Acta Dermatovener (Stockholm) 59: 341–345, 1979

AMYLOIDOSIS OF THE SKIN: A COMPARISON BETWEEN LOCALIZED AND SYSTEMIC AMYLOIDOSIS

Per Westermark

Department of Pathology, University of Uppsala, Uppsala, Sweden

Abstract. Skin biopsies from patients with different forms of localized and systemic amyloidoses were studied. Subepidermal deposits, typical of lichen amyloidosus, were also seen in other types of amyloidosis, least frequent in the secondary systemic form. Amyloid within the epidermis and especially the horny layer as well as pigmented cells close to the deposits were found in all cases of lichen amyloidosus but in no other specimens. Plasma cells, on the other hand, were numerous in nodular amyloidosis but were not found in any other cases. It is concluded that in the pathogenesis of lichen amyloidosus the epidermis and perhaps dermal melanocytes are involved. In the pathogenesis of localized nodular amyloidosis the plasma cells might be of importance.

Key words: Skin amyloidosis; Localized amyloidosis; Systemic amyloidosis

Skin involvement is a very common finding in primary and myeloma-associated systemic amyloidosis (8, 23). The amyloid deposits are found at different levels of the skin, but quite often deposits occur at the dermal–epidermal junction. The amounts of amyloid are often enough to produce clinical symptoms. In secondary systemic amyloidosis, amyloid is also very often found in the skin but usually only in the deep dermis and in the subcutaneous layer (19, 21, 24) and is clinically not detectable.

Two main types of localized cutaneous amyloidosis exist, namely nodular amyloidosis (NA) and lichen amyloidosus (LA) including macular amyloidosis. In LA, the deposits are seen in the dermal papillae but, unlike systemic amyloidosis, not in the subcutaneous layer (1–3, 5, 7, 11). In NA, on the other hand, the pattern of deposition in the skin is comparable to that of primary systemic amyloidosis (7).

The pathogenesis of LA has been a matter of debate (2–5, 9, 10, 13–15), and the possibility that the epidermis might be of importance for the formation of amyloid has received attention (2–5, 14). In the present study, skin biopsies from patients with different types of systemic and localized amyloidosis have been studied, especially with the respect to the pattern of deposition in the upper corium and in the epidermis. The findings indicate that the epidermis is involved in the formation of amyloid in LA but not in other forms of amyloidosis of the skin.

MATERIAL AND METHODS

Skin biopsies, usually including subcutaneous fat tissue, were studied in localized amyloidosis (lichen amyloidosus and nodular amyloidosis) and systemic amyloidosis (primary, secondary and myeloma-associated amyloidosis). Usually only one biopsy sample was available from each patient. The biopsies were taken from clinically involved skin in all cases of localized amyloidosis but in the patients with systemic amyloidosis only one with myelomatosis had signs of skin involvement.

Sections about 4 μm thick were stained with hematoxylin and eosin or according to van Gieson. Amyloid was demonstrated by staining with Congo red on examination under polarized light. Bright green birefringence was taken as evidence of amyloid.

RESULTS

Some typical findings in the four groups are summarized in Table I.

Lichen amyloidosus

The amyloid deposits were confined to the papillary corium. Usually the deposits were separated from the epidermis by a narrow zone, but in several places there was an obvious contact between the basal cell layer and the amyloid substance (Fig. 1). Sometimes small amyloid fragments seemed to be interposed between cells in the basal cell layer. In all 4 cases, amyloid particles of varying size occurred within the horny layer (Fig. 2). These particles exhibited a bright green birefringence when examined in polarized light after staining with Congo red. Sometimes several such bodies were

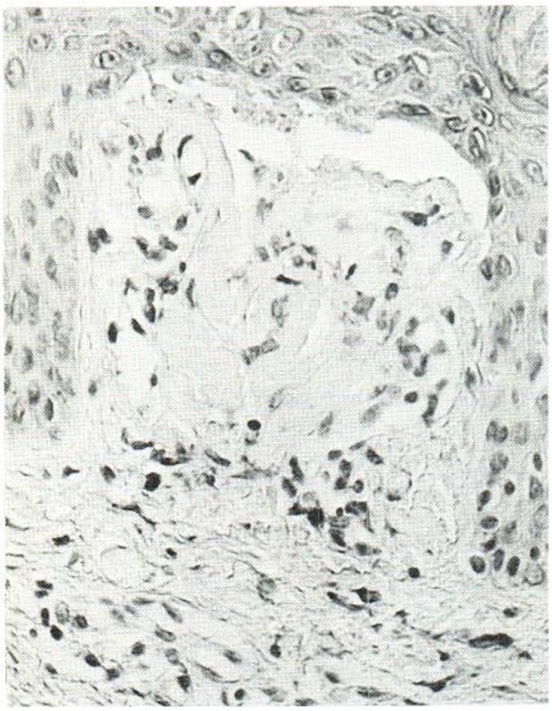

Fig. 1. Lichen amyloidosus. Amyloid deposits in a papilla. The basal epidermis is partly degenerated. Congo red, ×220.

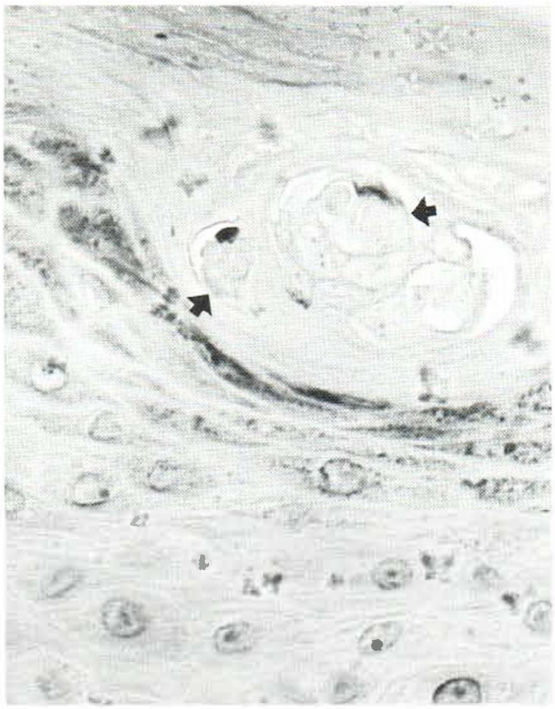

Fig. 2. Lichen amyloidosus. Corpuscular deposits (arrows) in the stratum corneum. These deposits have typical staining properties of amyloid. Congo red, ×700.

found within one area. These bodies were often closely attached to a nuclear remnant or contained pigment. In one case, amyloid also occurred in stratum granulosum. Small intra-epidermal bodies resembling amyloid but without staining properties of this substance were also seen.

The amyloid in the papillary corium also often occurred as rounded, faceted corpules. A typical feature, seen in all cases, was the occurrence of pigmented cells within the amyloid deposits. Some such cells seemed dendritic with long, slender projections which often lay very close to amyloid deposits (Fig. 3). The pigment in the dendritic cells was usually finely granular. More plump, non-dendritic cells containing a coarser pigment were also common. Amyloid was not found in the deep corium, in the vessels, or in the subcutaneous tissue. In some specimens small groups if inflammatory cells, predominantly histiocytes and lymphocytes, were seen.

Table I. *Some findings in biopsies from patients with differentforms of amyloidosis of the skin*

	No. of biopsies (= patients)	Number of biopsies with				
		Amyloid deposits			Pigmented cells within the amyloid deposits	Plasma cells close to deposits
		In vessels	Sub-epidermally	Intra-corneally		
Lichen amyloidosus	4	0	4	4	4	0
Nodular amyloidosis	3	3	2	0	0	3
Primary and myeloma-associated systemic amyloidosis	7	6	5	0	0	0
Secondary systemic amyloidosis	8	4	2	0	0	0

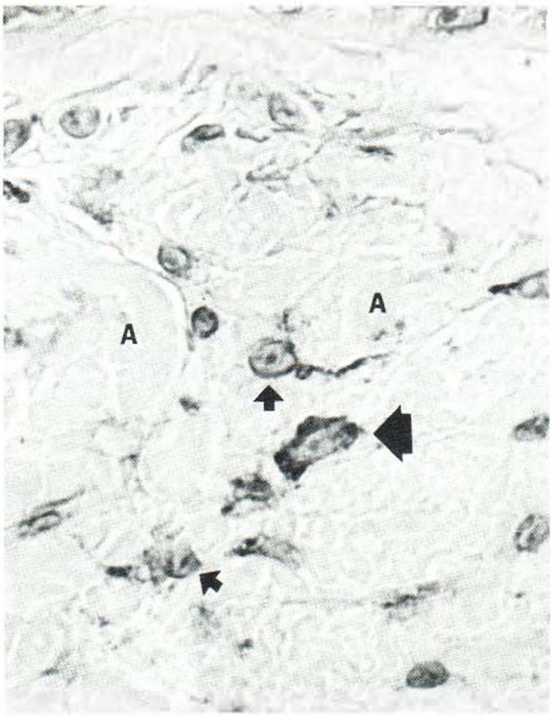

Fig. 3. Lichen amyloidosus. Amyloid deposits (A) sometimes surrounded by pigmented, branching cells (small arrows). A more plump cell with coarse pigmentation (large arrow) is also seen. Congo red, ×860.

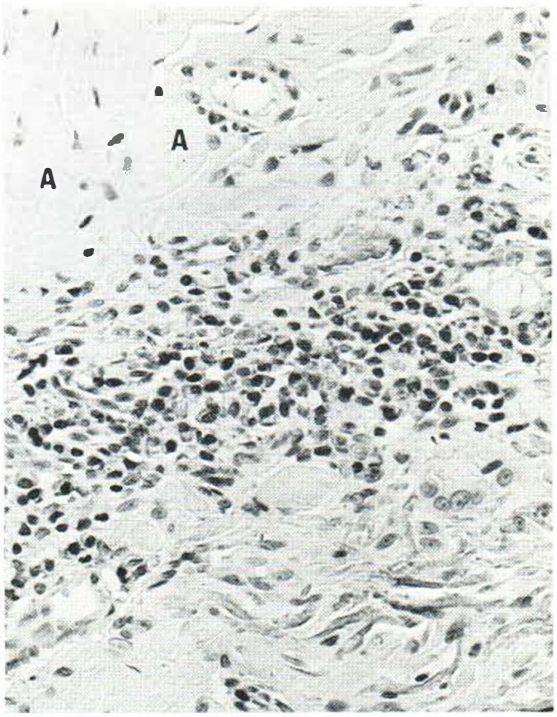

Fig. 4. Nodular amyloidosis. Amyloid deposits (A) surrounded by an inflammatory infiltrate which almost only contains plasma cells. Congo red, ×280.

Nodular amyloidosis

In the three specimens of nodular amyloidosis, a large amount of amyloid substance was found within a limited area of the corium. The amyloid was more homogeneous and not as corpuscular as seen in lichen amyloidosus. The border with normal tissue was not sharp, as small amyloid deposits were found between the collagen fibres outside the main deposit. The amyloid occurred in some areas in close contact with the basal cell layer but no amyloid was found in the epidermis. There were no pigmented cells within the deposits. In all these three cases amyloid was demonstrated in the walls of vessels in the deep corium but not in the subcutaneous tissue. In some areas and in direct contact with the amyloid, infiltration of inflammatory cells—predominantly plasma cells—were found (Fig. 4).

Primary and myeloma associated systemic amyloidosis

Of the seven specimens in this group, five exhibited amyloid infiltration in the uppermost corium just subepidermally and in obvious contact with the epidermis (Fig. 5). No amyloid was seen between the basal cells or elsewhere in the epidermis. No pigmented cells occurred in the deposits. In six of the cases, the biopsies contained the deep corium and in all of these amyloid was found in the walls of vessels and between collagen bundles. In those five biopsies which included fat tissue, amyloid was seen as rings around fat cells. Inflammatory cells were scarse.

Secondary systemic amyloidosis

In 2 of the 8 patients in this group, amyloid was found in the subepidermal zone (Fig. 6). No Congo red positive substance was seen within the epidermis, however. In all the specimens, amyloid was seen around adnexa, especially eccrine sweat glands and in four cases within the walls of vessels on the border between the dermis and the subcutis. In seven of the biopsies, subcutaneous fat tissue was included and all of these exhibited amyloid infiltration around fat cells. No infiltration of inflammatory cells was seen.

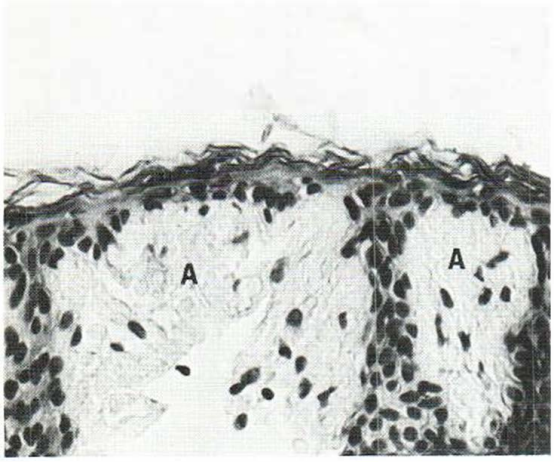

Fig. 5. Myeloma-associated systemic amyloidosis. A heavy amyloid infiltration (A) just beneath the epidermis which is thin but otherwise unchanged. No pigmented cells occur in the deposits. Congo red, ×220.

DISCUSSION

From the present study it is obvious that there is a distinct difference between LA on the one hand, and the other studied forms of amyloidosis on the other. Features seen only in LA were the globular shape of the deposits, the numerous pigmented cells in the amyloid area and the finding of intra-epidermal amyloid clumps.

The pathogenesis of local amyloidosis of the skin is essentially unknown. Electron microscopic studies of LA have revealed a close relationship between dermal fibroblasts and amyloid fibrils and these cells have therefore been thought to be the producers of amyloid (9, 13–16, 20, 22). Black and co-workers (2–5), however, have drawn attention to the changes in the basal cell layer of the epidermis in LA and believe that these cells take part in the formation of amyloid and that the amyloid might consist of transformed keratinocytes.

In light microscopic studies, by using metachromatic stains, Freudenthal (11) and Anekoji & Irisava (1) have reported amyloid-like particles within the epidermis of some patients with LA. Similar particles were also noted by Black (3) and Black & Wilson Jones (5), who however found them not to stain with Congo red. Civatte bodies, which resemble small amyloid deposits (5), often occur in LA (10), though these bodies do not have the staining properties of amyloid (10). In the present study, definite amyloid deposits with typical staining properties with Congo red and exhibiting green birefringence were seen within the horny layer in all the specimens from patients with LA. This was not seen in any other case of skin amyloidosis.

Another typical feature of LA was the finding of pigmented cells within the amyloid masses. Such cells have constantly been noted previously and interpreted as a result of pigment incontinence due to damage of the basal epidermis (2, 3, 5–7, 16). Many of the cells had the appearance of pigment macrophages but other cells seemed dendritic and were more finely pigmented and thus looked more like melanocytes. Indeed, many cells that have been considered to be pigment macrophages in other skin lesions might in reality be melanocytes (17).

The interpretation of the occurrence of pigmented cells as being due to damage of the epidermis through interference with nutrition seems improbable. Amyloid infiltration close to the epidermis was heavy in several of the biopsies from patients with primary and myeloma-associated systemic amyloidosis, without any sign of epidermal degeneration or pigment incontinence being seen. Also in two of the cases of NA, large deposits occurred close to the epidermis.

The finding of amyloid deposits in the epidermis in LA but in no other type of cutaneous amyloidosis can support the conclusion by Black and co-workers (2–5) that the epidermis is involved in the pathogenesis of LA. However, the close contact

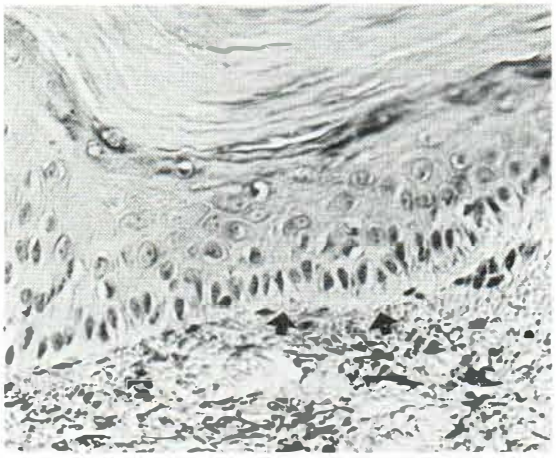

Fig. 6. Secondary systemic amyloidosis. A thin deposit of amyloid (arrows) is in obvious contact with the epidermal basal cells. The epidermis is unchanged. Congo red, ×220.

between the amyloid deposits in LA and often melanocyte-like pigmented cells might indicate that these cells—and not only keratinocytes—may be associated in the production of amyloid.

The pattern of deposition in NA is quite different from that in LA. In NA the amyloid deposits were also seen in the deep parts of the corium and within the walls of vessels. The pattern of deposition was identical with some cases of primary or myeloma-associated systemic amyloidosis. However, in all the three cases of NA, infiltrates of inflammatory cells—predominantly plasma cells—occurred and this was not seen in the other forms of amyloidosis of the skin. In this respect NA is reminiscent of localized amyloidosis elsewhere, e.g. the urinary bladder and respiratory system, where infiltrates of plasma cells are the rule (12). It is possible that the NA is an immunoglobulin-derived amyloid, originating from plasma cells at the site of deposition. Such an immunoglobulin derivation has been demonstrated in a case of localized amyloidosis of the respiratory tract (18). Obviously it is quite probable that the chemical composition of the amyloid fibril in LA differs fundamentally from that in NA. Studies on this subject are in progress.

ACKNOWLEDGEMENTS

This work was supported by grants from the Swedish Medical Society and the King Gustaf V Research Fund.

Thanks are due to Christer Tengvar for skilled assistance.

REFERENCES

1. Anekoji, K. & Irisawa, K.: Five cases of lichen amyloidosus. Arch Dermatol *84:* 101, 1961.
2. Black, M. M.: The role of the epidermis in the histopathogenesis of lichen amyloidosus. Histochemical correlations. Br J Dermatol *85:* 524, 1971.
3. Black, M. M.: Primary localized amyloidosis of the skin: clinical variants, histochemistry and ultrastructure. *In* Amyloidosis (ed. O. Wegelius and A. Pasternack) p. 479. Academic Press, London and New York 1976.
4. Black, M. M. & Heather, C. J: The ultrastructure of lichen amyloidosus with special reference to the epidermal changes. Br J Dermatol *87:* 117, 1972.
5. Black, M. M. & Wilson Jones, E.: Macular amyloidosis. A study of 21 cases with special reference to the role of the epidermis in its histogenesis. Br J Dermatol *84:* 199, 1971.
6. Brownstein, M. H. & Hashimoto, K.: Macular amyloidosis. Arch Dermatol *106:* 50, 1972.
7. Brownstein, M. H. & Helwig, E. B.: The cutaneous amyloidoses. I. Localized forms. Arch Dermatol *102:* 8, 1970.
8. Brownstein, M. H. and Helwig, E. B.: The cutaneous amyloidoses. II. Systemic forms. Arch Dermatol *102:* 20, 1970.
9. Ebner, H.: Licht- und elektronenmikroskopische Untersuchungen über das Amyloid der Haut. Z Haut Geschlechtskr *43:* 833, 1968.
10. Ebner, H. & Gebhart, W.: Light and electron microscopic differentiation of amyloid and colloid or hyaline bodies. Br J Dermatol *92:* 637, 1975.
11. Freundenthal, W.: Amyloid in der Haut. Arch Dermatol Syph *162:* 40, 1930.
12. Glenner, G. G. & Page, D. L.: Amyloid, amyloidosis and amyloidogenesis. *In* International Review of Experimental Pathology (ed. G. W. Richter and M. A. Epstein), p. 1. Academic Press, London and New York, 1976.
13. Hashimoto, K.: Skin function and amyloidosis. Ultrastructural studies. *In* Amyloidosis (ed. O. Wegelius and A. Pasternack), p. 515. Academic Press, London and New York, 1976.
14. Hashimoto, K. & Brownstein, M. H.: Amyloidogenesis in healing wound. Electron microscopic studies of biopsied wounds in macular amyloidosis. Am J Pathol *68:* 371, 1972.
15. Hashimoto, K. & Onn, L. L. Y.: Lichen amyloidosus. Electron microscopic study of a typical case and a review. Arch Dermatol *104:* 648, 1971.
16. Kurban, A. K., Malak, J. A., Afifi, A. K. & Mire, J.: Primary localized macular cutaneous amyloidosis: histochemistry and electron microscopy. Br J Dermatol *85:* 52, 1971.
17. Okun, M.: Dermal Dopa-positive cells in lichen planus. Arch Dermatol *106:* 422, 1972.
18. Page, D. L., Isersky, C., Harada, M. & Glenner, G. G.: Immunoglobulin origin of localized nodular pulmonary amyloidosis. Res Exp Med *159:* 75, 1972.
19. Rubinov, A. & Cohen, A. S.: Skin involvement in generalized amyloidosis. A study of clinically involved and uninvolved skin in 50 patients with primary and secondary amyloidosis. Ann Intern Med *88:*781, 1978.
20. Runne, U. & Orfanos, C. E.: Amyloid production by dermal fibroblasts. Electron microscopic studies on the origin of amyloid in various dermatoses and skin tumours. Br J Dermatol *97:* 155, 1977.
21. Schilder, P.: Über die amyloide Entartung der Haut. Frankf Z Pathol *3:* 782, 1909.
22. Shapiro, L., Kurban, A. K. & Azar, H. A.: Lichen amyloidosis. A histochemical and electron microscopic study. Arch Pathol *90:* 499, 1970.
23. Symmers, W. St. C.: Primary amyloidosis: a review. J Clin Pathol *9:* 187, 1956.
24. Westermark, P.: Occurrence of amyloid deposits in the skin in secondary systemic amyloidosis. Acta Pathol Microbiol Scand (A) *80:* 718,1972.

Received December 15, 1978

P. Westermark, M.D.
Department of Pathology
University of Uppsala
S-751 22 Uppsala
Sweden