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Research Article

Cardiac AA Amyloidosis in Rheumatoid Arthritis – A Postmortem Clinicopathologic Study of 161 Patients

Miklós Bély[1]* and Ágnes Apáthy[2]

[1]*Department of Pathology, Hospital of the Order of the Brothers of Saint John of God in Budapest, Hungary*

[2]*Department of Rheumatology – St. Margaret Clinic Budapest, Hungary*

***Corresponding Author:** Miklós Bély, Department of Pathology, Hospital of the Order of the Brothers of Saint John of God in Budapest, Hungary.

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Abstract

Aim: The aim of our study was to determine the prevalence and severity of amyloid A deposits in different tissue structures of the heart, to outline the progression of amyloid A deposition in the heart, and to determine the role of cardiac amyloidosis in mortality.

Patients and Methods: One hundred sixty one (161) non- selected autopsy patients with rheumatoid arthritis (RA) were studied. RA was confirmed clinically according to the criteria of the ARA. Tissue samples of heart were available for histologic evaluation in 138 patients. The presence of amyloid A deposits in various structures of the heart was determined histologically. The extent of amyloid A deposition was evaluated by semi-quantitative, visual estimation on a 0 to 3 plus scale.

Results: Systemic AA amyloidosis (AAa) complicated RA in 33 (23.91 %) of 138 patients. AAa was histologically excluded in 105 (76.08 %) of 138 RA patients.

The heart was involved in 29 (21.81 % of 138; 87.88 % of 33) patients.

Systemic AAa was lethal in 16 (48.48 % of 33) patients due to renal insufficiency and uremia. Cardiac AAa (cAAa) led to death in further 3 (9.09 % of 33) patients, and contributed to the lethal outcome in 5 (15.15 % of 33). Nine (27.27 % of 33) patients with systemic AAa died of other causes such as peritonitis, lethal septic infection, etc. Systemic AAa was clinically diagnosed in 9 (27.27 %) and missed in 24 (72.73 %) of 33 patients, but cardiac AAa or its pathogenic role in mortality was not recognized.

Discussion and Conclusions: Systemic AAa is one of the main and the most insidious complications of rheumatoid arthritis affecting the heart with high prevalence and severity.

Systemic AAa is related to the cardiovascular system, and cardiac AAa is associated with it. In systemic AAa the cardiac amyloid A deposition starts after a latent stage.

Systemic and cardiac amyloid A deposition is a progressive and cumulative process, involving in its early stage only a few structures in the heart, and increasingly more in the later stages of the disease.

Nearly one tenth of the patients died of cAAa, which contributed to the lethal outcome in further 5 cases and all of these were clinically missed. From prognostic point of view, cAAa should be considered a very serious, life-threatening complication of RA.

Keywords: *Rheumatoid Arthritis; Systemic; Cardiac AA Amyloidosis; Mortality*

Abbreviations

RA: Rheumatoid Arthritis; ARA: American College of Rheumatology; AAa: Systemic AA Amyloidosis; cAAa: Cardiac AA Amyloidosis; CoD: Cause of Death; U: Uremia; Cl+: Clinically Diagnosed; Cl-: Clinically Not Diagnosed; ND: No Data

Introduction

Amyloidosis is a systemic or localized disorder characterized by the extracellular deposition of chemically heterogeneous fibrillar protein [1].

Several diseases or disorders may be complicated by systemic or localized deposition of amyloid proteins [2-12].

The main types of amyloidosis (with precursors in parentheses) are summarized in table 1.

1.	Systemic (generalized) amyloidosis
1.1	Secondary (reactive) AA – (SAA – serum amyloid A)
1.2	Primary (Myeloma-associated, B-cell dyscrasia) (immunoglobulin light chain – AL: λ-chain, κ-chain, immunoglobulin heavy chain – AH)
1.3	Senile – (Transthyretin – ATTR)
1.4	Hemodialysis-associated – (β2-microglobulin – Aβ2M)
1.5	Hereditary Familial Mediterranean fever (SAA – AA) Familial amyloid polyneuropathy (Transthyretin – ATTR) Other hereditary forms of amyloidosis: (Apolipoproiein AI – AapoAI, Apolipoproiein AII – AapoAII, Apolipoproiein AIV – AapoAIV, Gelsolin – Agel Lysozyme – Alys, Cystatin C – Acys, Fibrinogen alfa-chain – Afib)
2.	Organ (tissue)-limited (isolated, localized) amyloidosis
	Cerebral β protein-related amyloidosis (Alzheimer's disease – Aβ) Cerebral extravascular amyloidosis – "amyloid plaque" Cerebral amyloid angiopathy Non-β protein-related amyloid diseases Prion protein (PrP) amyloidosis (APrP): kuru, fatal familial insomnia, Creutzfeld-Jakob disease, Gerstmann-Sträussler-Schenker disease, PrP cerebral angiopathy Aging pituitary (Prolactin – Apro)
2.1	Dystrophic (Aging related) localized to articular cartilage – Femoral head localized to articular cartilage – Acetabula localized to articular capsule or ligaments (transthyretin – ATTR)
2.2	Endocrine related localized to islets of Langerhans (Islet amyloid polypeptide – AIAPP) Cardiac – atrial myocyte associated (atrial natriuretic factor – AANF) Aorta (media) localized isolated Localized to parathyroid gland (parathormone prohormone?) Localized to endocrine tumors: Medullary carcinoma of thyroid gland – C-cell thyroid tumors ((Pro)calcitonin – ACal)
2.3	Localized to epithelial tumors (keratin) Basal cell carcinoma Calcifying epithelioma of Malherbe (Pilomatrixoma) Squamous cell carcinoma Calcifying epithelial odontogenic tumor of Pindborg
2.4	Localized amyloidosis caused by concentrated secretion, and/or of inflammatory origin Renal retention cysts (concentrated glomerular filtrate – β2-microglobulin–Aβ2M) Prostatic corpora amylacea (β2-microglobulin – Aβ2M) Seminal vesicle (concentrated secretion in seminal vesicles) Pulmonary corpora amylacea (β2-microglobulin – Aβ2M) Colloid cyst of thyroid gland (concentrated glandular secretion?)
2.5	Isolated AL λ-, AL κ-chain (solitary plasmocytoma, B-cell dyscrasia)
2.6	Cornea (Lactoferin – Alac?)
2.7	Iatrogenic (Insulin – Ains)

Table 1

Different types of amyloid deposits may exist simultaneously in patients with rheumatoid arthritis (RA). Only systemic AA amyloidosis (AAa) may be considered as a true complication of RA, any other types of amyloidosis may be present in RA as an associated phenomenon or complication of associated diseases [13].

Most studies discuss myeloma or B-cell dyscrasia associated cardiac AL amyloidosis. The aim of our study was to determine the prevalence and severity of amyloid A deposits in different tissue structures of the heart, to outline the progression of amyloid A deposition in the heart (development of cardiac AAa – cAAa), and to determine the role of cardiac amyloidosis in mortality.

Patients (autopsy population) and methods

At the National Institute of Rheumatology 9475 patients died between 1969 and 1992; among them 161 with RA (females 116, average age: 64.95 years, range 87 - 16, onset of RA: 50.19, average disease duration: 14.79 years; males 45, average age: 66.29 years, range 88 - 19, onset of RA: 52.57, average disease duration: 13.46 years at death); all of them were autopsied [13].

RA was confirmed clinically according to the criteria of the American College of Rheumatology (ARA) [14].

Tissue samples of heart (atria and ventricular wall, aortic, mitral and tricuspid valves, main coronary vessels, and any macroscopically unusual areas) were available for histological evaluation in 138 patients.

AAa was diagnosed histologically according to Romhányi [15] by a modified (more sensitive) Congo red staining [16]. Amyloid A deposits were identified in serial sections by immunohistochemical and histochemical methods [17]. The prevalence (existence) and severity (extent) of amyloid A deposition were evaluated microscopically with an Olympus BX51 polarizations microscope [13].

Glossary of definitions

"Prevalence" concerns the presence of amyloid A deposits in different tissue structures. Prevalence of amyloid A was based on the presence of amyloid A in blood vessels of different calibers or in different tissue structures of the heart.

Vessels: Arteriole (a) no internal or external elastic membrane, less than 500 micrometers in diameter, small artery (A) – internal elastic membrane present, but no external elastic membrane – 500-1000 micrometers in diameter, medium size artery (AA) – more than 1000 micrometers in diameter, internal and external elastic membrane present, venule (v) –, small vein (V) –, medium size vein (VV) – accompanying vessels of (a), (A) or (AA).

Interstitial collagen fiber (I) – In subepicardial, endocardial and in intramural localisation, reticulin fiber (collagen IV) (r) – in subepicardial fat tissue, Myocardiocytes (Myo), nerve (n).

"Severity" means different amounts of amyloid A deposition in different tissue structures. Severity of vasculitis was evaluated by semi-quantitative visual estimation on a 0 to 3 plus scale (based on the number of involved vessels and tissue structures/light microscopic field x40 lens of Olympus BX51).

Semi-objective score system of "severity":

"0" – no amyloid deposits
"1" –sporadic, minimal amyloid deposits in different tissue structures
"2" – less than five involved tissue structures
"3" – five or more involved tissue structures

Remark: In case of AA or VV this corresponds to the absolute number of involved medium size vessels of a tissue sample, e.g. "0" none, "1" only one,"2" less than five, "3" 5 or more than five medium size vessels/tissue sample with a x20 objective lens.

The correlations were determined by Student (Welch) t-probe comparing the age, sex, onset of RA, and duration of disease at the time of death: with or without AAa, and with "mild" cardiac (amyloid A deposits in the heart / patient ≤ 1.0) or "severe" cardiac amyloidosis (amyloid A deposits in the heart / patient 1.1 ≤).

Results

AAa complicated RA in 33 (23.91 %) of 138 patients. AAa was histologically excluded in 105 (76.08 %) of 138 RA patients.

The heart was involved in 29 (21.81 % of 138; 87.88 % of 33) patients. Fifteen (45.45 %) of 33 patients revealed "marked (severe)" amyloidosis (with average amyloid A deposits / patient 1.1 ≤), massively involving many tissue structures of the heart. Fourteen (42.42 %) of 33 patients had "slight (mild)" amyloidosis (with average amyloid A deposits / patient ≤ 1.0), involving only a few tissue structures in the heart. Amyloid A deposits were not present in the heart in 4 (12.12 %) of 33 RA patients with AAa.

Demographics, onset and duration of disease complicated by AAa are summarized in table 2.

Gender	Number of autopsies	Average age in years at death	Range (in years)	Age at onset of disease	Disease duration (in years)
RA patients	138	65.10	88 - 16	51.18	14.25
Female	100	64.58	84 - 16	50.64	14.44
Male	38	65.95	88 - 19	52.74	13.71
With AAa	33 of 138	62.27	88 - 19	47.61	15.58
Female	28	64.25	83 - 32	48.56	15.70
Male	5	51.20	88 - 19	41.25	14.75
Without AAa	105 of 138	65.99	87 - 16	52.30	13.85
Female	72	64.99	84 - 16	51.45	13.94
Male	33	68.15	87 - 52	54.27	13.57
With cardiac AAa	29 of 33	60.97	88 - 19	46.93	15.00
Female	24	63.00	83 - 32	47.91	15.04
Male	5	51.20	88 - 19	41.25	14.75
With severe cardiac AAa	15 of 33	54.67	88 - 19	39.14	17.14
Female	11	58.73	73 - 32	40.45	18.27
Male	4	43.50	88 - 19	34.33	13.00
With mild cardiac AAa	14 of 33	67.71	83 - 44	55.31	12.69
Female	13	66.62	83 - 44	54.75	12.08
Male	1	82.00	82 - 82	62.00	20.00
Without cardiac AAa	4 of 33	71.75	82 - 57	52.25	19.50
Female	4	71.75	82 - 57	52.25	19.50
Male	0	-	-	-	-

Table 2: *Sex, average age (range), onset and duration of 138 RA in patients with or without AAa.*

RA started earlier ($p < 0.21$ – NS), the disease duration was longer ($p < 0.39$ – NS), and the age of the patients at death was lower ($p < 0.22$ – NS) in cases with systemic (generalized, global) AAa, compared to those without amyloidosis, but these differences were not significant.

Comparing the age, sex, onset of RA, and duration of disease at the time of death there was no significant difference in survival time, onset and duration of disease between patients with or without AAa ($p < 0.22$, $p < 0.39$, $p < 0.21$) or between males ($p < 0.30$, $p < 0.73$, p

< 0.51) and females (p < 0.78, p < 0.45, p < 0.42) with or without AAa. Amyloidosis developed in both sexes, and at any time in the course of the disease (Table 3).

33 RA Pts with AAa versus 105 Pts without AAa			28 Female RA Pts with AAa versus 72 female without AAa			5 Male Pts with AAa versus 33 male without AAa		
Age	Disease duration	Onset of disease	Age	Disease duration	Onset of disease	Age	Disease duration	Onset of disease
p < 0.22	p < 0.39	p < 0.21	p < 0.78	p < 0.45	p < 0.42	p < 0.30	p < 0.73	p < 0.51
NS	NS	NS	NS	NS	NS	NS	NS	NS

Table 3

In RA patients with AAa the risk of "severe" cardiac amyloidosis (1.1 ≤) was significantly higher (p < 0.024) with an early onset and with longer duration (p < 0.242 – NS) of RA, and in these patients the survival time was significantly shorter (p < 0.027). In female patients with an early onset of RA the risk of "severe" cardiac amyloidosis was similar (p < 0.031) (because of the small number of male patients the risk was not calculated) (Table 4).

p < between RA Pts with severe cardiac AAa versus mild cardiac AAa			p < between female Pts with severe cardiac AAa versus mild cardiac AAa		
Age	Disease duration	Onset of disease	Age	Disease duration	Onset of disease
p < 0.027	P < 0.242 - NS	p < 0.024	p < 0.086 – NS	p < 0.166 – NS	p < 0.031

Table 4

The quantitative differences of amyloid A deposits in the heart of 33 RA patients with AAa are summarized in table 5 and Figure 5.1-5.3.

	Pr n⁰/y	Sex	a	I	A	ret	v	V	VV	Myo	AA	n	Avg	CoD	Cl-/Cl-
1	76/79	f	0	0	0	0	0	0	0	0	0	0	0,000		
2	155/87	f	0	0	0	0	0	0	0	0	0	0	0,000		
3	240/88	f	0	0	0	0	0	0	0	0	0	0	0,000		
4	183/92	f	0	0	0	0	0	0	0	0	0	0	0,000		
1	243/87	f	1	1	0	1	0	0	0	1	0	0	0,400	cAAa	
2	39/76	f	1	1	0	1	1	0	0	0	0	0	0,400	U	
3	80/80	f	2	1	0	0	1	0	0	0	0	0	0,400	U	Cl+
4	430/80	f	1	1	1	1	0	0	0	0	0	0	0,400	cAAa	
5	266/78	f	2	1	1	1	0	0	0	0	0	0	0,500		
6	287/91	f	2	1	2	0	0	0	0	0	0	0	0,500	cAAa	
7	226/85	f	2	2	1	0	1	0	0	0	0	0	0,600		
8	322/81	f	2	1	1	1	0	1	1	0	0	0	0,700	cAAa	
9	306/90	f	2	2	2	1	1	0	0	0	0	0	0,800	U	Cl+
10	367/75	f	2	1	2	1	1	1	0	1	0	0	0,900	cAAa	
11	43/85	m	2	2	1	1	1	1	1	0	1	0	1,000	U	
12	174/88	f	2	2	1	1	1	2	0	1	0	0	1,000	U	
13	203/88	f	2	1	2	2	1	1	1	0	0	0	1,000	U	
14	52/92	f	3	3	2	2	0	0	0	0	0	0	1,000		
1	162/78	f	3	1	2	2	1	1	0	1	0	0	1,100		
2	342/86	m	2	3	1	1	1	1	1	1	0	0	1,100	U	
3	395/76	f	2	2	1	2	2	2	0	1	0	0	1,200	cAAa	
4	232/74	m	2	1	2	2	1	2	2	0	1	0	1,300	U	Cl+
5	V/T	f	2	2	1	2	2	2	2	0	0	0	1,300	U	
6	45/74	f	3	3	2	2	1	0	0	1	0	2	1,400	cAAa	
7	137/76	f	3	2	2	2	2	2	0	1	0	0	1,400	U	Cl+
8	265/80	f	3	3	2	1	2	1	0	1	1	0	1,400	U	Cl+
9	90/85	f	3	3	2	1	2	1	0	1	1	0	1,400		
10	181/80	m	2	3	1	3	3	2	1	0	0	0	1,500	U	Cl+
11	245/88	f	3	2	2	2	1	1	1	2	1	0	1,500	cAAa	
12	255/83	f	3	1	2	2	2	2	2	0	2	0	1,600	U	Cl+
13	73/87	f	3	2	2	2	2	2	2	0	1	0	1,600	U	Cl+
14	53/87	m	3	3	2	2	2	2	3	2	1	3	2,300	U	Cl+
15	101/90	f	3	3	3	3	2	2	2	3	1	2	2,400	U	
	Count		33	33	33	33	33	33	33	33	33	33	33	9	9
	Sum		66	54	43	42	34	29	19	17	10	7	32		
	Avg		2,00	1,64	1,30	1,27	1,03	0,88	0,58	0,52	0,30	0,21	0,97		
	0 values n		4	4	7	7	10	14	21	20	24	30	4		
	+ values n		29	29	26	26	23	19	12	13	9	3	29		
	Prevalence %		87,88	87,88	78,79	78,79	69,70	57,58	36,36	39,39	27,27	9,09	87,88		
	Severity%		66,67	54,55	43,43	42,42	34,34	29,29	19,19	17,17	10,10	7,07	32,42		

Table 5: *Prevalence and extent of amyloid A deposits in heart of 33 RA patients with AA amyloidosis arranged according to the increasing values of average amounts of amyloid A deposits/patient (horizontal lines) and A deposits/structure (vertical columns)*

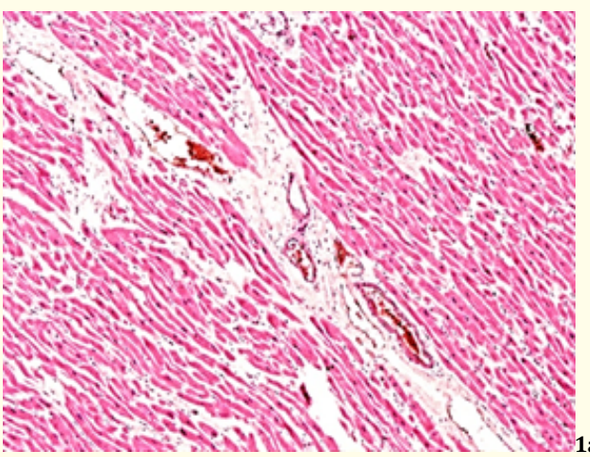
Remarks

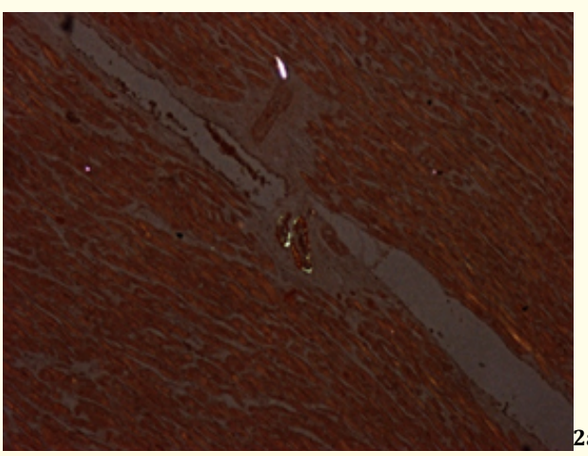
Pr n⁰/y: Protocol number/year; CoD: Cause of death: U: Uremia due to massive amyloid A deposition in the kidneys with consecutive renal insufficiency (n = 16); cAAa: lethal outcome exclusively caused by cardiac amyloidosis (n = 3); cAAa: cardiac amyloidosis only contributed to the death (n = 5); Cl+: Clinically Recognized; Cl- : Clinically not recognized; f: Female; m: Male

Abbreviations

a: Arteriole; A: Small Artery; AA: Medium Size Artery; v: Venule; V: Small Vein; VV: Medium Size Vein; I: Interstitial Collagen Fiber; ret: Reticulin Fiber (collagen IV); Myo: myocardiocytes; n: nerve

Regarding the regional distribution of amyloid A deposits in the heart, besides the constant involvement of blood vessels (Figures 1-2ac and 3-4ab), the relatively massive involvement of Interstitial collagen fibers was characteristic (Figures 3ab). Amyloid A deposits were more pronounced in the subendocardial and subepicardial regions of myocardium in comparison with its deeper (central) zones (Figures 4ab).


1a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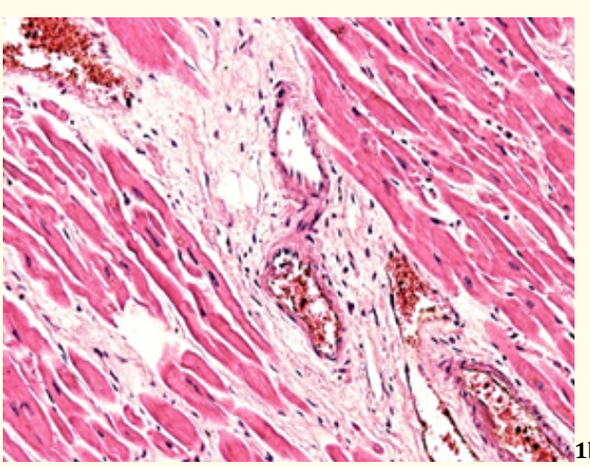
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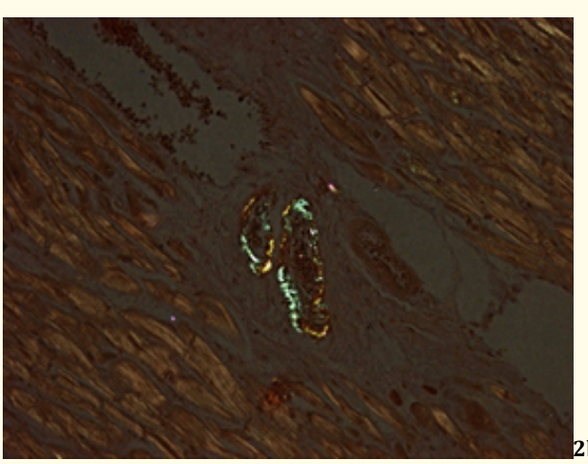
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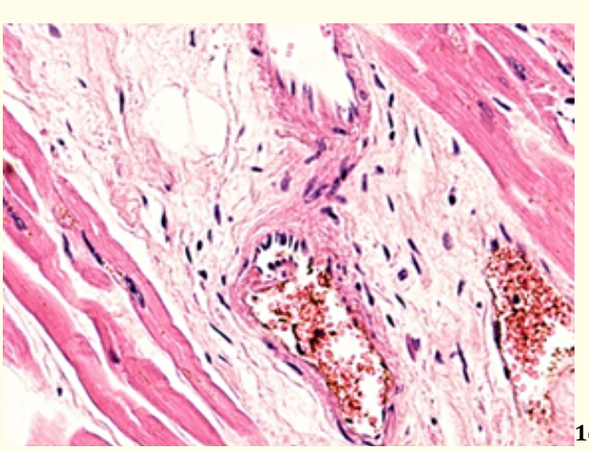
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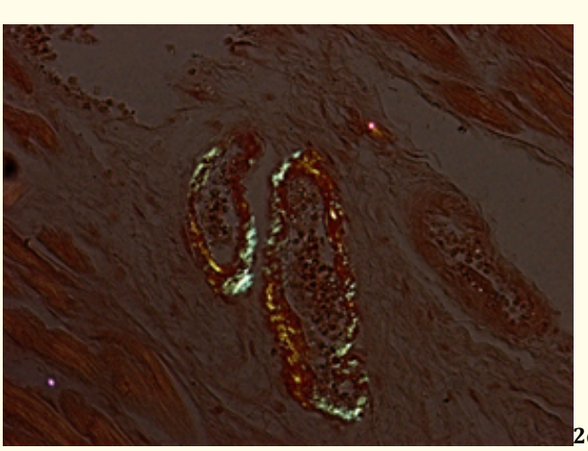

2c

Figures 1a-c and 2a-c

RA, heart, intramural region of myocard, early stage of cAAa

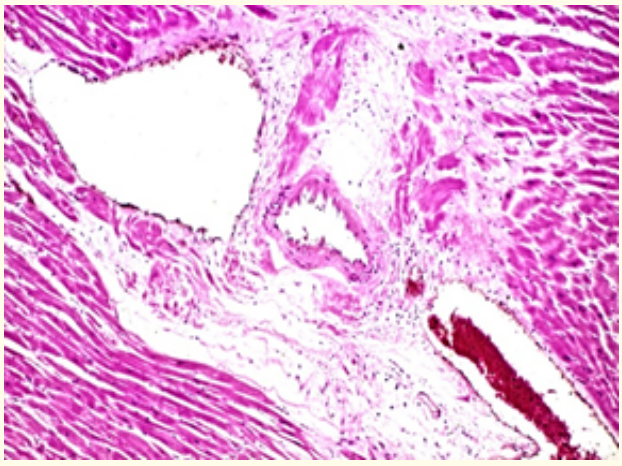
Detectable deposits of Amyloid A are present only in the wall of arterioles; the vemules are spared.

(1a) HE, x40 (1b) same field as (1a), HE, x100 (1c) same field as (1b), HE, x200

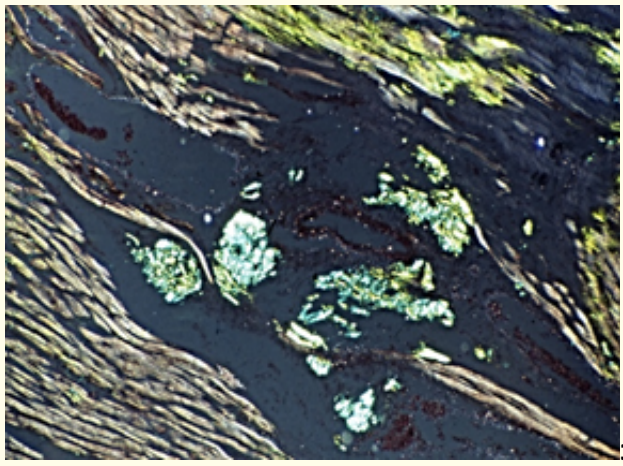
(2a) same field as (1a), stained with Congo red, and viewed under polarized light, x40 (2b) same field as (1b and 2a), x100 (2c) same field as (1c and 2a), x200

(The original magnification corresponds to the 24x36 mm transparency slide)

(the correct hight:weigth ratio is 2:3).



3a



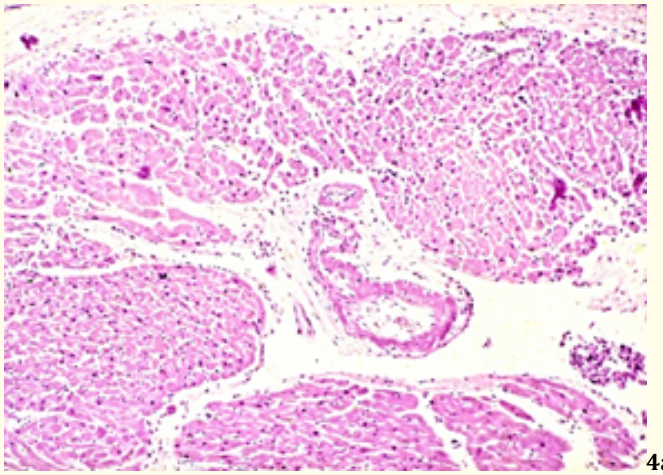
3b

Figures 3a and 3b

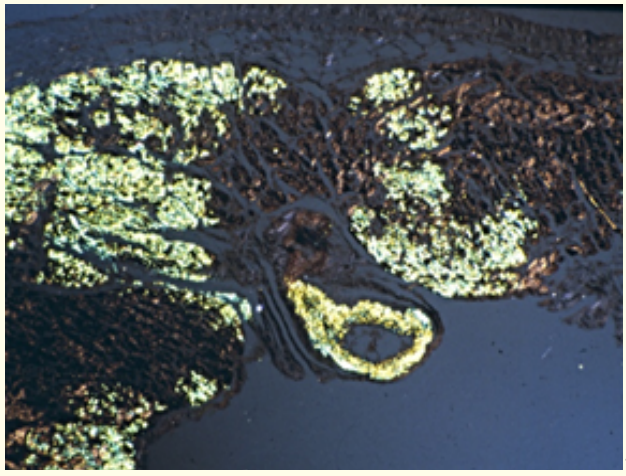
RA, heart, intramural region of myocardium, advanced stage of cAAa

Amyloid A deposits are within the wall of arterioles and intramural interstitial collagen fibers; venule and small veis are spared. (apple green birefringence corresponds to amyloid A deposits, in "white" birefringence is caused by paraffin remnants due to imperfect deparaffinizition)

(a) HE, x50 (b) same field as (a), stained with Congo red, and viewed under polarized light, x50



4a



4b

Figures 4a and 4b

RA, heart, subendocardial region, late stage of cAAa

Amyloid A deposits are within the wall of small arteries and arterioles, intramural interstitial collagen fibers and within cardiomyocytes.

(a) HE, x50 (b) same field as (a) stained with Congo red, and viewed under polarized light, x50

The distribution of 33 RA patients with AAa at death (according to increasing values of amyloid A deposits) is demonstrated in figure 5.1 and 5.2.

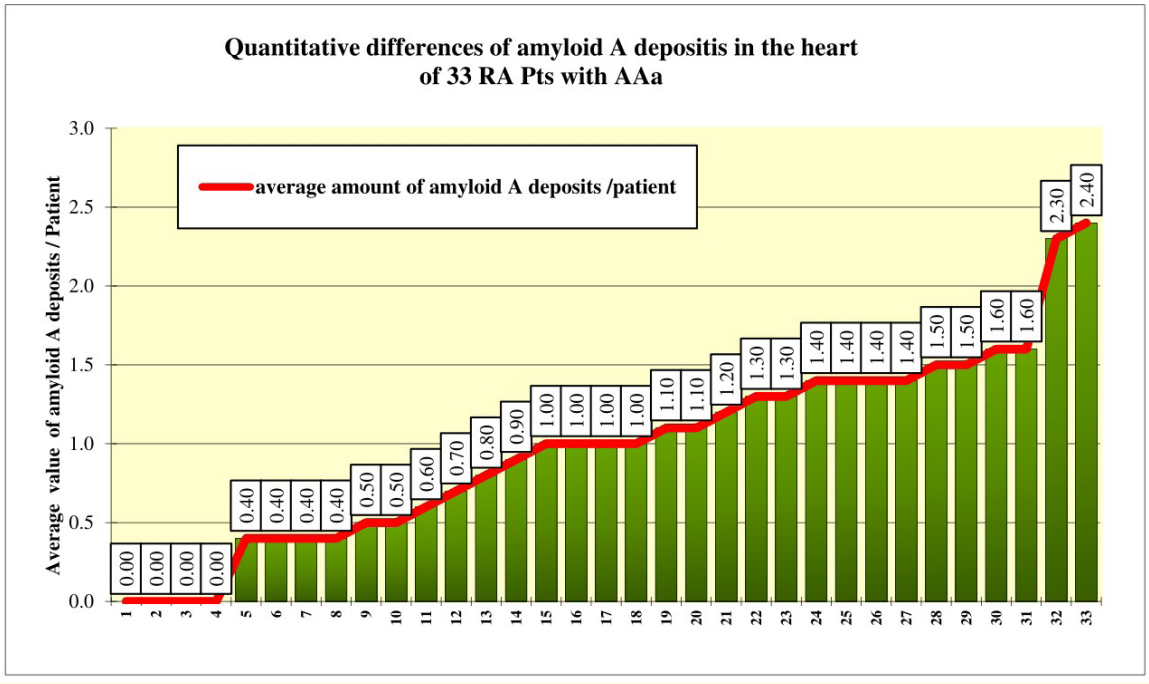


Figure 5.1: *Cohort of 33 RA patients with AAa at death, according to increasing values of amyloid A deposits ("average amount of amyloid A deposits/patient").*

In the heart amyloid A deposition started later than general (systemic) amyloid deposition in RA patients with AAa.

The distribution of RA patients with mild and severe amyloidosis showed basically a lineal growth curve, except at the early and end stages of amyloid deposition. In early stages of systemic AAa the amyloid A deposition started abruptly in the heart, and in the terminal stage amyloid A deposition progressed again rapidly and the growth curve showed an exponential increment (Figure 5.2).

In patients with mild and severe cardiac AAa, the amyloid A deposition in the heart, except in the early and late stages, showed basically a linear growth curve; development of cAAa was steady (Figure 5.2).

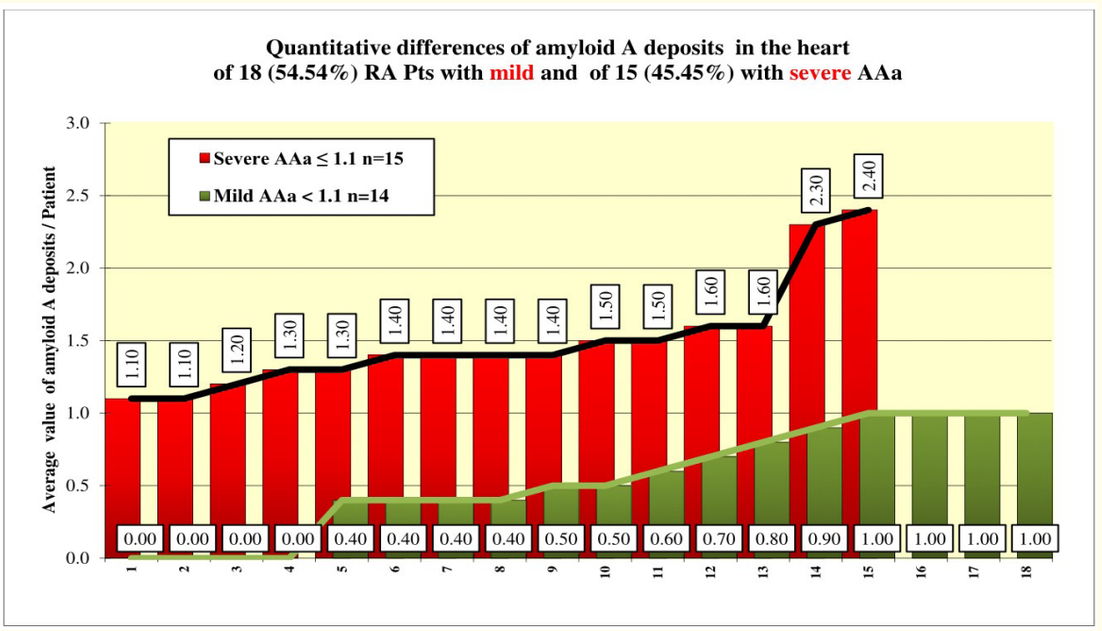


Figure 5.2: *Cohort of 33 RA patients with cardiac AAa.*

In 4 (12.12%) of 33 RA patients complicated with systemic AAa there was no cardiac amyloid A deposition, these represent a latent stage of cardiac amyloidosis (the amount of amyloid A deposits was: 0.00); in 14 (42.42%) pts with mild amyloidosis the amount of amyloid A deposits was: 0.40 – 1.00, and in 15 (45.45%) patients with severe cardiac amyloid A deposition the amount of amyloid A deposits was between 1.10 - 2.40. The increment showed a basically linear growth curve, representing the same rate of deposition.

The frequently involved tissue structures showed marked deposits of amyloid. Deposits were less striking in less frequently involved tissue structures (Table 4 and Figure 5.3).

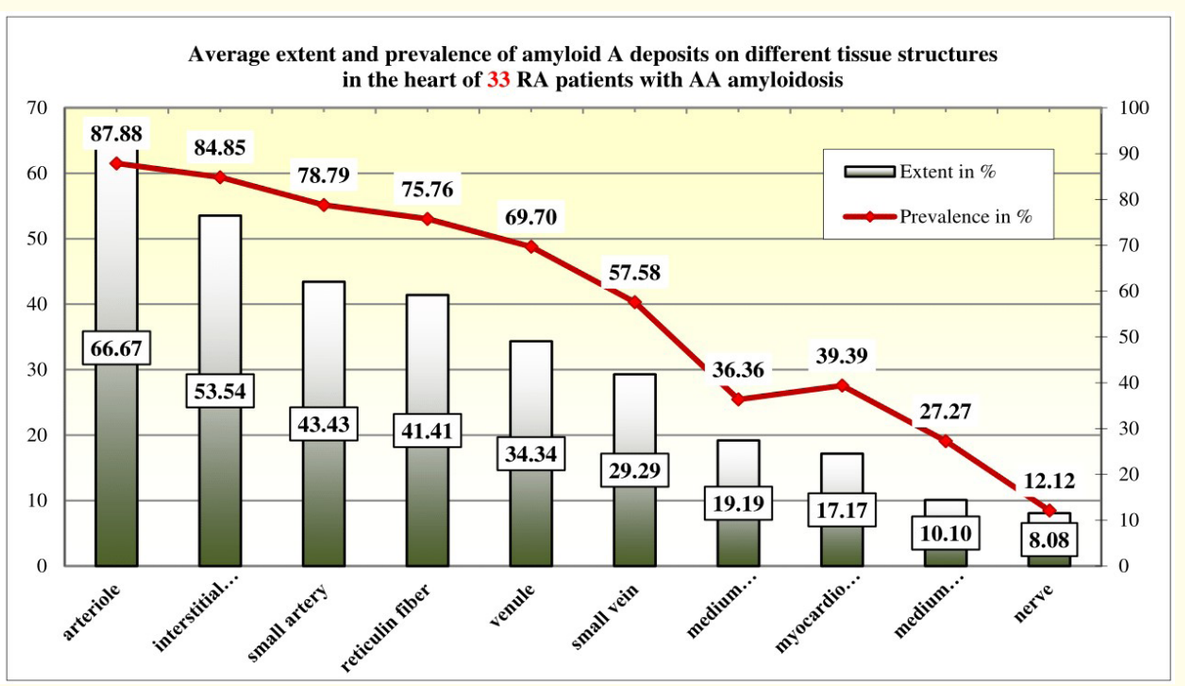


Figure 5.3: *The prevalence and extent of amyloid A deposits in different tissue structures of the heart were running basically parallel (except the myocardiocytes and medium size veins in which it was inverse.*

Detectable amounts of amyloid A deposits in different tissue structures of the heart did not appear simultaneously. In the early stage of systemic amyloidosis there were histologically detectable amyloid deposits only in a few structures (arterioles, interstitial collagen fibers, small arteries). In other structures of the heart (venules, small veins, myocardiocytes, medium size veins and arteries, nerves) deposits were seen only in late stages of amyloidosis (with massive involvement of the former.

The amount of deposited amyloid A was different in various tissue structures and increased simultaneously, but the proportion of deposited amyloid A was constant and independent of the stage of amyloidosis. The amounts of amyloid A deposits in various structures of the heart are demonstrated in figure 5.4.

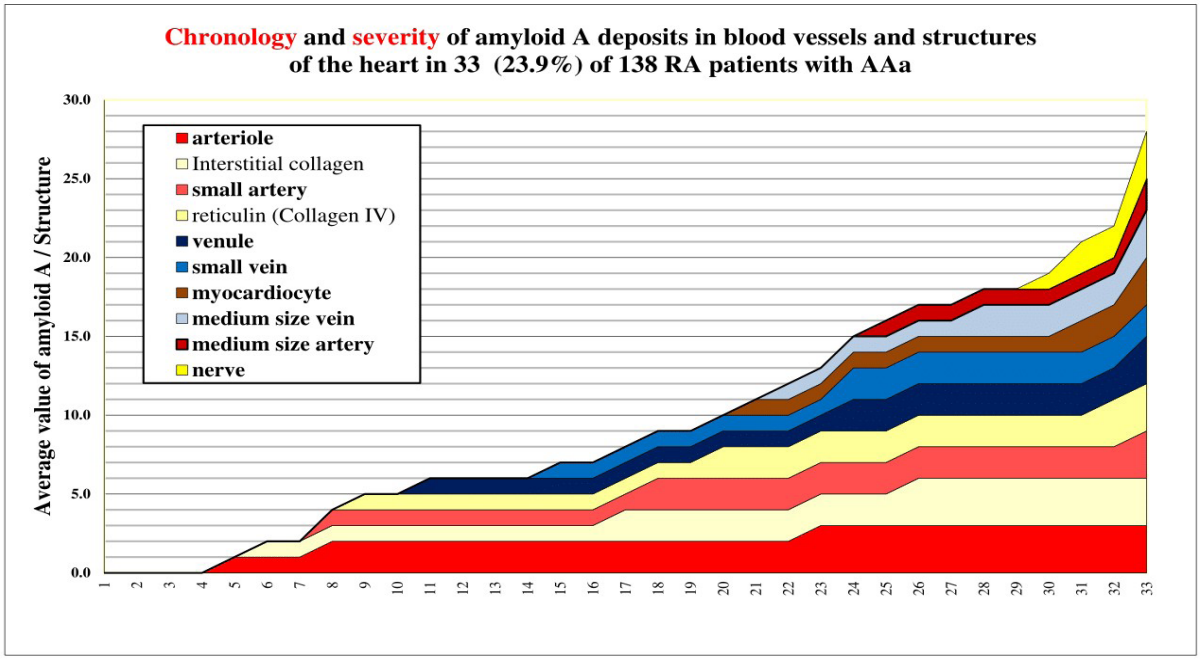


Figure 5.4: *Prevalence and extent of amyloid A deposits in different tissue structures of the heart arranged according to their increasing prevalence.*

Amyloid A deposition did not start at the same time in different tissue structures of the heart. The amount of amyloid A deposits in different tissues increased simultaneously, the rate was constant and independent of the stage of amyloidosis.

AAa was lethal in 16 (48.48 % of 33) patients due to renal insufficiency and uremia. Cardiac amyloidosis led to death in 3 (9.09 % of 33) patients only, in further 5 (15.15 % of 33) cases cardiac amyloidosis was associated with systemic vasculitis of autoimmune origin (A-SV), atherosclerosis (Ath) or obliterative bronchiolitis and played an additive role, contributing to the lethal outcome. Nine (27.27 % of 33) patients with systemic AAa died of other causes such as peritonitis, lethal septic infection (SI) etc (Table 6).

Systemic AAa was clinically diagnosed in 9 (27.27 %) and missed in 24 (72.73 %) of 33 patients, but cardiac AAa or its pathogenic role in mortality was not recognized (Table 6).

	Basic disease	Complication(s)		Cause of death	Associated disease(s)	Cl+/Cl-	Amount of cAAa	Pr n^0 /y
1	RA-AAa	Duodenal ulcer	Perforation	Peritonitis		Cl-	0,00	76/79
2	bTu-AAa	Ependymoma	Vertebral fracture	Pulmonary embolism	RA-Ath-Ht	Cl-	0,00	155/87
3	RA-AAa	Coronary arteriolitis		Myocardiocytolysis	Tb-F-mTb	Cl-	0,00	240/88
4	RA	Colitis - Colonic ulcers	Peritonitis	Lethal SI		Cl-	0,00	183/92
1	RA-AAa	Coronary arteritis	Coronary arteriolitis	Circulatory failure		Cl-	0,40	243/87
2	RA-AAa			Uremia 1	Ath	Cl-	0,40	39/76
3	RA-AAa			Uremia 2	Ath	Cl+	0,40	80/80
4	RA-AAa			Circulatory failure	Ca of gallbladder	Cl-	0,40	430/80
5	RA-AAa			Lethal SI	Ath	Cl-	0,50	266/78
6	RA-AAa	Nodular epicarditis		Myocardial necrosis	Breast Carcinoma	Cl-	0,50	287/91
7	RA-AAa	Sporadic vasculitis*		Pneumonia	Ca of lung-Ath	Cl-	0,60	226/85
8	RA-AAa			Circulatory failure		Cl-	0,70	322/81
9	RA-AAa			Uremia 3		Cl+	0,80	306/90
10	RA-AAa			Myocardial necrosis	Ath-DM	Cl-	0,90	367/75
11	RA-AAa	A-SV		Uremia 4	DM- Ht	Cl-	1,00	43/85
12	RA-AAa			Uremia 5		Cl-	1,00	174/88
13	RA-AAa	Femoral vein thrombosis	Femoral artery thrombosis	Uremia 6		Cl-	1,00	203/88
14	Ath	Hypertension	Myocardial fibrosis	Bronchopneumonia	RA	Cl-	1,00	52/92
1	RA-AAa	Gastric ulcer-Bleeding	Perforation-Peritonitis	Lethal SI		Cl-	1,10	162/78
2	RA-AAa			Uremia 7	Acoustic Neurinoma-Ath	Cl-	1,10	342/86
3	RA-AAa	Coronary arteritis	Coronary arteriolitis	Myocardiocytolysis	TbFc-mTb	Cl-	1,20	395/76
4	RA-AAa			Uremia 6		Cl+	1,30	232/74
5	RA-AAa			Uremia 9		Cl-	1,30	V/T
6	RA-AAa			Heart failure		Cl-	1,40	45/74
7	RA-AAa			Uremia 10		Cl+	1,40	137/76
8	RA-AAa			Uremia 11	Ca of pancreas	Cl+	1,40	265/80
9	RA-AAa	A-SV		Myocardial necrosis	Ath-DM	Cl-	1,40	90/85
10	RA-AAa			Uremia 12	Neurinoma	Cl+	1,50	181/80
11	RA-AAa	Bronchiolitis obliterans	Multifocal pneumonia	Heart failure	DM	Cl-	1,50	245/88
12	RA-AAa			Uremia 13	DM	Cl+	1,60	255/83
13	RA-AAa			Uremia 14		Cl+	1,60	73/87
14	RA-AAa			Uremia 15		Cl+	2,30	53/87
15	RA-AAa			Uremia 16	Ht	Cl-	2,40	101/90

Table 6: *Mortality of AAa in 33 of 138 RA patients.*

Remarks

*Pr n^0/y: Protocol number/year; Cl+: Clinically recognized AAa in 9 (27.27 %) of 33 patients; Cl- : Clinically not recognized 24 (72.73 %) of 33 patients; *sporadic vasculitis associated to Ca; bTu: Benign Tumor (Ependymom)*

Abbreviations

Ath: Atherosclerosis; Ht: Hypertension; SI: Lethal Septic Infection; A-SV: Systemic Vasculitis of Autoimmune Origin; Tb: Post-primary (Fc– fibrocaseous) tuberculosis; mTb: Active Miliary Dissemination of Tb; DM: Adult Type II Diabetes Mellitus; Myocardiocytolysis: Multiple (multifocal) Microinfarction Of Myocardium; Ca: Carcinoma

Discussion

Numerous publications discuss the prevalence of AAa (Table 7) in RA with or without its role in mortality, but only a few of these mention cardiac involvement [20-44].

References	Year of Publication	Autopsy n	Prevalence of amyloidosis n - %	Mortality of amyloidosis n - %	Prevalence of cardiac amyloidosis n - %
Bayles	1943 [18]	23	ND*	3 of 23 - 13.0%	not mentioned
Baggenstoss and Rosenberg	1943 [19]	30	2 - 6.6%	1 of 30 - 3.3%	not mentioned
Rosenberg and Baggenstoss	1943 [20]	30	2 - 6.6%	1 of 30 - 3.3%	not mentioned
Young and Schwedel	1944 [21]	33	5 - 15.2%	0 of 33 - 0%	not mentioned
Unger., *et al.*	1948 [22]	58	4 - 6.9%	ND	1 of 58 - 1.7%
Teilum and Lindahl	1954 [23]	28	17 - 60.7%	7 of 28 - 25.0%	not mentioned
Gedda	1955 [24]	45	11 - 24.4%	9 of 45 - 20.0%	not mentioned
Sinclair and Cruickshank	1956 [25]	16	4 - 25.0%	0 of 16 - 0%	1 of 16 - 6.25%
Missen and Tailor	1956 [26]	47	8 - 17.0%	4 of 47 - 8.5%	2 of 47 - 4.25%
Lebowitz	1963 [27]	62	6 - 10.0%	ND	not mentioned
Sokoloff	1964 [28]	19	0 - 0%	0 of 19 - 0%	ND
Cohen	1968 [29]	42	11 - 26%	ND	"may be present"
Karten	1969 [30]	95	1 - 1.05%	ND	ND
Gritsman	1969 [31]	15	6 - 40.0%	ND	not mentioned
Ozdemir., *et al.*	1971 [32]	47	1 - 2.1%	ND	1 of 46 - 2.17%
Gardner	1972 [33]	142	17 - 11.97%	ND	"may be present"
Püschel	1973 [34]	143	15 - 10.5%	ND	ND
Vroninks., *et al.*	1973 [35]	62	3 - 4.84%	0 of 62 - 0%	not mentioned
Hajzok., *et al.*	1976 [36]	16	7 - 43.7%	ND	not mentioned
Eulderink	1976 [37]	111	ND	6 of 111 - 5.4%	not mentioned
Rainer., *et al.*	1978 [38]	79	ND	4 of 79 - 5.0%	not mentioned
Boers., *et al.*	1987 [39]	132	14 - 10.6%	ND	not mentioned
Bély**	1993 [40]	161	34 - 21.1%	17 of 161 - 11%	**29 of 138 - 21.01%
Suzuki., *et al.*	1994 [41]	81	17 - 21.0%	6 of 81 - 7.4%	not mentioned
Bély and Apáthy**	2006 [42]	234	48 - 20.5%	20 of 234 - 8.5%%	**47 of 181 - 25.0%

Table 7: *Prevalence and mortality of AA amyloidosis of patients with rheumatoid arthritis at autopsy*.*

Remarks

ND: *No Data*

**: Amyloid deposits were identified with different staining methods: Toluidine blue, Crystal violet, Syrius red, Congo red staining according to Romhányi, Bennhold's, Puchtler's, Bély's Congo red method.*

*****:*** *Prevalence of cardiac involvement by AA amyloidosis was not mentioned in the original publications and could be determined retrospectively.*

It is difficult to estimate the true prevalence of AAa in RA since it depends on the specificity and sensitivity of the demonstration technique. Using a less sensitive staining method some positive cases remain undetected. A more specific method potentially detects more cases, and reveals earlier stages. Amyloidosis in most studies was diagnosed with different methods of diverse specificities and sensitivities. In most of the early studies the prevalence or mortality of AAa seems to be underestimated, presumably due to the limited micro-

scopic examination of various organs, including heart, of the autopsied patients. Unfortunately only a few studies specify the relationship between systemic AAa and cardiac amyloid A deposition (cAAa).

According to our best knowledge a detailed analysis regarding the rate of amyloid A deposition and its relationship to cardiac AA amyloidosis has not been available in the literature.

The precursors of amyloid A protein fibrils are produced by the liver. The serum amyloid A proteins spread via the bloodstream and are deposited throughout the body. The level of precursors in the blood depends on the production and/or elimination of amyloid proteins or, more succinctly, on the dynamics of these two processes.

Systemic amyloidosis is related to the cardiovascular system and becomes generalized via the bloodstream, while organ- or tissue-limited isolated amyloidosis is not directly related to the systemic circulation and remains a localised process [43,44].

"All forms of amyloidosis related to the circulation of blood are systemic, and all forms of amyloidosis not connected to the circulation are isolated (localized)" [44]. This statement was confirmed by Sipe as an important conclusion of XIth International Symposium on A myloidosis, held in Woods Hole, Massachusetts, USA, November 5-9, 2006 [45].

Amyloidosis is a progressive, cumulative process, involving in its early stage only a few structures in some organs, and increasingly more in the later stages of the disease [13,42].

The degree of amyloid A in the 33 RA patients demonstrates (Figure 5.1) a progressive cumulative process, the development of cAAa. Cardiac amyloid A deposition, despite of a copious blood supply and lavish vascularisation of the heart, is delayed in comparison with systemic manifestation of AAa in some other organs. This latency may be caused by a not specified local protective mechanism, e.g. due to motility or oxygenisation etc. The role of relative hypoxemia is supported by the fact that amyloid A deposits are present earlier and are more prominent in the relative less oxygenated subepicardial and subendocardial regions of the myocardium in comparison with its deeper, more supplied central portions.

The stages of amyloidosis in 14 RA patients with mild and 15 with severe cAAa demonstrate the same progressive, cumulative basically linear pathological process shown in Figure 5.2. The latent stage of cAAa changed abruptly, which may have been caused by overloading of the local protection, and the terminal rapid accretion may be due to massive amyloidosis of the kidneys in the end tage of AAa, with the totally blocked renal excretion of precursors.

Development of mild and severe amyloidosis is based on the linear growth course; only the production and circulating amounts of precursors are different. Quantitative differences in production of serum amyloid A may be related to a "benign" or "aggressive" clinical course of RA, which may be due to genetical and/or other factors.

Prevalence and severity of amyloid A deposits in different tissue structures of the heart signify different aspects of the same pathological process which usually run parallel to each other (Figure 5.3).

Amyloid A deposition starts in the most frequently involved structures of the most frequently involved organ [13,42,43].

In the heart the deposition of amyloid A starts in the wall of arterioles and interstitial collagen fibers of the myocardium.

Small arteries and subepicardial reticulin fibers (collagen IV of fatty tissue) are involved later. Deposition within the myocardiocytes and involvement of the nerves indicates advanced stages of amyloidosis in the heart. The involvement of venules, small and medium size veins seems to be overlapping the mentioned sequence of amyloid A deposition; but its frequency increases in congestive heart failure. This chronology of amyloid A deposition allows an indirect assessment of the stage of amyloidosis. Based on the involved structures in biopsy specimens or surgical tissue samples the pathologist may estimate the involvement of other structures.

Involvement of arterioles alone (without involvement of small arteries) indicates an early stage of cardiac amyloidosis, whereas amyloid A deposits in peripheral nerves suggest an advanced stage with massive involvement of numerous structures.

The constant and permanent relationship between amyloid A deposits in different structures approximately indicates the amount of amyloid depositions in other structures of the heart, even in cases in which some structure is not present in a cardiac biopsy specimen. Based on this assumption the biopsy specimen may have prognostic value in everyday pathological practice.

Conclusions

Systemic AAa is one of the main and the most insidious complications of rheumatoid arthritis affecting the heart with high prevalence and severity [13].

Systemic AAa is related to the cardiovascular system [43,44], and cardiac AAa is associated with it. In systemic AAa the cardiac amyloid A deposition starts after a latent stage. Systemic and cardiac amyloid A deposition is a progressive and cumulative process, involving in its early stage only a few structures in the heart, and increasingly more in the later stages of the disease. Amyloid A deposition starts in the most frequently involved structures of the heart with more massive deposits. The chronology of amyloid A deposition allows an indirect assessment of the stage of cardiac amyloidosis, which may have a prognostic value in everyday surgical pathology as well.

From a prognostic point of view, cAAa should be considered a very serious, life-threatening complication of RA.

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