions), and nodular amyloidosis, amino acid sequence analysis demonstrated that the amyloid fibril protein of the nodular type has homology with the immunoglobulin-light chain [8–10]. Thus, the amyloid of this type of PLCA seems to be derived from the immunoglobulin-light chain. Although it has been generally believed that the epidermal cells are closely related to the deposition of amyloid substance in lichenoid and macular types of PLCA [11–13], how the amyloid is produced in the skin remains controversial. Intensive observations of PLCA skin lesions by Hashimoto and his colleagues using electron microscopy and immunohistochemistry demonstrated the fibrillar degeneration of epidermal cells and consequent dropping off of the fibrillar bodies into the dermis as the origin of amyloid in LA and MA [14–18]. They speculated that the further modification of the fibrillar bodies by histiocytes and/or fibroblasts is the cause of amyloidogenesis in these types (fibrillar body theory).

However, it is true that the skin lesions of lichen planus and discoid lupus erythematosus, in which fibrillar degeneration of epidermal cells is frequently seen [19,20], are rarely accompanied by amyloid deposits. Furthermore, the basic biochemical structure of keratin filaments is that of the α-helical chain, whereas that of amyloid is a β-pleated sheet, which is why amyloid presents birefringence on Congo-red staining [1]. The former of these two contradictions is postulated by the presence of specific immunologic tolerance to necrotic keratin masses in LA and MA, whereas in lichen planus and discoid lupus erythematosus, an inflammatory response ensures removal of fibrillar bodies and prevents amyloid deposition [21–23]. However, the latter contradiction still remains to be elucidated.

Another hypothesis concerning histogenesis in these two types of PLCA is that the amyloid is produced in the interface of the epidermis and dermis by living basal keratinocytes, which produce the precursor of amyloid due to disturbed keratin metabolism (secretion theory) [24–26]. Supporting this theory is the close relationship between dissociated lamina densa-like material and amyloid depos-

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its [27,28]. Specifically, malformed lamina densa and anchoring fibrils are present within amyloid islets detectable just beneath the basal cells. In order to clarify the involvement of lamina densa malformation in the histogenesis of LA and MA, we immunohistochemically studied the epidermal-dermal interface of the skin lesions of these conditions using antibodies against several basement membrane zone (BMZ) components of the skin.

MATERIALS AND METHODS

Tissue Preparation Punch-biopsied samples from skin lesions of LA (five patients), MA (two patients), and biphasic amyloidosis (three patients; both types of eruptions were examined) were cryoprotected by soaking in a phosphate-buffered saline (PBS) series supplemented with 10% glycerine and 10–20% sucrose for 2 h each step, embedded in optimum cutting temperature compound, Tissue-Tek (Miles, Naperville, IL) containing 8% glycerin and 16% sucrose, and frozen with acetone-carbon dioxide as previously described [29].

Antibodies The following five mouse monoclonal antibodies against BMZ components of human skin and a polyclonal antibody against the amyloid-P component were used for immunohistochemistry. 1-2B7B monoclonal antibody [29] recognizes a 120-kDa polypeptide component of the hemidesmosome and the hemidesmosome-like adhesion junction structure between the endothelial cells and the surrounding lamina densa of capillary vessels. Anti-human type IV collagen monoclonal antibody was commercially obtained (Dakopatts, Glostrup, Denmark). LDA-1 monoclonal antibody [30] reacts to a noncollagenous component of the lamina densa and sublamina densa region of the skin. LH 7:2 monoclonal antibody [31] recognizes a domain of type VII collagen, which is known to be a major polypeptide component of anchoring fibrils. Anti-human laminin monoclonal antibody (4C7/B4) was produced by immunizing mice with human placental extract [32]. The polyclonal rabbit antibody against the amyloid-P component was commercially obtained (Dakopatts).

Immunofluorescence Staining Six serially cut 6-μm–thick cryosections were mounted on albuminized glass slides and air dried. Each section was first incubated with 1-2B7B monoclonal antibody (5 μg/ml), anti-type IV collagen antibody (×100 dilution), LDA-1 monoclonal antibody (10 μg/ml), LH 7:2 monoclonal antibody (×40 dilution of culture supernatant), anti-human laminin monoclonal antibody (×8000 dilution of ascites fluid), or anti-amyloid P component antibody (×5000 dilution) overnight at 4°C. After three washes with PBS, the sections incubated with monoclonal antibodies were reacted with biotinylated anti-mouse IgG (Vectastain kit, Vector Laboratories, Burlingame, CA) for 2 h at room temperature. The sections incubated with anti-amyloid P component antibody were reacted with biotinylated anti-rabbit IgG (Vectastain kit) under the same staining conditions. The sections were washed with PBS and incubated with FITC-labeled avidin (×1000 dilution, Vector Laboratories) for 2 h at room temperature. After final washes with PBS, each slide was mounted under a coverslip with 90% glycerin and examined under an epifluorescence microscope (Nikon, Tokyo, Japan). The negative control study used anti-trinitrophenol (TNP) monoclonal antibody [33] and normal rabbit serum.

Immunoelectron Microscopy The ultrastructural localization of the BMZ components was determined by the avidin-biotin-peroxidase-complex method applied to immunoelectron microscopy. In brief, 6-μm–thick serial cryosections were incubated with 1-2B7B, anti-type IV, LDA-1 LH 7:2, or anti-human laminin monoclonal antibody, then with biotinylated anti-mouse IgG, at the same concentration and under the same conditions as those for immunofluorescence staining. After PBS washes, the sections were reacted with soluble avidin-biotin-peroxidase-complex (Vectastain kit) for 2 h at room temperature. After washes with PBS, the sections were treated with 1% glutaraldehyde solution in PBS for 5 min, then serially incubated with 0.2 mg/ml diaminobenzidine (DAB) and a mixture of DAB and 0.005% hydrogen peroxide. These sections were post fixed with 1% osmium tetroxide, dehydrated with a graded alcohol series, and embedded in Spurr's resin, as previously described [29]. Ultrathin sections were counterstained with Reynold's lead citrate and examined under an H500 electron microscope (Hitachi, Tokyo, Japan). As a negative control, anti-TNP monoclonal antibody was substituted for the monoclonal antibodies.

RESULTS

Immunofluorescence microscopy revealed deposits of the BMZ components in the same areas as the amyloid aggregates, as well as along the BMZ of the epidermal-dermal junction and dermal vasculature. Although 1-2B7B monoclonal antibody retained only linear staining along the BMZ, anti-type IV and VII collagen monoclonal antibodies showed thick granular deposits in the areas of amyloid aggregates. Immunofluorescence of LDA-1 and anti-laminin monoclonal antibodies showed rather fine granular deposits in the dermis. These staining patterns were seen in all of the samples from LA, including biphasic type (Fig 1). The MA sections contained a lesser amount of, but virtually the same proportions of BMZ components in the dermis.

Sections and areas estimated by immunofluorescence to include masses of amyloid islets were selected and intensively investigated

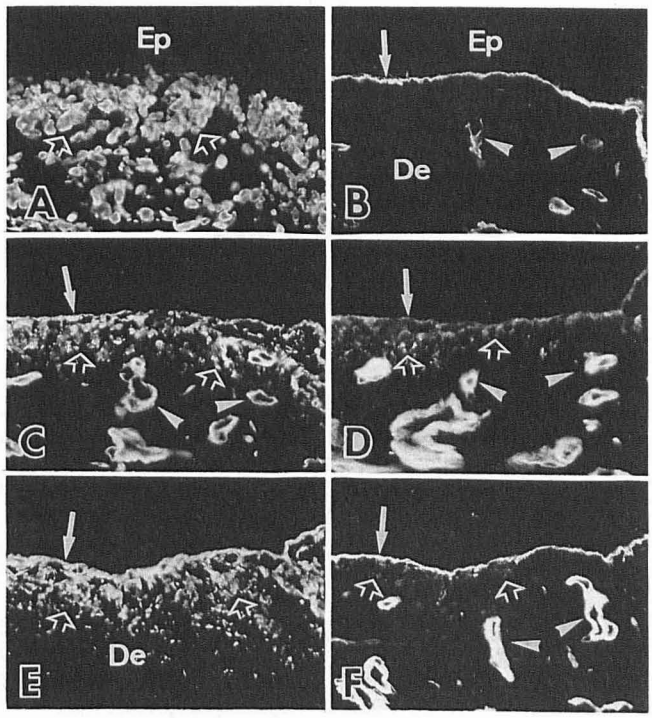


Figure 1. Immunofluorescence micrographs of serial sections from a skin lesion of LA stained with anti-amyloid P component antibody *(A)*, 1-2B7B *(B)*, anti-type IV collagen *(C)*, LDA-1 *(D)*, LH 7:2 *(E)*, and anti-laminin *(F)* monoclonal antibodies. *(A)* Amyloid bodies *(open arrows)* are aggregated beneath the epidermis (Ep). *(B)* 1-2B7B monoclonal antibody stains the BMZ *(arrow)* of the epidermis (Ep) and capillary vessels *(arrowheads)* of the dermis (De). *(C,D)* Immunofluorescence of anti-type IV collgen and LDA-1 monoclonal antibodies indicated the presence of lamina densa components granularly distributed in the uppermost dermis *(open arrows)* as well as along the BMZ *(arrow)* and capillary vessels *(arrowheads)*. *(E)* Immunofluorescence of LH 7:2 monoclonal antibody reveals granularly thick distribution of type VII collagen *(open arrows)* in the uppermost dermis (De) and along the BMZ *(arrow)* of the epidermis. *(F)* A little amount of laminin is descended down into the uppermost dermis *(open arrows)* from the BMZ *(arrow)* of the epidermis. *Arrowheads,* capillary vessels. Magnification × 350.

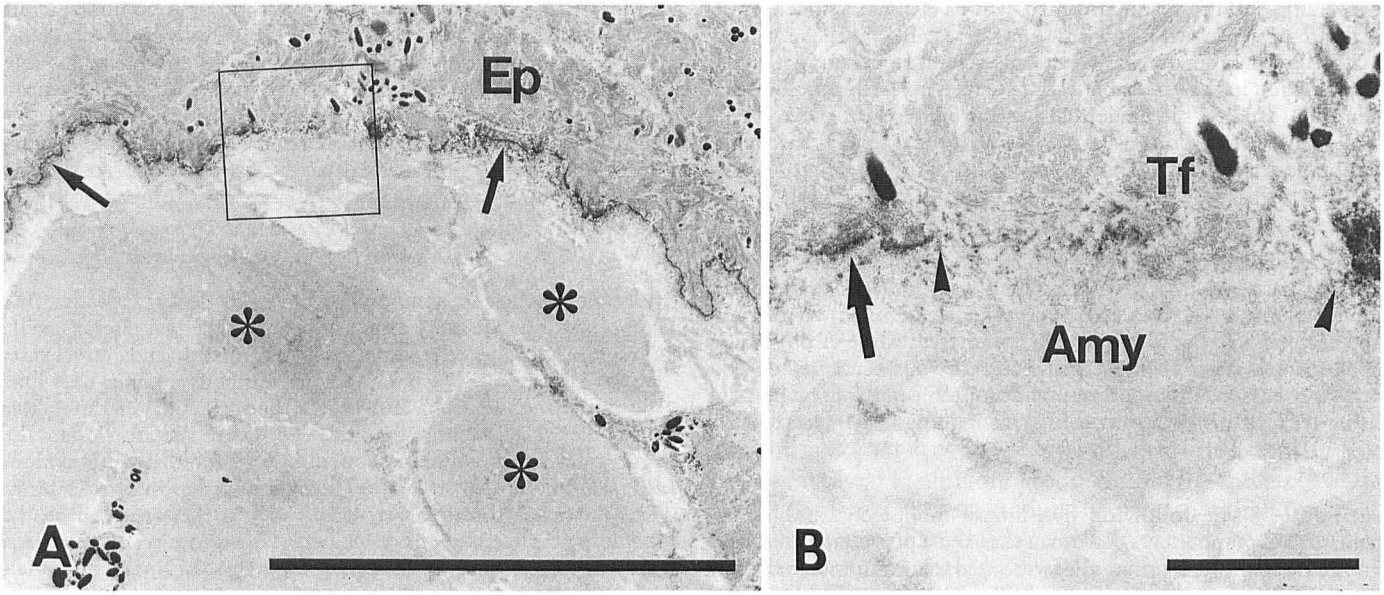
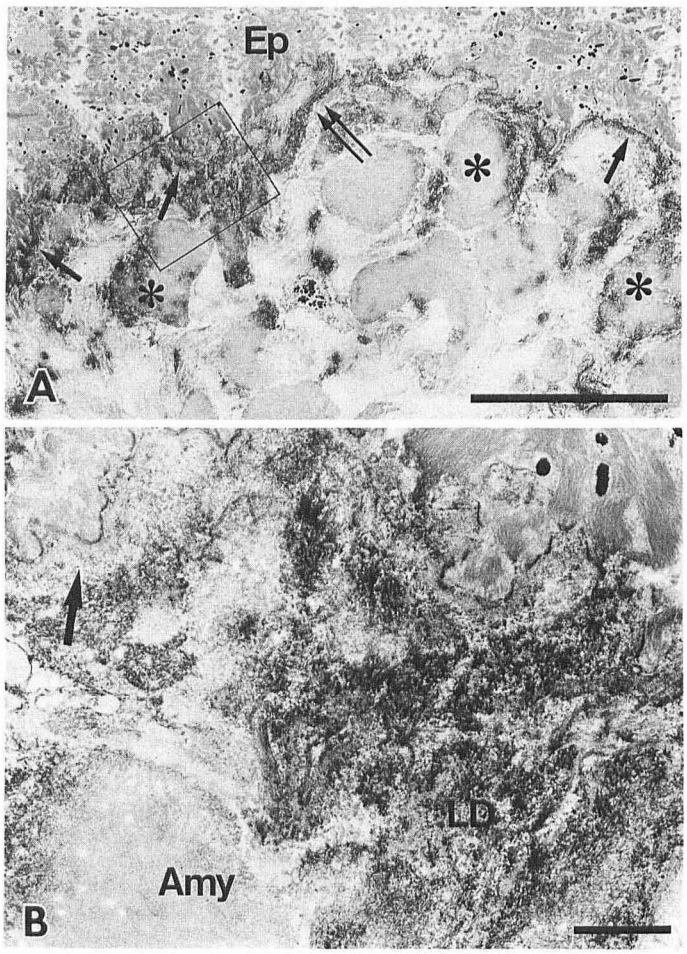


Figure 2. *(A)* A low-powered immunoelectron micrograph of LA reacted with 1-2B7B monoclonal antibody. Reaction products are distributed along the BMZ *(arrows)* of the epidermis (Ep). No reaction products are detectable among the amyloid islets *(asterisks)*. *Bar,* 10 μm. *(B)* An enlarged photograph of the rectangular area of A shows that the distribution of reaction products beneath the hemidesmosomes *(arrow)* is disrupted at the area *(between arrowheads)* where tonofilaments (Tf) of the basal cell are directly apposed to the aggregate of amyloid filaments (Amy) without interposing lamina densa. *Bar,* 1 μm.



by immunoelectron microscopy. The reaction products of 1-2B7B monoclonal antibody were distributed along the dermal surface of the basal cells, but were not associated with the amyloid islets in the dermis. In the areas where the amyloid islets were close to the basal cells, the distribution of 1-2B7B immunoreactants was partly discontinuous, and neither the lamina densa nor hemidesmosomes was detectable in these areas. The tonofilaments of the basal cells were directly apposed to the aggregates of amyloid filaments (Fig 2). The reaction products of anti-type IV collagen monoclonal antibody were irregularly dense in the lamina densa and sublamina densa region, and were also seen patchily or diffusely within individual amyloid islets. The aggregates of immunoreactants of anti-type IV collagen appeared to be continuously distributed from the lamina densa or the sublamina densa region to amyloid islets in the uppermost dermis (Fig 3). Immunoelectron microscopy of LDA-1 monoclonal antibody staining revealed fine granular distribution of the immunoreactants in the small amyloid islets and in the peripheral areas of large amyloid islets, as well as in the lamina densa and sublamina densa region. In portions where the immunoreactants were irregularly distributed beneath the basal cells, the lamina densa was disrupted, dissociated from the basal cell, and continuous to aggregates of amyloid filaments (Fig 4). The distribution pattern of the reaction products of LH 7 : 2 monoclonal antibody was coarsely granular in those areas within the sublamina densa region where lamina densa-like amorphous material and amyloid filaments irregularly coexisted. Patchy aggregates of immunoreactants were also noted within individual amyloid islets. Some basal cells contained

Figure 3. *(A)* A low-powered immunoelectron micrograph of LA stained with anti-type IV collagen antibody shows patchily or diffusely distributed aggregates of reaction products among the amyloid islets *(asterisks)* and the regular and irregular arrangement of reaction products along the BMZ *(arrows)* of the epidermis (Ep). Some arrays of reaction products *(double arrows)* indicate the reaction along the dissociated lamina densa. *Bar,* 10 μm. *(B)* An enlarged photograph of the rectangular area of A shows dislocated lamina densa materials (LD) containing type IV collagen continuing to the amyloid islet (Amy). In some areas, the basal cell faces amorphous material *(arrows)* that lacks the epitope for this monoclonal antibody. *Bar,* 1 μm.

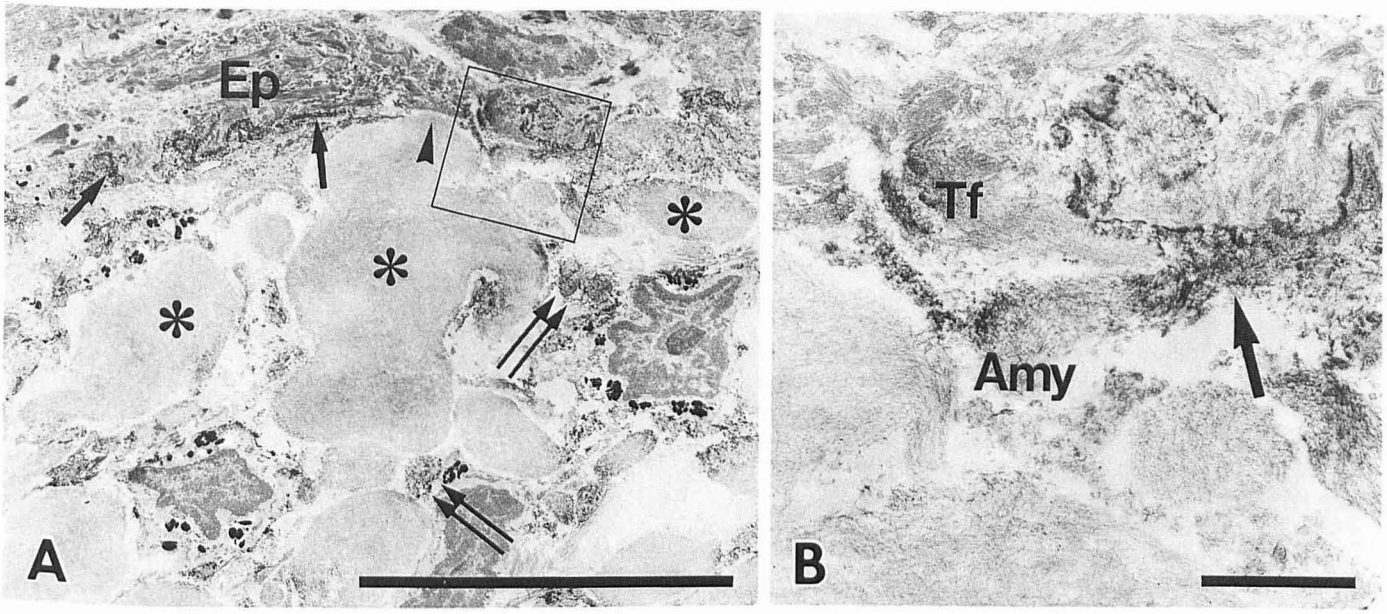


Figure 4. *(A)* A low-powered view of immunoelectron microscopy of LA stained with LDA-1 monoclonal antibody shows reaction products distributed in the small amyloid islets *(double arrows)*, peripheral areas of large amyloid islets *(asterisks)*, and along the BMZ *(arrows)* of the epidermis (Ep). The distribution of reaction products are absent in some areas of the BMZ *(arrowhead)*. *Bar*, 10 μm. *(B)* An enlarged photograph of the rectangular area of A shows that the LDA-1–positive lamina densa *(arrow)* shifts to the aggregate of amyloid filaments (Amy), and that the loosened tonofilaments (Tf) protrude into the dermis. *Bar*, 1 μm.

type VII collagen-reactive immunodeposits within the cytoplasm. It seemed that perinuclear space and enlarged endoplasmic reticulum contained the immunoreactants (Figs 5–7). Immunoreactants to the anti-laminin monoclonal antibody were diffusely involved in the amyloid islets. The distribution of laminin along the BMZ was disrupted along portions of the epidermal-dermal junction where the lamina densa was absent. In such areas, tonofilaments of the basal cells seemed to directly face the amyloid islets (Fig 8). There were no histiocytes or fibroblasts phagocytizing the amyloid deposits in the areas where aggregates of the BMZ components coexisted with amyloid deposits. Amyloid islets in the deeper dermis contained smaller quantities of BMZ components.

DISCUSSION

The presence of a lamina densa-like substance and anchoring fibrils within the amyloid deposits in the skin lesions of PLCA was first demonstrated by Kumakiri et al [27], who detected the BMZ substance in the dermis not only with electron microscopy but also with immunohistochemistry using a bullous pemphigoid serum, and concluded that apoptotic keratinocytes of the epidermis brought

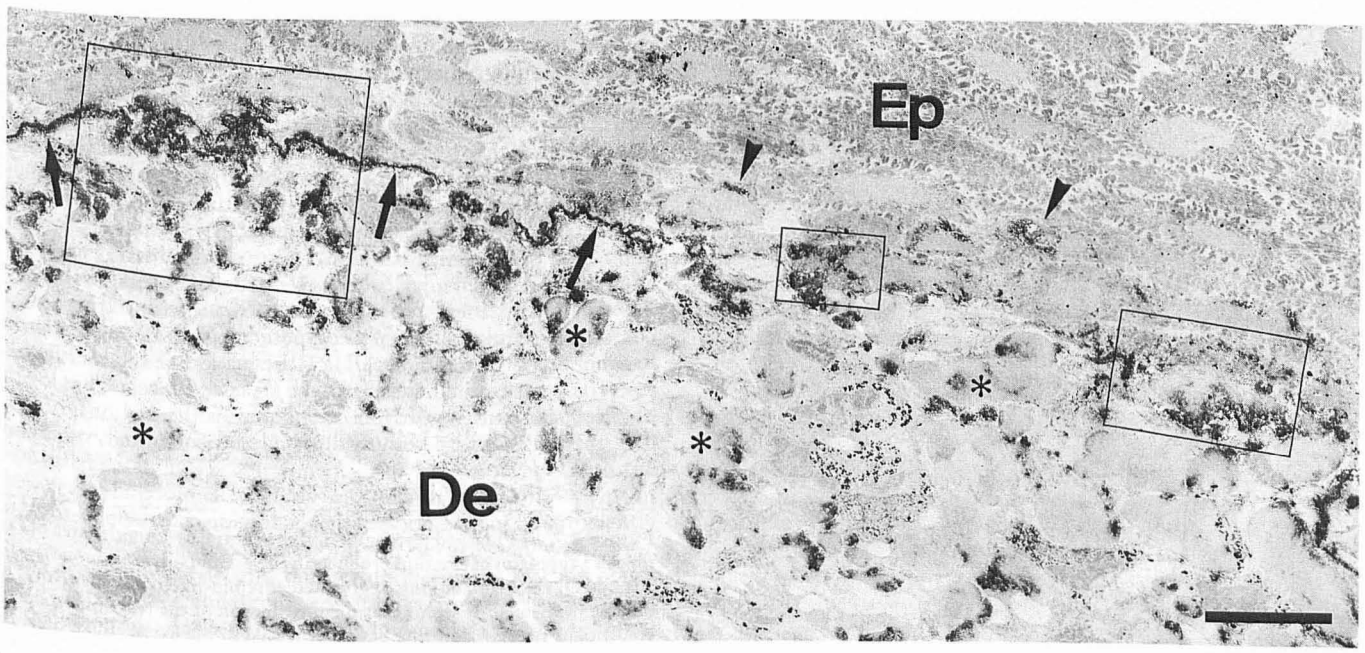


Figure 5. Immunoelectron microscopic scanning view of the uppermost dermis (De) and BMZ of the epidermis (Ep) of LA stained with LH 7 : 2 monoclonal antibody shows reaction products continuously distributed along the BMZ at the *left side* of the field *(arrows)*. Reaction products are along granularly distributed among the amyloid islets *(asterisks)* and in the epidermal cells *(arrowheads)*. *Bar*, 10 μm.

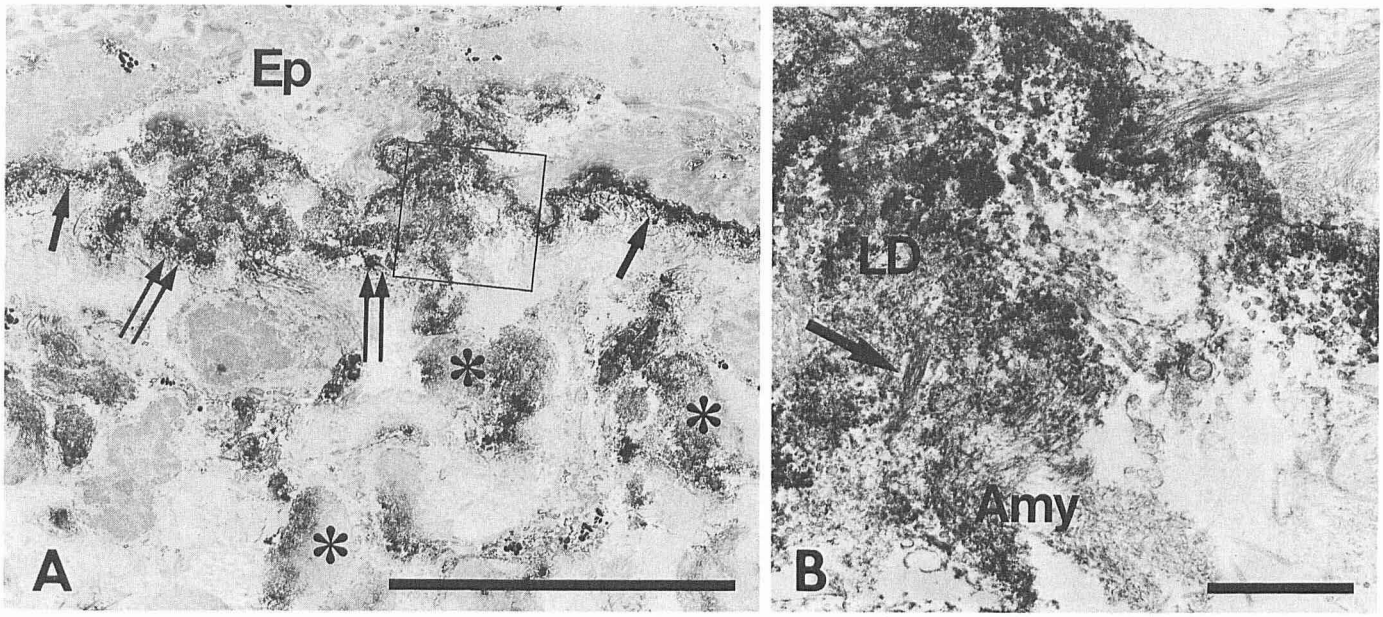


Figure 6. *(A)* In this low-powered view of the left rectangular area of Fig 5, irregularly thick distribution of reaction products *(double arrows)* just beneath the epidermis (Ep) and among amyloid islets *(asterisks)* are seen, as well as along normally looking lamina densa *(arrows)*. *Bar,* 10 μm. *(B)* An enlarged photograph of the rectangular area of A shows reaction products distributed along the dissociated lamina densa-like material (LD) and aggregates of amyloid filaments (Amy). In the aggregate of reaction products, a tonofibril-like bundle of filaments is seen *(arrow)*. *Bar,* 1 μm.

down the lamina densa and fine fibrous components attached to it when these cells dropped to the papillary dermis and became the source of amyloid. Lee et al [34] demonstrated aggregates of anchoring fibrils in amyloid islets associated with trichoepithelioma, supporting the fibrillar body theory. However, it is rather difficult to imagine how the degenerating keratinocytes involve the components of the lamina densa and anchoring fibrils inside themselves or how, once completed, the lamina densa is drawn down into the dermis with a dropping-off of fibrillar bodies. Furthermore, the immunohistochemical study using a bullous pemphigoid serum to detect the BMZ substance in aggregates of amyloid [27] has two problems. The first is that the bullous pemphigoid antigen is a component of the hemidesmosome [35–38], not of the lamina densa. The second is that, because the amyloid deposits carry in vivo bound immunoglobulins themselves [39–41], it is hard to determine whether the labeled anti-human IgG antibody reacted to applied bullous pemphigoid serum, or to in vivo bound IgG.

The generally accepted fibrillar body theory of the amyloidogenesis of PLCA is virtually based upon ultrastructural findings that the amyloid substance coexists with the filamentous body, sometimes known as the colloid-amyloid body [14–16,42] and immunohistochemical findings that amyloid has common antigenicities with keratin filaments [17,18]. The finding that histiocytes and fibroblasts contain amyloid bodies in their cytoplasm [43] also supports this theory. The key point of this theory is that the fibrillar bodies, namely the aggregated cytoskeleton of the keratinocytes, supposedly composed of keratin, are phagocytized by the histiocytes and/or fibroblasts, converted to amyloid substance, and discharged outside of the cytoplasm. Although the amyloid substance in LA and MA is not yet biochemically characterized, it is natural to think that the amyloid in these types, which shows also birefringence on Congo-red staining, is mainly composed of β-pleated sheets similar to other types of amyloid [1]. How the histiocyte and/or fibroblast converts the α-chain of keratin to the β-pleated sheet of amyloid has not been substantially proven. Even if this is the case, it is unlikely that only the fibrillar body is digested and converted to amyloid,

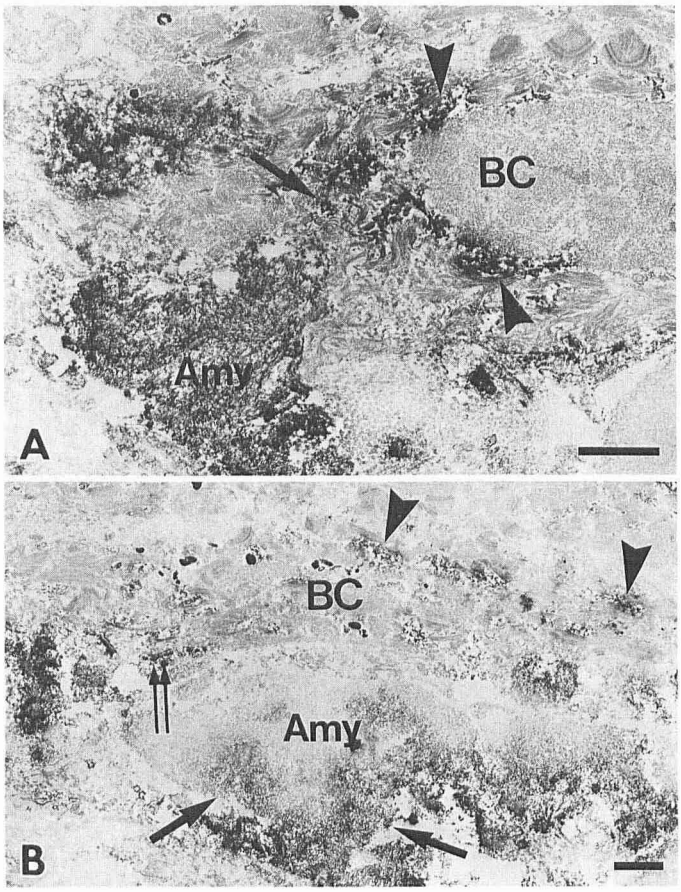


Figure 7. *(A)* Enlarged photograph of the central rectangular area of Fig 5 reveals aggregates of reaction products in the perinuclear area *(arrowheads)* of a basal cell (BC) and among aggregated amyloid-like filaments (Amy) just outside of the cell. It seems that the distribution of the reaction products is continuous *(arrow)* from the perinuclear area to the extracellular area. *Bar,* 1 μm. *(B)* An enlarged photograph of the right rectangular area of Fig 5 shows a mixture of the reaction products *(arrows)* in the amyloid islet (Amy) and patchy distribution of reaction products *(arrowheads)* in the basal cell (BC). The lamina densa *(double arrows)* is rarely seen. *Bar,* 1 μm.

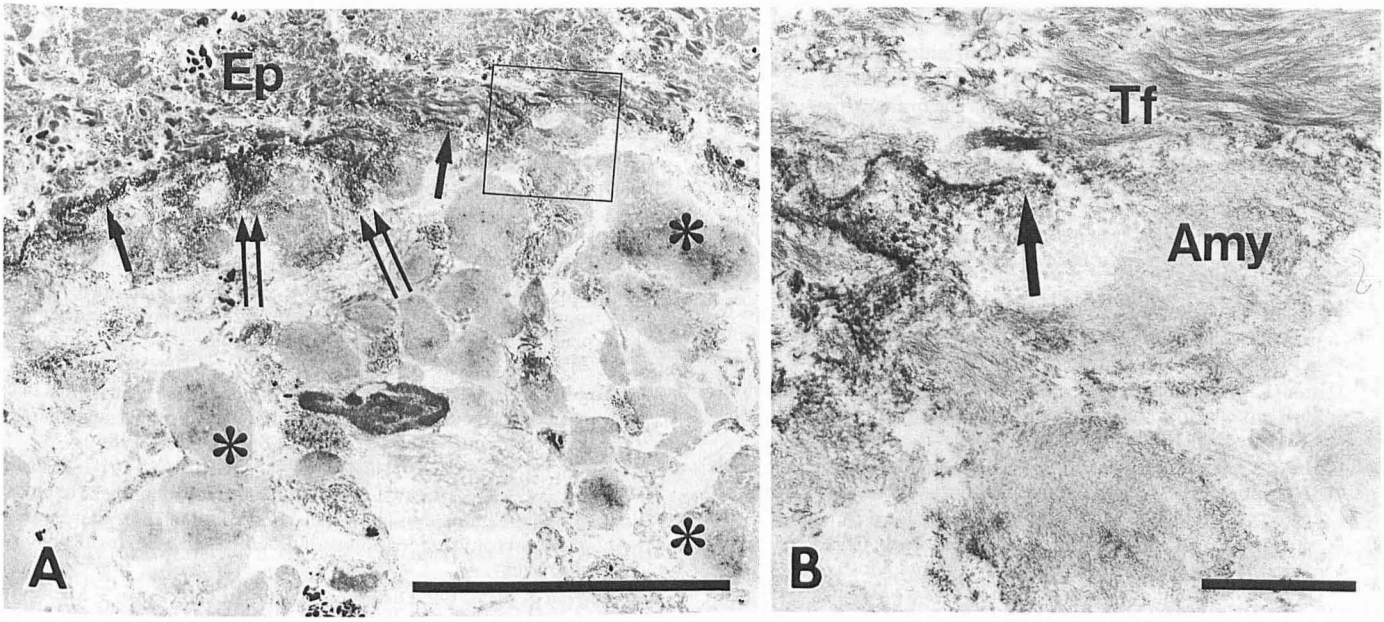


Figure 8. *(A)* A low-powered immunoelectron micrograph of LA stained with anti-laminin monoclonal antibody. Reaction products are seen along the BMZ *(arrows)* of the epidermis (Ep), in the uppermost dermis *(double arrows)* and diffusely in the amyloid islets *(asterisks)*. *Bar,* 10 μm. *(B)* An enlarged photograph of the rectangular area of A shows disruption of the lamina densa *(arrow)* and apposition of aggregated amyloid filaments (Amy) and tonofibrils (Tf) of the basal cell *Bar,* 1 μm.

whereas the dissociated lamina densa and anchoring fibrils remain unchanged, associating with the amyloid.

Another hypothesis for amyloidogenesis of PLCA, excepting nodular amyloidosis, is the secretion theory proposed by Yanagihara et al [24,25]. Their theory states that amyloid is produced in the interface of the epidermis and dermis, and that the precursor of the amyloid is possibly secreted from the basal cells. They reached this hypothesis on the basis of electron microscopic findings that the amyloid deposits just beneath the basal cells are small and directly apposed to the basal cells without interposition of the lamina densa. Westermark et al [26] postulated disturbed keratin metabolism in the basal cells, which secrete the precursor of the amyloid in LA. Horiguchi et al [28] electron microscopically examined skin lesions of a case of biphasic amyloidosis, and revealed the absence of normal structures of lamina densa and hemidesmosomes between the uppermost amyloid deposits and the basal cells, as well as the close relationship between dissociated lamina densa-like substance and amyloid. They speculated that the amyloid in this case was produced in the epidermal-dermal interface involving lamina densa malformation.

In this study, immunofluorescence and immunoelectron microscopy revealed the rare contribution of a hemidesmosomal component in the amyloid deposits in LA and MA. However, four other components of epidermal BMZ were also involved in the aggregates of amyloid deposits but in a slightly different manner. Type IV collagen, a major component of the lamina densa, was patchily and diffusely involved, and type VII collagen, a major component of anchoring fibrils, was patchily involved in individual amyloid islets. Laminin, another major component of the lamina lucida and lamina densa was rather diffusely seen with amyloid islets. LDA-1 antigen, a noncollagenous BMZ component [30], was associated with the periphery of amyloid islets. This re-distribution of components of the lamina densa and sublamina densa region cannot be sufficiently explained by the theory that dropping-off fibrillar bodies bring the lamina densa into the dermis. Furthermore, some aggregates of the BMZ components seemed to be continuous from the lamina densa and the sublamina densa region to amyloid islets. In addition, some basal cells above amyloid aggregates demonstrated intracytoplasmic aggregates of type VII collagen that seemed to be retained in the perinuclear area and endoplasmic reticulum. The continuous distribution of these BMZ components along the interface was disrupted in many areas where the cytoplasm of the basal cells directly faced the amyloid bodies. These findings suggest that lamina densa formation is highly disturbed in the areas of amyloid deposition, and that individual amyloid islets may be closely related to the lamina densa malformation. We can conclude here that, though these findings do not directly certify the secretion theory of amyloidogenesis in LA and MA, they are more appropriately explained by the secretion theory than by the apoptotic fibrillar body theory.

The secretion theory can explain several other characteristic features of the histology of LA and MA. The intracytoplasmic aggregate of the amyloid filaments occasionally seen in the keratinocytes [28,44] should represent the retention of amyloid that was produced but not discharged outside of the basal cells. The presence of colloid-amyloid body [14], or collagen fibrils woven among the amyloid fibrils [45] should result from the involvement of fibrillar bodies or collagen fibrils within the amyloid secretion by the basal cells. The reason the amyloid islets in the mid-dermis are large, round or oval, and well demarcated, whereas the uppermost amyloid islets are small, irregularly shaped, and have a fuzzy outline, may be that amyloid is produced beneath the basal cells, then repeatedly enclosed, treated, and packaged by cytoplasmic projections of migrating histiocytes and fibroblasts, thus changing its size and shape. The amyloid bodies enclosed in the cytoplasm of fibroblasts and histiocytes should not be undergoing digestion, but merely packaging. Routine histologic preparation of the skin lesions of LA frequently shows cleavage at the epidermal-dermal interface where amyloid is massively aggregated [46]. This should result from the fact that the epidermal-dermal interface is only incompletely integrated due to malformed hemidesmosome and lamina densa structures.

Westermark et al [26] postulated two different histogenetic pathways in LA and MA: secretion in LA and via the filamentous body in MA. However, in our study there were no substantial differences in involvement of malformed lamina densa between LA and MA. In both LA and MA, amyloid substance is most likely produced in the interface of the epidermal-dermal junction by living basal cells accompanied by malformation of the lamina densa.

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