

Amyloid in Basal Cell Carcinoma and Seborrhic Keratosis

KAREN E. OLSEN and PER WESTERMARK

Department of Pathology, University of Linköping, Linköping, Sweden

The frequency of amyloid substance was studied in two different types of skin tumours: basal cell carcinoma and seborrhic keratosis. In 9 out of 49 cases of seborrhic keratosis amyloid substance was found. In the basal cell carcinomas, 194 out of 260 cases showed amyloid deposits, a rate that is higher than that previously reported. The basal cell carcinoma material was further studied regarding the amount of amyloid, mitotic rate, degree of apoptosis and the age of the patients. There was no correlation between the amount of amyloid and the mitotic rate, or the degree of apoptosis. There was a slightly higher incidence of amyloid-positive cases among elderly patients. *Key words: skin tumours; apoptosis; mitotic rate.*

(Accepted January 12, 1994.)

Acta Derm Venereol (Stockh) 1994; 74: 273–275.

K. E. Olsen, Department of Pathology, University of Linköping, S-581 85 Linköping, Sweden.

Amyloid is a generic name for a group of substances in which small protein molecules stack to characteristic, fine fibrils. Several different proteins are known to give rise to amyloid in humans, but each type of amyloid is characterized by its own protein (1). Amyloid can either occur as widely spread infiltration in many organs or as limited deposits in a tissue. The latter is by far the most common, as is seen in conjunction with aging (2) and with certain diseases, e.g. Alzheimer's disease (3).

Amyloid deposits are well-known from several distinctive types of tumours and are sometimes of diagnostic value. An example of this is the C-cell tumours (medullary carcinomas) of the thyroid gland. With the exception of the iatrogenic insulin-derived amyloid, the so far characterized localized amyloids are products of cells in close connection with the deposits. Thus, the amyloid fibrils in the thyroid C-cell tumour consist of calcitonin and procalcitonin (4).

The existence of amyloid deposits in basal cell carcinomas (BCC) of the skin has been an established fact since 1930 (5). Several studies have shown that this form of localized amyloid is common, and over the years the found frequency of amyloid in BCC has increased from 8% to 66% (6–10). Less well-known is the existence of amyloid deposits in seborrhic keratosis (SK) (5, 11–13). The nature of this type/these types of amyloid has not been elucidated, although some immunohistochemical studies have indicated that keratin is a possible amyloid precursor protein in BCC (9, 10, 14–16).

Since studies of other localized types of amyloid have given new and important information on previously known and unknown proteins, we have started a project concerning the nature of the amyloid in BCC and SK. In this first study, we have investigated the frequency of amyloid deposits in different subtypes of BCC. We have also studied the occurrence of amyloid in SK.

MATERIAL AND METHODS

Cases of BCC and of SK were taken from the files of the Department of Pathology at the University Hospital in Linköping. The BCC cases were randomly chosen within a 1-year period. The slides were checked microscopically, and curettage materials and very small (< 1 mm) punch biopsies were excluded. After that, 260 cases of BCC remained. In the same way, specimens of SK were obtained through the files. Only specimens with the classical acanthotic type were included; 49 such lesions were studied.

In all instances, the specimens had been fixed in 10% formalin and routinely embedded in paraffin. Sections were dehydrated and stained with hematoxylin and eosin or van Gieson's stain and with alkaline Congo red. The sections stained with Congo red were investigated in polarized light for green birefringence, typical of amyloid.

The BCC material was from patients born in 1900–1959 and was divided into age groups of 10-year intervals. The material was further investigated regarding the amount of amyloid in the positive cases, based on the following principle: +: tiny amount, just detectable, ++: moderate amount, easily detectable, and +++: abundant amount. In all BCC material the degree of apoptosis was evaluated on sections stained with hematoxylin and eosin as follows: +: few degenerating cells, ++: moderate number of degenerating cells, and +++: abundant number of degenerating cells. The number of mitoses was counted in 10 high-power fields (HPF) ($\times 500$).

RESULTS

Basal cell carcinomas

Of a total number of 260 cases of BCC, 194 specimens (75%) contained amyloid. As is seen in Table I, the oldest patients showed a slightly higher incidence, although the overall frequency was fairly even. In most cases, the amount of amyloid was very sparse and only a few cases (9% of the amyloid positive cases) showed abundance of amyloid (Table II).

In all instances, the amyloid deposits were seen in the connective tissue and often in close connection with tumour cells (Fig. 1) but only occasionally between the tumour cords. Amyloid occurred as thin streaks along the surface of the cords or as rounded lumps. Amyloid was never found within tumour cells or in the epidermis.

In Table III, the material has been divided into the three main

Table I. Occurrence of amyloid deposits in 260 basal cell carcinomas

Patients born	Number of tumours	Tumours with amyloid	% tumours with amyloid
1900–09	41	35	85
1910–19	47	38	81
1920–29	48	33	69
1930–39	42	29	69
1940–49	40	31	78
1950–59	42	28	67
Total	260	194	75

Table II. Semiquantitative estimation of the amount of amyloid in 194 amyloid-positive basal cell carcinomas

	Amount of amyloid		
	+	++	+++
No (%)	129 (67%)	47 (24%)	18 (9%)

groups: superficial, nodular and sclerosing BCC. Amyloid was a very characteristic finding of nodular BCC, 85% of these tumours containing amyloid. Of the 18 cases with the largest amount of (+++) amyloid, 15 cases (83%) were of the nodular subtype. Amyloid was also a very common finding in the two other subtypes. Surprising and noteworthy was the fact that 53% of the superficial subtype tumours were positive for amyloid, although the majority of the superficial BCC only had very small amyloid deposits.

The relationship between the amount of amyloid and the degree of apoptosis is shown in Table IV by the number of cases in each category. There is no correlation between the degree of apoptosis and the amount of amyloid.

The mitotic rate varied from 0–59 mitoses per 10 HPF. The relationship between the amount of amyloid and the mean mitotic rate is shown in Table IV. There is no significant difference between the groups.

Seborrheic keratosis

Of the 49 specimens with SK, 9 (18%) contained amyloid. As in BCC the amount of amyloid was often very sparse, but 3 tumours contained abundant amyloid (Fig. 2). The distribution of amyloid was the same as in BCC.

DISCUSSION

The present study verifies that amyloid deposits are extremely common in BCC. In previous studies, amyloid has been found in up to 66% of the tumours (6–10). The very large number in our material (75%), and the even larger in the subgroup of elderly patients (85%), is hard to explain but may be due to our including even small deposits of amyloid. Since some of the

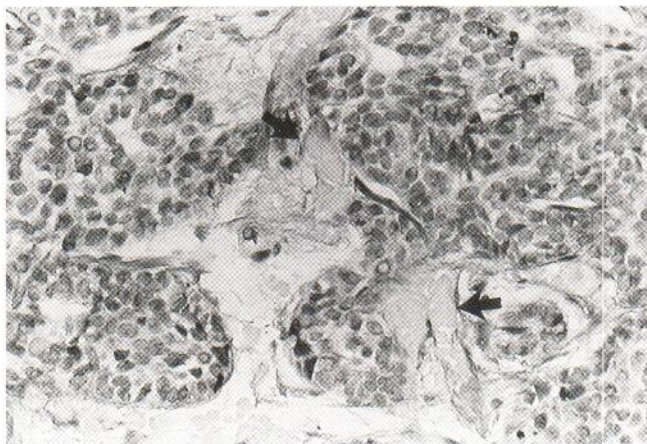


Fig. 1. Nodular basal cell carcinoma with amyloid deposits (arrows) in the stroma. van Gieson stain, $\times 725$.

Table III. Occurrence of amyloid in different subtypes of basal cell carcinoma

Type of basal cell cancer	Tumours (No)	Tumours with amyloid (No)	Tumours with amyloid (%)
Superficial	68	36	53
Sclerosing	32	22	69
Nodular	144	123	85
Undetermined*	16	13	81

* Tumours with insufficient material for subtyping

specimens contained only parts of the tumour tissue, it is possible that an even higher frequency of BCC-related amyloid could be found. Serial sectioning of the tumours might also give a higher rate of amyloid-positive cases. The investigation method with Congo Red stain and birefringence in the light microscope also puts a limit to the amounts detectable.

Very little has been reported concerning amyloid in SK, although its existence has been mentioned in a few instances (5, 11–13). The present study shows that this form of localized amyloid is common, although not as frequent as amyloid in BCC. Also in SK, the amount of amyloid was usually sparse but in 3 instances, large deposits were seen.

Looi (8) has discussed the possibility of amyloid formation from apoptotic cells in BCC. As seen in Table IV, there is no correlation between the amount of amyloid and the degree of apoptosis. The mean mitotic rate did not differ between the amyloid groups (+ \rightarrow +++), nor between any of them and the amyloid-negative group. Consequently, this study gives no support for speculations as to a connection between amyloid formation, growth rate or tumour degeneration.

Several clinical forms of localized cutaneous amyloidosis exist. In addition to the commonly defined primary forms, lichen amyloidosis, macular amyloidosis and nodular amyloidosis, other types have been described, e.g. poikiloderma-like (17). While lichen amyloidosis and macular amyloidosis are probably closely related, nodular amyloidosis is a distinctive amyloid type and the only form that has been chemically characterized (18, 19). The amyloid fibrils are here composed of fragments of monoclonal immunoglobulin light chains, and this rare type of amyloid is most probably the result of a local production of an amyloid protein precursor by plasma cells. The amyloid in lichen amyloidosis and macular amyloidosis has been supposed

Table IV. Relation between the amount of amyloid vs apoptosis and mitotic rate

	Amount of amyloid			
	-	+	++	+++
<i>Apoptosis</i>				
+	46 (18%)	84 (32%)	20 (8%)	10 (4%)
++	16 (6%)	37 (14%)	20 (8%)	7 (3%)
+++	4 (2%)	8 (3%)	7 (3%)	1 (<1%)
<i>Mitotic rate</i>				
(Mean \pm SEM)	10.1 \pm 1.2	10.3 \pm 0.8	11.7 \pm 1.7	9.1 \pm 1.7

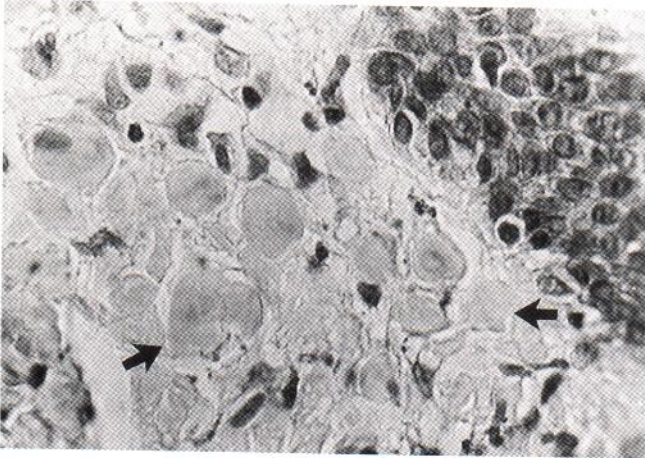


Fig. 2. Seborrheic keratosis with many small and rounded amyloid deposits in the stroma. Congo red, $\times 375$.

to be derived from keratin on the basis of some immunohistochemical and ultrastructural studies (14–16, 20, 21) and due to the close topographical association between the amyloid deposits and epidermis. It is likely, but completely unproven, that this form of amyloid is identical with the amyloid in BCC and SK. Therefore, elucidation of the nature of the tumour-associated amyloids may shed light also on the nature and pathogenesis of lichen amyloidosis and macular amyloidosis.

ACKNOWLEDGEMENTS

Thanks are due to Anna Helena Holtin for skilled assistance. This study was supported by the Swedish Medical Research Council (Project No. 5941).

REFERENCES

1. Glenner GG. Amyloid deposits and amyloidosis. *N Engl J Med* 1980; 302: 1283–1292 & 1333–1343.
2. Westermark P. Amyloid and polypeptide hormones: what is their inter-relationship? *Amyloid*. In press.
3. Castaño EM, Frangione B. Human amyloidosis, Alzheimer disease and related disorders. *Lab Invest* 1988; 58: 122–132.
4. Sletten K, Westermark P, Natvig JB. Characterization of amyloid fibril proteins from medullary carcinoma of the thyroid. *J Exp Med* 1976; 143: 993–998.

5. Freudenthal W. Amyloid in der Haut. *Arch Dermatol Syph* (Berlin) 1930; 162: 40–94.
6. Malak JA, Smith EW. Secondary cutaneous amyloidosis. *Arch Dermatol* 1962; 86: 465–477.
7. Weedon D, Shand E. Amyloid in basal cell carcinomas. *Br J Dermatol* 1979; 101: 141–146.
8. Looi LM. Localized amyloidosis in basal cell carcinoma. A pathologic study. *Cancer* 1983; 52: 1833–1836.
9. Satti MB, Azzopari JG. Amyloid deposits in basal cell carcinoma of the skin. *J Am Acad Dermatol* 1990; 22: 1082–1087.
10. Toyoda M, Ebihara Y, Kobayashi S, OOI T, Tokuta A, Kita S. Amyloid associated with basal epithelioma. In: Kisilevsky R, Benson MD, Frangione B, Gaudie J, Muckle TJ, Young ID, eds. *Amyloid and amyloidosis 1993*. Park Ridge: Parthenon Publishing Group. In press.
11. Quiñones PA, Pérez-Olivía Narciso, Toribio J. Amiloidosis cutánea localizada secundaria en queratosis seborreicas. *Actas Dermosifiliograficas* 1980; 71: 283–286.
12. Aso M, Hagari Y, Nakamura K, Mihara M, Shimo S. A case of secondary cutaneous amyloidosis: epidermal keratinocytes produce amyloid in the cytoplasm. *J Cutan Pathol* 1990; 17: 176–181.
13. Brownstein MH, Helwig EB. The cutaneous amyloidoses. I. Localized forms. *Arch Dermatol* 1970; 102: 8–19.
14. Hashimoto K, Kobayashi H. Histogenesis of amyloid in the skin. *Am J Dermatopath* 1980; 2: 165–171.
15. Eto H, Hashimoto K, Kobayashi H, Fukaya T, Matsumoto M, Sun T. Differential staining of cytooid bodies and skin-limited amyloids with monoclonal anti-keratin antibodies. *Am J Pathol* 1984; 116: 473–481.
16. Masu S, Hosokawa M, Seiji M. Amyloid in localized cutaneous amyloidosis: immunofluorescence studies with anti-keratin antiserum especially concerning the difference between systemic and localized cutaneous amyloidosis. *Acta Derm Venereol* (Stockh) 1981; 61:381–384.
17. Ogino A, Tanaka S. Poikiloderma-like cutaneous amyloidosis. *Dermatologica* 1977; 155: 301–309.
18. Husby G, Sletten K, Blumenkrantz N, Danielsen L. Characterization of an amyloid fibril protein from localized amyloidosis of the skin as λ immunoglobulin light chains of variable subgroup I (A λ I). *Clin Exp Immunol* 1981; 45: 90–96.
19. Sletten K, Westermark P, Pitkänen P, Thyresson N, Olstad OK. Amino acid sequences in amyloid proteins of KIII immunoglobulin light-chain origin. *Scand J Immunol* 1983; 18: 557–560.
20. Kobayashi H, Hashimoto K. Amyloidogenesis in organ-limited cutaneous amyloidosis: an antigenic identity between epidermal keratin and skin amyloid. *J Invest Dermatol* 1983; 80: 66–72.
21. Kumakiri M, Hashimoto K. Histogenesis of primary localized cutaneous amyloidosis: sequential change of epidermal keratinocytes via filamentous degeneration. *J Invest Dermatol* 1979; 73: 150–162.