Senile Systemic Amyloidosis

PETER PITKÄNEN, MD, PER WESTERMARK, MD and GIBBONS G. CORNWELL III, MD

From the Departments of Pathology, University Hospital of Uppsala and County Hospital, Sundsvall, Sweden, and the Department of Internal Medicine, Dartmouth School, Hanover, New Hampshire.

The senile amyloidoses comprise a heterogeneous group of disorders with deposition of amyloid in a variety of tissues. Most of these amyloidoses are localized to one tissue. It has been shown previously that the amyloid fibrils in one form of senile amyloidosis affecting the heart contains a prealbumin-related protein, ASc_1. It is shown in this paper by immunohistochemical study using a specific anti-protein ASc_1 antiserum that this type of amyloidosis, previously called senile cardiac amyloidosis, is a systemic disease with amyloid deposits in many organs. The designation senile systemic amyloidosis is prosed for this disease, which differs from other systemic amyloidoses in distribution of amyloid deposits. (Am J Pathol 1984, 117:391-399)

SENILE AMYLOIDOSES is a group of disorders which are very common. Well-known examples are amyloid deposits in the brain,[1-5,12] in the islets of Langerhans,[6-9,12] in the cardiovascular system,[10-12] and in the seminal vesicles.[13-15]

Three distinct forms of senile amyloid deposits in the cardiovascular system have been described. One form, called isolated atrial amyloidosis (IAA), has small amyloid deposits restricted to the atria.[11] The nature of this amyloid has not yet been elucidated. A second type, the senile aortic amyloidosis (SAoA), is extremely common in the old aorta.[10,16,17] Again, this amyloid has not been chemically elucidated but differs histochemically from IAA.[17]

The third type of cardiovascular amyloidosis is the senile systemic amyloidosis (SSA). This form of amyloid, which has previously been named "senile cardiac amyloidosis" (SCA),[11] has generally been regarded as a localized amyloidosis with deposits in the atria and the cardiac ventricles but sometimes also in extra cardiac tissues as well, especially the lungs and vessels of different organs.[18-26] The subunit protein of the amyloid fibrils in SSA, preliminarily named ASc_1, has been partially characterized and shown to be closely related to human prealbumin.[27] Although the yield of protein ASc_1 is low at gel filtration,[11] electrophoretic studies have shown no other subunit proteins in the SSA fibrils (unpublished observation). There is therefore little doubt that protein ASc_1 is the main fibril component in SSA. Protein ASc_1 does not occur in IAA or SAoA.[17]

Three main clinically and chemically different groups of systemic amyloidosis can be encountered[28]: 1) systemic amyloidosis in immunocytic dyscrasia (primary and myeloma-associated amyloidosis), in which the amyloid fibril protein is a portion of or a whole immunoglobulin light chain; 2) reactive (secondary) systemic amyloidosis, in which the fibrils contain protein AA; and 3) familial systemic amyloidoses, most or all of which appear to contain prealbumin or a prealbumin variant. To these three forms we would like to add SSA as a fourth distinct type. In this report, we describe the distribution of amyloid deposits in typical cases of SSA. We show that although deposits in the heart often predominate, deposits in the lungs and many other organs appear to be very common.

Materials and Methods

Selection of Patients

Tissues from 13 patients have been studied. Material from 4 of the patients (HL, 84, 120, 335) was used in the original characterization of protein ASc_1.[11] The

Supported by the Swedish Medical Research Council (Project 5941), the Research Fund of King Gustaf V, and the Swedish Society of Medical Sciences.

Accepted for publication June 26, 1984.

Address reprint requests to Per Westermark, MD, Department of Pathology, University Hospital, S-751 85 Uppsala, Sweden.

Table 1—Data on Patients With Prealbumin-Related Senile Systemic Amyloidosis

Patient	Sex	Age	Heart weight (g)	Number of tissues with amyloid/ number of tissues studied	Type of amyloid shown by*
HL	M	74	950	12/12	IH, GF, DD, AAA, ASA
272	F	89	500	5/8	IH
622	M	90	870	5/8	IH
335	M	90	600	6/7	IH, GF, DD, AAA
402	M	89	615	3/3	IH, DD
120	M	96	450	2/4	IH, DD
170	M	91	950	11/16	IH, GF, DD, AAA
Gi	M	102	NK†	9/16	IH
42	M	83	430	6/11	IH
576	M	87	510	10/14	IH
724	M	87	740	6/12	IH
24	M	98	NK	6/8	IH
S168	M	94	370	23/24	IH

* IH, immunohistochemistry; GF, gel filtration; DD, double immunodiffusion; AAA, amino acid analysis; ASA, amino acid sequence analysis.
† NK, not known.

9 further patients were selected because they had fairly heavy amyloid infiltration of the heart and because paraffin blocks of several different tissues were available. The mean age of the 13 patients was 90.2 years (range, 74–102 years). All but 1 patient were men, and most of the patients had cardiomegaly (mean, 598 g: range, 370–950 g). Some data about the patients are given in Table 1.

Recognition of SSA

SSA was recognized by the presence of protein ASc_1. Initially this protein was identified by its typical elution pattern by gel filtration and by immunoprecipitation of purified solubilized fibrils with a specific anti-protein ASc_1 antiserum.[29] Later studies have employed peroxidase-antiperoxidase (PAP) staining of tissue sections with this same antiserum.[30] The anti-ASc_1 antiserum has previously been shown to be nonreactive with amyloid of AA- or AL-type[29,31] or with other forms of senile amyloidosis.[12,15,17]

Histologic Screening

Formalin-fixed and paraffin-embedded pieces of tissue which had been collected between 1970 and 1983 from 13 patients with SSA were included in this study. The studied tissues are shown in Table 2. In most cases, heart (atria and ventricles), lungs, liver, kidney, and spleen tissues were available. In some cases, brain, pituitary, adrenal glands, thyroid, parathyroid, tongue, small intestines, stomach, rectum, pancreas, gallbladder, aorta, lymph nodes, urinary bladder, prostate, seminal vesicles, and bone marrow were also available. Usually, there was only one block from each tissue. From all tissues, 5-μ-thick sections were stained with Congo red and studied in polarized light.

Immunohistochemistry

PAP staining[32,33] was performed on two sections of each tissue with the use of anti-protein ASc_1 antiserum in dilutions of 1:400 and 1:800, respectively. Sections treated in the same way with nonimmune rabbit serum were included as controls. The specificity of the reaction was established by absorbing the anti-protein ASc_1 antiserum with purified protein ASc_1.

Table 2—Distribution of Amyloid Deposits Identified by a Specific Anti-ASc_1 Antiserum in 13 Cases of Senile Systemic Amyloidosis

	Number of patients with amyloid	Number of patients studied
Heart		
Atrium	11	11
Ventricle	13	13
Lung	12	12
Aorta*	6	8
Liver	7	11
Spleen	2	11
Kidney	6	12
Pancreas	4	6
Tongue	2	2
Stomach	2	2
Small intestines	3	3
Colon, rectum	6	6
Gall bladder	1	1
Parotid gland	1	1
Thyroid	3	5
Parathyroid	2	2
Adrenal gland	7	7
Hypophysis	1	2
Urinary bladder, ureter	2	2
Prostate	2	2
Seminal vesicles	6	6
Subcutaneous fat	3	7
Lymph node	1	2
Brain†	0	7
Bone marrow	1	2

* All patients had senile localized aortic amyloid.
† All patients had Congophilic angiopathy localized to brain vessels.

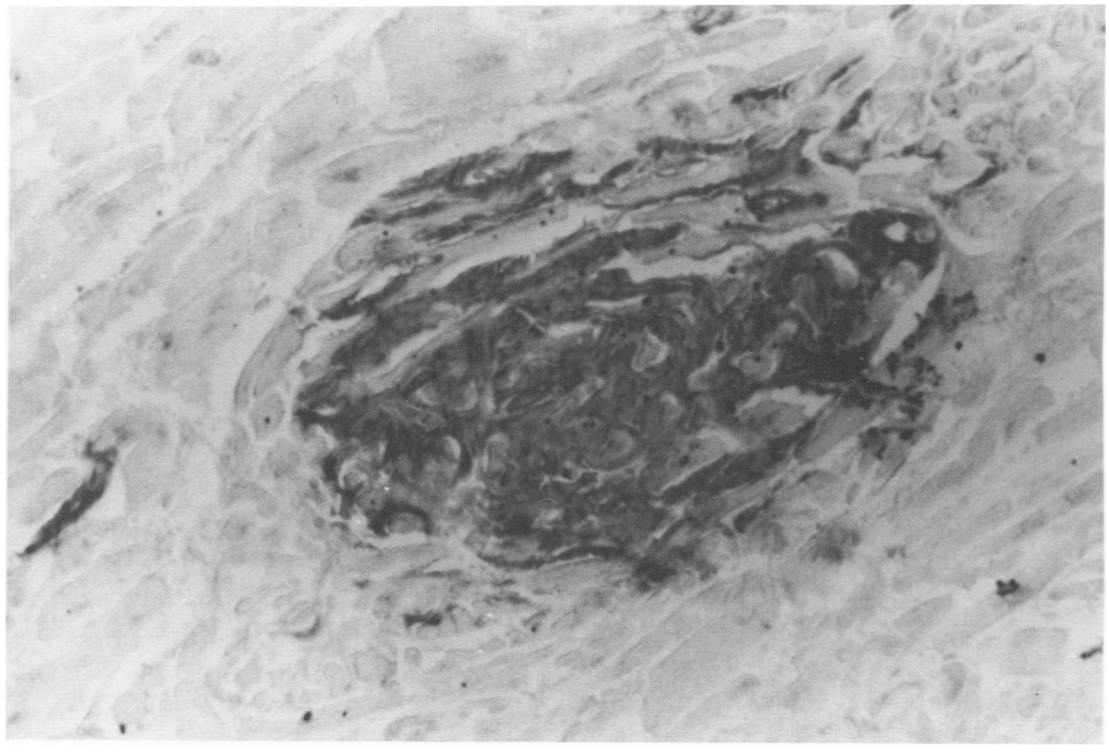


Figure 1—Amyloid deposits (*black*) in the left ventricular wall of the heart in a patient with senile systemic amyloidosis, demonstrated by the PAP method with a specific antiserum to the prealbumin-related amyloid fibril protein ASc_1. The technique and antiserum are the same for all illustrations. (×325)

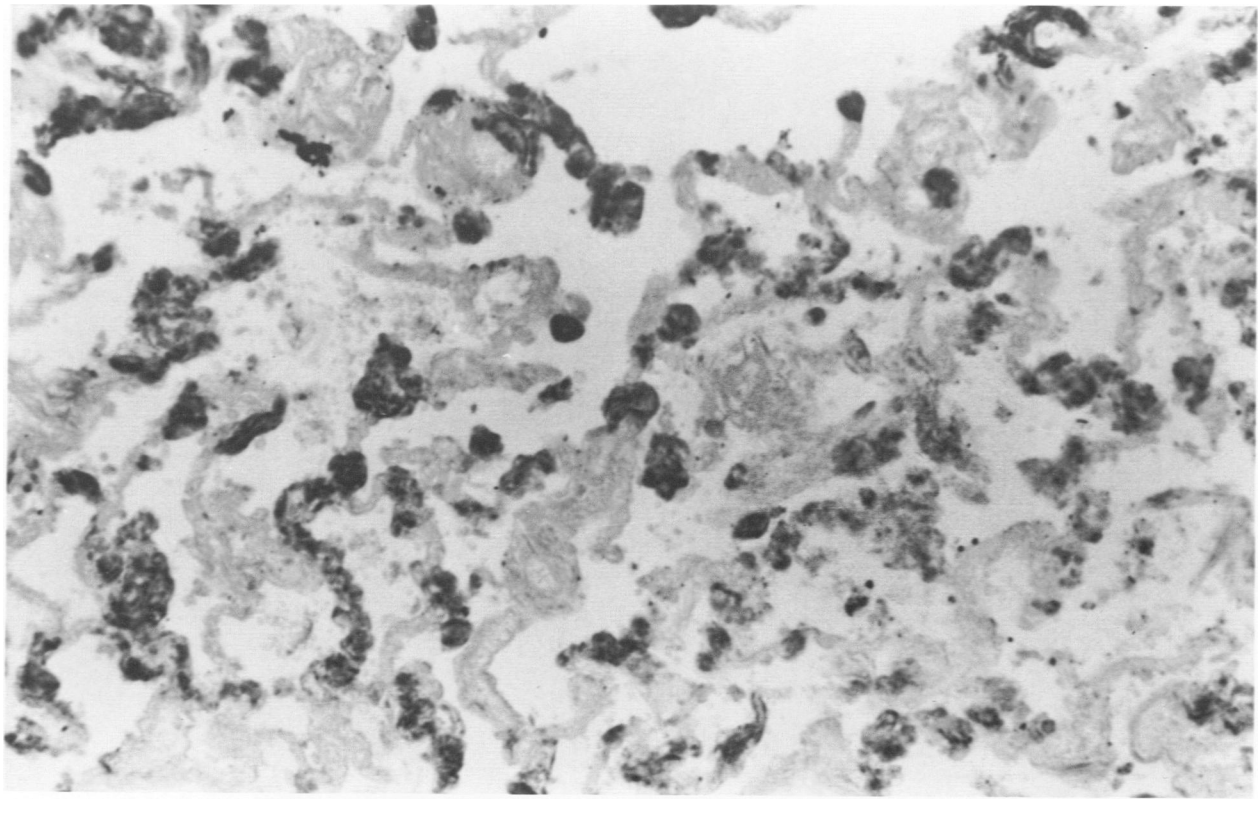


Figure 2—Amyloid deposits in alveolar walls of the lung. The amyloid occurrs mainly as small nodules, but more continuous depositions also occur. (×200)

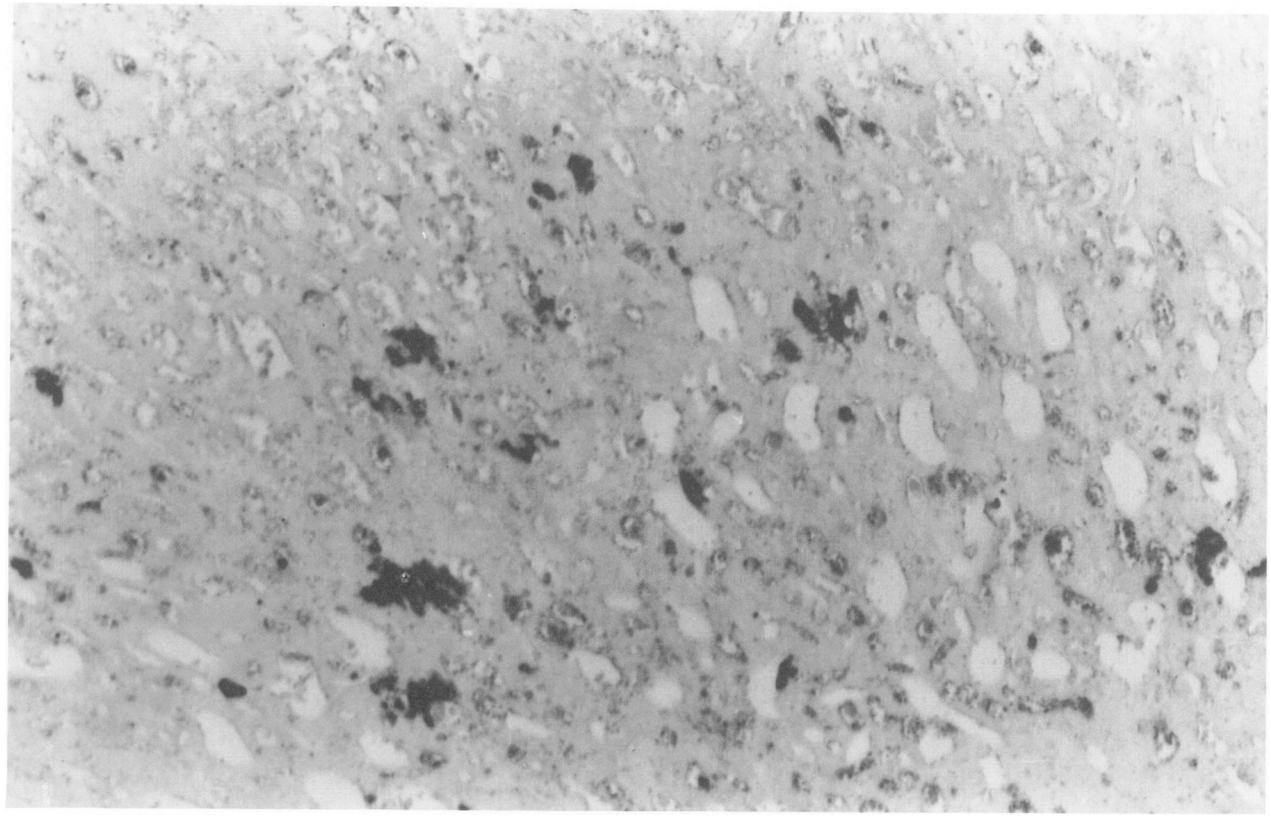


Figure 3 – Renal papilla with many small amyloid lumps in the interstitium without obvious connection with blood vessels. Amyloid occurred rarely in the renal blood vessels and never in the glomeruli. (×80)

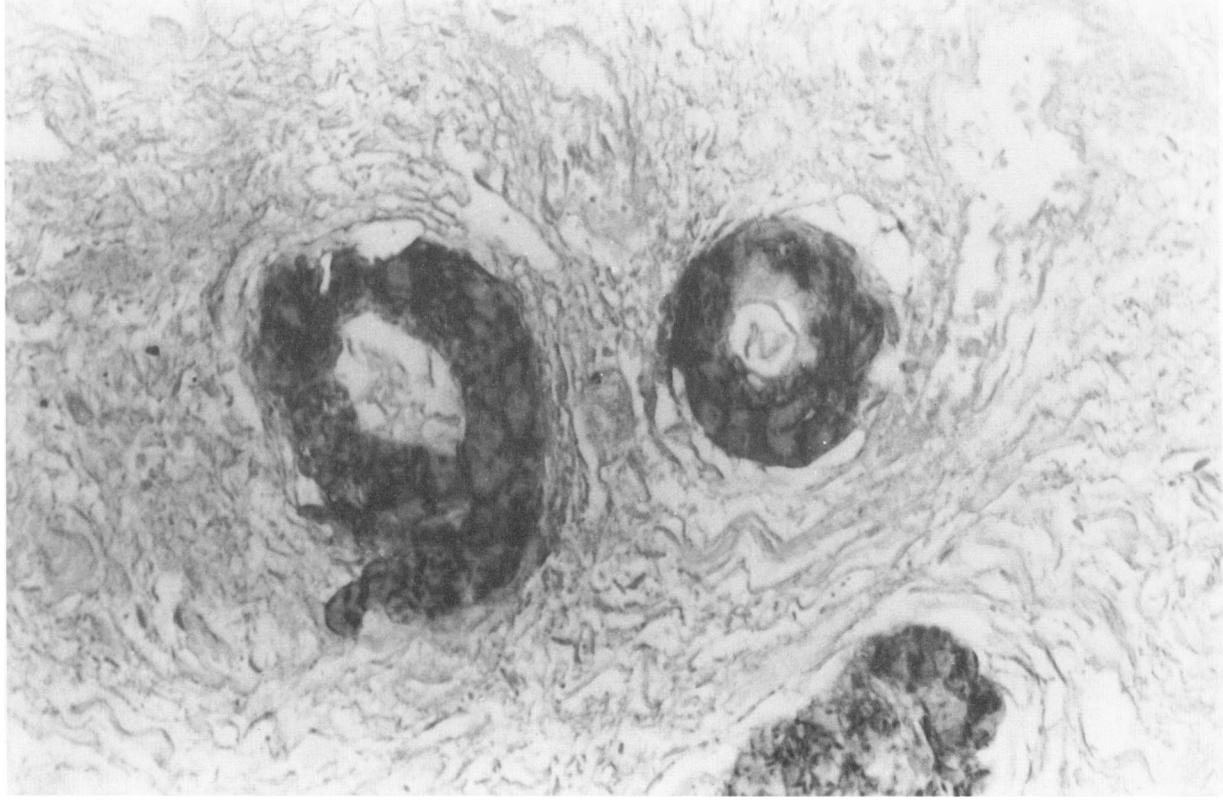


Figure 4 – Blood vessels in the wall of the gallbladder, heavily infiltrated with amyloid. Vessels of this appearance were found mainly in the submucosa throughout the gastrointestinal tract, including the rectum. (×325)

Results

Staining Properties of SSA

The amyloid of SSA exhibited affinity for Congo red, but the staining was generally a little weaker than usually seen in AA amyloidosis and in most cases of AL amyloidosis. There was a typical green birefringence, however. The amyloid tended to occur in homogeneous areas or lumps and often affected well-demarcated sectors of vessels.

The amyloid showed a strong reactivity with the anti-protein ASc_1 antiserum when the PAP technique was used. No reaction with other tissue components was seen except for the A cells in the pancreatic islets, which showed a strong reaction (Figure 5). Likewise, no reaction occurred with amyloid in Congophilic angiopathy of the brain, senile aortic amyloid, or senile seminal vesicle amyloid, all of which were represented in the material. Antisera to protein AA and to different protein AL:s showed no reaction with the amyloid in SSA.

Distribution of ASc_1 Amyloid

Heart

Most often the amyloid appeared as fairly large homogeneous depositions compressing the heart muscle cells. The deposition was diffuse or patchy (Figure 1). Usually lumps of amyloid occurred in the walls of small and intermediate-sized vessels. The atria and ventricles were equally involved. In patients in whom amyloidosis was recognized macroscopically, the depositions were massive and diffuse.

Lung

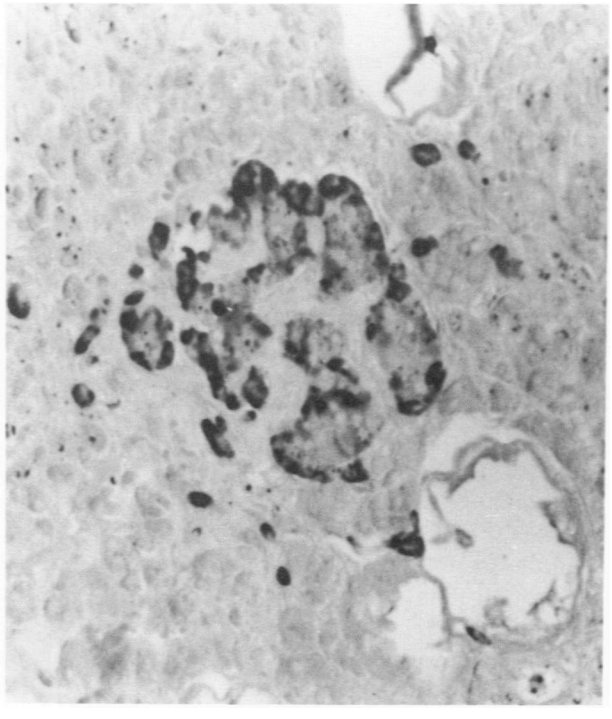
Amyloid occurred in the lung tissue in all studied cases. Deposits were seen as small nodules in the alveolar septa, often close to each other, giving the appearance of a band of pearls (Figure 2). More massive amyloid infiltration of alveolar septa also occurred. Deposits were seen in the walls of vessels of all sizes and in advanced cases also in the lamina propria of bronchi. In some cases, amyloid was seen around bronchial glands.

Aorta

In 6 of 8 cases studied, amyloid deposits occurred diffusely in the adventitia and focally in the vasa vasorum. Small amyloid deposits which did not react with the anti-ASc_1 were seen in the media in addition to ASc_1 amyloid in all cases.

Liver

In 7 of 11 cases, amyloid deposits occurred in the walls of arteries and veins in the portal zones. Small deposits were also seen in the capsule, but no amyloid occurred in the liver parenchyma.



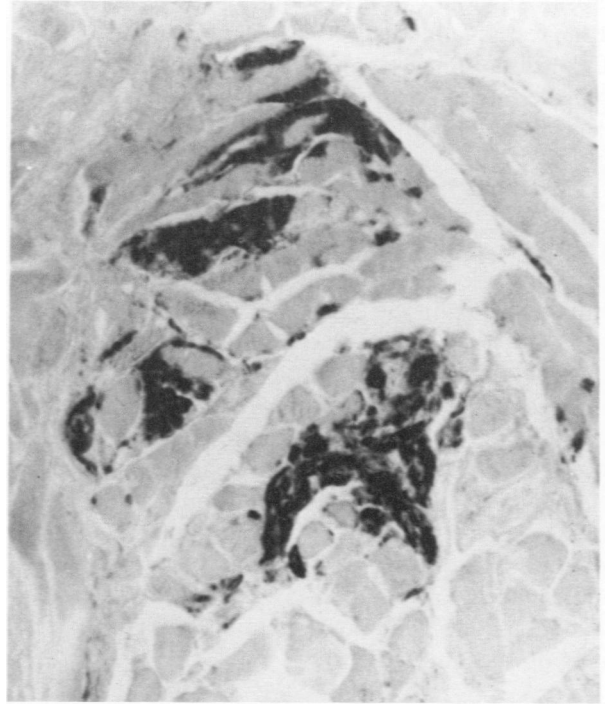


Figure 5 — Islet of Langerhans. Besides the amyloid of ASc_1 type, only the A cells of the pancreatic islets reacted with the anti ASc_1 antiserum. (×325) **Figure 6** — Small deposits of amyloid occurred interstitially in the striated muscle of the tongue. (×200)

Kidney

Amyloid deposits were present in 6 of 12 cases. The amyloid appeared as scattered irregular, sometimes fairly large lumps in the papillae (Figure 3). In addition, amyloid occurred in the vessel walls of the fibrous capsule, the cortex, and the medulla. Deposits were also seen in vessel walls in the pelvis and within small peripelvic nerves. Glomerular amyloid was not seen in any renal tissue.

Spleen

In 2 of the 11 cases studied minimal amounts of amyloid were found in a few vessels. No amyloid occurred in the red or white pulp.

Lymph Nodes

Amyloid deposits occurred in some vessels of a lymph node in 1 of the 2 cases studied. Abundant amyloid was seen in the fat tissue surrounding this node.

Gastrointestinal Tract

The stomach was studied in 2 cases. Amyloid deposits were seen in vessels in the submucosa, muscularis propria, and subserosa, but not in lamina propria. In 1 of these cases, amyloid was present in several nerves. In the small intestines of 3 studied cases and in the colon of 1, the amyloid distribution was the same as in the stomach. Amyloid was present in all 6 rectal tissues studied, and sometimes as fairly large lumps in the vessel walls in the submucosa, muscularis propria, and the serosa. Amyloid was also found in the muscle tissue of the rectum and in adjacent striated muscle without any obvious connection with vessels. In the only case studied, amyloid deposits were found in intermediate sized vessels of the gallbladder wall (Figure 4).

Pancreas

In the pancreas, 4 of 6 cases studied exhibited amyloid deposits in vessel walls of the parenchyma and in the peripancreatic fat tissue. Anti-ASc_1 reacted strongly with the A cells in the islets of Langerhans (Figure 5).

Endocrine Organs

Amyloid deposits occurred in vessel walls in the periglandular fat tissue of the adrenal glands in all 7 cases studied. Sometimes periglandular nerves were also affected (Figure 7). No amyloid was seen in the parenchyma. Three of 5 cases exhibited amyloid deposits in vessel walls of the thyroid. Amyloid occurred in vessels of the parathyroid gland in 1 case and in vessels of the adenohypophysis and in fat tissue adjacent to the neurohypophysis in 1 case.

Tongue

The tongue showed widely distributed amyloid in both cases studied. Deposits were seen in the vessels of the lamina propria and muscle tissue and interstitially in the striated muscle (Figure 6). Amyloid also occurred around salivary glands.

Subcutaneous Tissue

Three of 7 cases had amyloid deposits subcutaneously between fat cells and in vessel walls focally.

Seminal Vesicles

In all 6 cases, studied, amyloid appeared in the media of vessels. Two of these cases also showed localized senile seminal vesicle amyloid, which did not react with anti ASc_1.

Prostate

Amyloid occurred in prostatic vessels in both cases studied.

Urinary Bladder and Urethra

Amyloid was found in vessels in the muscle layer of the urinary bladder in 1 case and the urethra in another studied case.

Brain

No amyloid reacting with the anti ASc_1 could be found in the brain in 7 investigated cases. In all of these, however, amyloid with the distribution and appearance that associated with Congophilic angiopathy was seen in vessel walls.

Bone Marrow

Amyloid was present in some vessels of the bone marrow in 1 of the 2 cases evaluated.

Discussion

The first description of cardiac amyloidosis associated with aging was probably made by Soyka in 1876.[34] Scattered reports followed, but it was not until 1950 that larger series were reported (see Hodkinson and Pomerance[24]). The reported prevalence of cardiac amyloidosis among elderly persons varied widely from 2% to 80%. These differences have been said to be related to differences both in selection of tissues and in staining techniques.[24]

Senile cardiac amyloidosis has traditionally been regarded as one entity. Because atrial deposits are more common than ventricular deposits, the former have been regarded as early senile amyloidosis, while cases with both atrial and ventricular amyloidosis have been thought to represent a later stage of the disease.[24] However, we have previously shown that there are two chemically different forms of SCA of which one only affects the atria and which therefore is called "isolated atrial

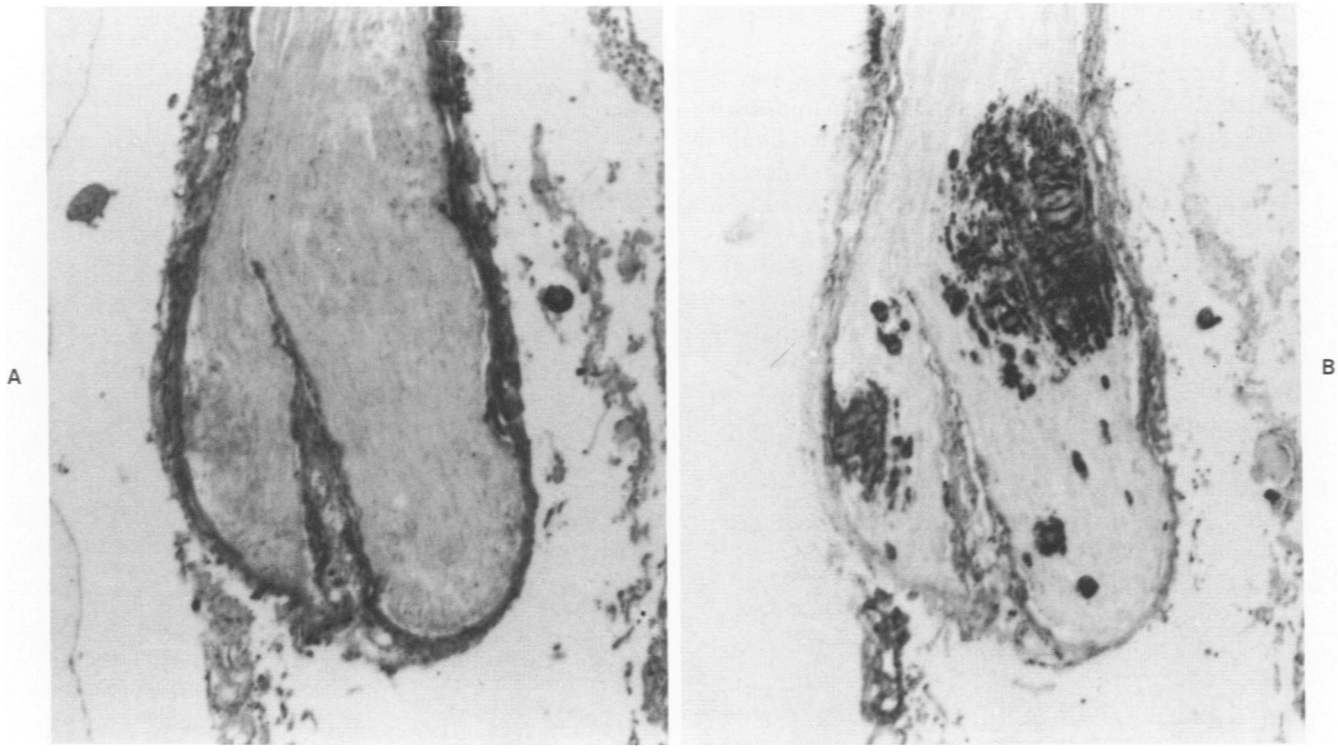


Figure 7 — Nerve in the periadrenal tissue. Fairly large deposits of amyloid are seen in the nerve. **A** — Section treated with rabbit nonimmune serum. The dark staining of the perineurium is unspecific. **B** — Section treated with anti-protein ASc_1 antiserum. (×80)

amyloidosis". IAA is thus a chemically distinct localized form of senile amyloidosis, other examples of which include the localized amyloidosis of the pancreas,[6-9, 12] the brain[1-5, 12] the seminal vesicles,[13-15] and the aorta.[17] The ASc_1-containing senile amyloidosis of the heart is the form previously called "senile cardiac amyloidosis."[29,34]

"SCA" has until recently generally been regarded as a localized form (eg, see Cohen et al[35]), although some previous reports have suggested its systemic nature.[20-25] In such studies, however, a differentiation between SSA and other systemic amyloidoses or localized forms of senile amyloidosis has not been possible. With a specific antiserum against the ASc_1 subunit protein of SSA, it has been possible to show that the amyloid deposits found in different organs were of the same nature as the heart deposits. This antiserum was recently utilized in showing that a high percentage of elderly patients with ASc_1-type amyloid of the heart also had amyloid deposits of the same immunologic type in the lung and/or the rectum.[26] The present study shows that SCA of the ASc_1 type is truly a systemic form of amyloidosis involving more than 20 different tissues studied and that the designation of SSA is therefore justified. SSA is chemically related to but probably not identical to the familial systemic amyloidosis of Portuguese,[36] Japanese,[37] Israeli,[38] Swedish,[39,40] and Indiana[41] types. We propose that SSA be added to the three main groups of systemic amyloidosis as a fourth and distinct type. The systemic amyloidoses thus comprise 1) immunocytic dyscrasias with AL amyloidosis (primary and myeloma-associated amyloidosis), 2) reactive systemic (secondary) AA amyloidosis, 3) familial systemic amyloidosis, and 4) senile systemic amyloidosis.

The wide distribution of amyloid deposits in advanced cases of SSA is noteworthy. The most extensive infiltration is found in the heart and in the lungs. In the heart, deposition is seen in both ventricular chambers and atria as a diffuse or patchy infiltration between the muscle cells as well as in vessels of different sizes. In tissues with small quantities of amyloid, the deposits may occur either in vessels or interstitially. In routine heart sections, there are no reliable morphologic means of differentiating between IAA, SSA, and other forms of systemic amyloidosis. In the lungs, the amyloid occurs both in vessel walls and in the alveolar walls. The latter deposits usually have a very typical nodular appearance. The deposits in other organs are usually small and mainly in vessel walls. However, deposits also occur in striated and smooth muscle, in fat tissue, and in the papillae of the kidneys. The finding that senile systemic amyloid rarely occurs in the spleen and then

only in very small amounts and never in the glomeruli of the kidneys is remarkable. In these respects, SSA differs from other forms of systemic amyloidosis, including the Swedish form of familial amyloidosis.[42]

A typical feature of the prealbumin-related familial amyloidoses is polyneuropathy. Small amyloid deposits were found in nerves in some of the present cases of SSA, but the clinical records did not indicate any symptoms or signs of polyneuropathy. The reason for this discrepancy in pattern of deposition in different forms of prealbumin-related amyloidoses is unknown, but it is possible that the prealbumin in SSA has a normal amino acid sequence, whereas prealbumin in the various familial amyloidoses appears to have an abnormal structure.[38,43,44]

The reaction of anti-ASc$_1$ with the A cells of the pancreatic islets was not surprising. A cells have been shown normally to contain a component antigenically identical to prealbumin.[45]

The clinical diagnosis of SSA is usually regarded as very difficult as a result of its previously presumed localized nature, in contrast to the three other major variants of systemic amyloidosis, in which the diagnosis can readily be made by rectal biopsy or subcutaneous fat biopsy.[46,47] These studies indicate that SSA may be distributed very widely and that careful examination of readily available tissues, such as rectum and subcutaneous fat, may provide a premortem diagnosis.

References

1. Hechst B: Zur Histochemie und Histogenese der senilen Plaques. Arch Psychiatr 1929, 88:126–148
2. Pantelakis ST: Un type particular d'angiopathie sénile du système nerveux central: l'angiopathie congophile: Topographie et fréquence. Mschr Psychiatr Neurol 1954, 128:219–256
3. Braunmühl AV: Alterserkrankungen des Zentralnervensystems. Senile Involution. Senile Demenz. Alzheimersche Krankheit. Handbuch der speziellen pathologischen Anatomie und Histologie. Edited by O Lobarsch, F. Henke, R Rössle. XIII, Erster Teil, Brandteil A. Erkrankungen des zentralen Nervensystems. Berlin, Springer, 1957, pp 333–539
4. Glenner GG: Current knowledge of amyloid deposits as applied to senile plaques and congophilic angiopathy, Alzheimer's Disease: Senile Dementia and Related Disorders. Edited by R. Katzman, R. Terry. New York, Raven Press, 1978, pp 493–502
5. Shirahama T, Skinner M, Westermark P, Rubinow A, Cohen AS, Brun A, Kemper TL: Prealbumin as a common constituent in the neuritic plaque, in the neurofibrillary tangle, and in the microangiopathic lesion. Am J Pathol 1982, 107:41–50
6. Bell ET: Hyalinization of the islets of Langerhans in diabetes mellitus. Diabetes 1952, 1:341–344
7. Bell ET: Hyalinization of the islets of Langerhans in nondiabetic individuals. Am J Pathol 1959, 35:801–805
8. Ehrlich JC, Ratner IM: Amyloidosis of the islets of Langerhans: A restudy of islet hyalin in diabetic and nondiabetic individuals Am J Pathol 1961, 38:49–59
9. Westermark P: Fine structure of islets of Langerhans in insular amyloidosis Virch Arch Pathol Anat 1973, 359:1–18
10. Schwarz P, Wolfe KG, Bath JS, Ahluwalia HS, Beuttas JT: Amyloidosis in human and animal pathology: a comparative study, Amyloidosis. Edited by O Wegelius, A Pasternack. London, Academic Press, 1976, 71–102.
11. Westermark P, Johansson B, Natvig JB: Senile cardiac amyloidosis: Evidence of two different amyloid substances in the ageing heart. Scand J Immunol 1979, 10:303–308
12. Cornwell GG III, Westermark P: Senile amyloidosis: A protean manifestation of the aging process. J Clin Pathol 1980, 33:1146–1152
13. Bursell S: Beitrag zur Kenntnis der Paraamyloidose im urogenitalen System unter besonderer Berücksichtigung der sog. senilen Amyloidose in den Samenbläschen und ihres Verhältnisses zum Samenbläschenpigment. Upsala Läkaref Förh 1942, 47:313–331
14. Goldman H: Amyloidosis of seminal vesicles and vas deferens: Primary localized cases. Arch Pathol 1963, 75:94–98
15. Pitkänen P, Westermark P, Cornwell GG III, Murdoch W: Amyloid of the seminal vesicles, a distinctive and common localized form of senile amyloidosis. Am J Pathol 1983, 110:64–69
16. Iwata T, Kamei T, Uchino F, Mimaya H, Yanagaki T, Etoh H: Pathological study on amyloidosis relationship of amyloid deposits in the aorta to aging. Acta Pathol Jpn 1978, 28:193–203
17. Cornwell GG III, Westermark P, Murdoch W, Pitkänen P: Senile aortic amyloid. A third distinctive type of age-related cardiovascular amyloid. Am J Pathol 1982, 108:135–139
18. Josselson AJ, Pruitt RD, Edwards IE: Amyloid localized to the heart. Analysis of twenty-nine cases. Arch Pathol 1952, 54:359–367
19. Lee HY, Kaufmann W: Cardiac amyloidosis in the aged. Arch Pathol 1957, 64:494–500
20. Buerger L, Braunstein H: Senile cardiac amyloidosis. Am J Med 1960, 28:357–367
21. de Jager H, Stam FC: Pathology and histochemistry of amyloidosis in old age Gerontologia 1962, 6:19–35
22. Pomerance A: The pathology of senile cardiac amyloidosis J Pathol Bacteriol 1966, 91:357–367
23. Wright IR, Calkins F: Amyloid in the aged heart: Frequency and clincial significance. J Am Geriat Soc 1975, 23:97–103
24. Hodkinson HM, Pomerance A: The clinical significance of senile cardiac amyloidosis: A prospective clinicopathological study Q J Med 1977, 46:381–387
25. Westermark P, Cornwell GG III, Johansson B, Natvig JB: Senile cardiac amyloidosis, Amyloid and Amyloidosis. Edited by GG Glenner, PP Costa, F de Freitas. Amsterdam, Excerpta Medica Foundation, 1980, pp 217–225
26. Cornwell GG III, Murdoch WL, Kyle RA, Westermark P, Pitkänen P: Frequency and distribution of senile cardiovascular amyloid, a clinicopathologic correlation. Am J Med 1983, 75:618–623
27. Sletten K, Westermark P, Natvig JB: cardiac amyloid is related to prealbumin. Scand J Immunol 1980, 12:503–506
28. Glenner GG: Amyloid deposits and amyloidosis: The β-fibrilloses. N Engl J Med 1980, 302:1283–1292, 1333–1343
29. Westermark P, Natvig JB, Johansson B: Characterization of an amyloid fibril protein from senile cardiac amyloid. J Exp Med 1977, 146:631–636
30. Westermark P, Pitkänen P, Benson L, Vahlquist A, Olofsson B-O, Cornwell GG III: Serum prealbumin and retinol binding protein in the prealbumin related senile and familial forms of systemic amyloidosis. Lab Invest (In press)

31. Cornwell GG III, Westermark P, Natvig JB, Murdoch W: Senile cardiac amyloid: evidence that the fibrils contain a protein immunologically related to prealbumin. Immunology 1981, 44:447–452
32. Sternberger LA: Immunocytochemistry. 2nd edition. New York, John Wiley and Sons, 1979
33. Shirahama T, Skinner M, Cohen AS: Immunocytochemical identification of amyloid in formalin-fixed paraffin sections. Histochemistry 1981, 72:161–171
34. Soyka J: Über amyloide Degeneration. Prag Med Wochenschr 1876, 1:165–171
35. Cohen AS, Shirahama T, Sipe JD, Skinner M: Amyloid proteins, precursors, mediator and enhancer. Lab Invest 1983, 48:1–4
36. Costa PP, Figueira AS, Bravo FR: Amyloid fibril protein related to prealbumin in familial amyloidotic polyneuropathy. Proc Natl Acad Sci USA 1978, 75:4449–4503
37. Tawara S, Araki S, Toshimori K, Nakagawa H, Ohtaki S: Amyloid fibril protein in type I familial amyloidotic polyneuropathy in Japanese. J Lab Clin Med 1981, 98:811–822
38. Pras M, Prelli F, Franklin EC, Frangione B: Primary structure of an amyloid prealbumin variant in familial polyneuropathy of Jewish origin Proc Natl Acad Sci USA 1983, 80:539–542
39. Skinner M, Cohen AS: The prealbumin nature of the amyloid protein in familial amyloid polyneuropathy (FAP): Swedish variety. Biochem Biophys Res Commun 1981, 99:1326–1332
40. Benson MD: Partial amino acid sequence homology between an heredofamilial amyloid protein and human plasma prealbumin J Clin Invest 1981, 67:1035–1041
41. Benson MD, Dwulet FE: Prealbumin and retinol binding protein serum concentrations in the Indiana type hereditary amyloidosis. Arthritis Rheum 1983, 26:1493–1498
42. Hofer PÅ, Andersson R: Postmorten findings in primary familial amyloidosis with polyneuropathy. Acta Pathol Microbiol Scand [A] 1975, 83:309–322
43. Dwulet FE, Benson MD: Polymorphism of human plasma thyroxine breeding prealbumin. Biochem Biophys Res Commun 1983, 114:657–662
44. Saraiva MJ, Goodman DS, Costa PP, Canfield RE, Birken S: Presence of an abnormal transthyretin (prealbumin) in Portuguese patients with familial amyloidotic polyneuropathy (Abstr). Clin Res 1983, 31:533A
45. Jacobsson B, Petterson T, Sandstedt B, Carlström A: Prealbumin in the islets of Langerhans. IRCS Med Sci 1979, 7:590
46. Gafni J, Sohar E: Rectal biopsy for the diagnosis of amyloidosis Am J Med Sci 1960, 240:332–336
47. Westermark P, Stenkvist B: A new method for the diagnosis of systemic amyloidosis. Arch Intern Med 1973, 132:522–523