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Research Article

AA Amyloidosis and Lung Diseases in Rheumatoid Arthritis - A Postmortem Clinicopathologic Study of 147 Autopsy Patients

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Abstract

Aim of the Study: The aim of this study was to determine the incidence of systemic AA amyloidosis (sAAa) in rheumatoid arthritis (RA), to identify the amyloid A deposition on different tissue structures of the lung (pAAa), and assess the influence of sAAa and pAAa on lung diseases related or not related to RA.

Patients and Methods: 147 random autopsy patients with RA were studied. RA was confirmed clinically according to the criteria of the ARA.

The prevalence (existence) and severity (extent) of sAAa and pAAa was specified histologically. Amyloid A deposition was diagnosed histologically according to Romhányi by a modified (more sensitive) Congo red staining.

Distinct forms of multifocal inflammation, such as purulent bronchitis or bronchiolitis (purBr), bronchopneumonia (BrPn), infarct pneumonia (InfPn), obliterative pneumonia (OblPn), rheumatoid pneumonia (RhPn), furthermore interstitial pneumonia (IPn) were determined post-mortem and analyzed retrospectively, reviewing the clinical and pathological reports.

Demographics of different patient cohorts were compared with the Student t-probe. The possible role of sAAa or pAAa on the prevalence of purBr or BrPn, InfPn, OblPn, RhPn and IPn was analyzed with chi-squared (χ^2) test.

Results: sAAa complicated RA in 34 (23.13%) of 147 patients. Branches of pulmonary and bronchial blood vessels were involved in 25 (73.53%) of these 34 cases.

PurBr or BrPn were associated with RA in 18 (12.23%), InfPn in 5 (3.4%), OblPn in 2 (1.4%), RhPn in 3 (2.1%) of 147 patients (only the fatal cases were considered). IPn was present in 35 (23.8% of 147) patients and contributed to the death only in association with cardiac, circulatory or cardio-respiratory insufficiency.

Conclusion: sAAa or pAAa may develop in both sexes, and at any time in the course of RA. According to our study interstitial pneumonia (IPn) is influenced by sAAa or pAAa. The relatiomship between pAAa and obliterative pneumonia (OblPn) seems to be more direct. Lung diseases, such as purulent bronchitis or bronchiolitis (purBr), bronchopneumonia (BrPn), infarctpneumonia (InfPn), rheumatoid pneumonia (RhPn) are independent entities.

Keywords: *Systemic and Pulmonary Amyloidos; Lung Diseases*

Abbreviations

RA: Rheumatoid Arthritis; sAAa: Systemic AA Amyloidosis; pAAa: Pulmonary AA Amyloidosis; ARA: American College of Rheumatology; purBr: Purulent Bronchitis or Bronchiolitis; BrPn: Bronchopneumonia; InfPn: Infarct Pneumonia; OblPn: Obliterative (Obstructive Necrotizing) Pneumonia; RhPn: Rheumatoid Pneumonia; IPn: Interstitial Pneumonia; SD: Standard Deviation; ND: No Data

Introduction

Systemic AA amyloidosis (sAAa) is one of the main and the most insidious complications of rheumatoid arthritis (RA) characterized by amyloid A deposition in various organs [1].

A wide spectrum of lung diseases may complicate RA or associate with RA [2-4].

Aim of the Study

The aim of this study was to determine the incidence of sAAa in RA, to identify the amyloid A deposition on different tissue structures of the lung (pAAa), and assess the influence of sAAa and pAAa on lung diseases related or not related to RA (not to mention all possibilities).

Patients and Methods

147 random autopsy patients with RA were studied [4]. RA was confirmed clinically according to the criteria of the American College of Rheumatology (ARA) [5].

The prevalence (existence) and severity (extent) of sAAa and pAAa was specified histologically, based on evaluation of 6 organs (heart, lung, liver, kidney, pancreas, and brain).

Amyloid A deposition was diagnosed histologically according to Romhányi [6] by a modified (more sensitive) Congo red staining [7]. Amyloid A deposits were identified in serial sections by immunohistochemical and histochemical methods [8,9]. The prevalence and severity of amyloid A deposition were evaluated microscopically with an Olympus BX51 polarizing microscope.

Distinct forms of multifocal inflammation, such as purulent bronchitis or bronchiolitis (purBr), bronchopneumonia (BrPn), infarct pneumonia (InfPn), obliterative pneumonia (OblPn), rheumatoid pneumonia (RhPn), furthermore interstitial pneumonia (IPn) [1-4] were determined post-mortem and analyzed retrospectively, reviewing the clinical and pathological reports.

Demographics of different patient cohorts were compared with the Student (Welch) t-probe [10]. The possible role of sAAa or pAAa on the prevalence of purBr or BrPn, InfPn, OblPn, RhPn and IPn was analyzed with Pearson's chi-squared (χ^2) test [10].

Glossary of definitions

- **Prevalence of sAAa**: Concerns the proportion of amyloid A deposits in various organs of our autopsy population and conveys information about the risk of complications. Prevalence of sAAa was specified histologically based on the presence of amyloid A in blood vessels of different calibers or in different tissue structures of six organs (heart, lung, liver, kidney, pancreas, and brain) in each patient.
- **Prevalence of pAAa:** Concerns how widespread the amyloid A deposits are in pulmonary or bronchial blood vessels of different calibers or in different tissue structures of the lung.
- **Size of blood vessels [11] in tissue samples of the lungs:** 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)
- Reticulin fiber (collagen IV) (ret)
- Basement membrane - (BM) peribronchial, (brBM), perilubular (lobBM) or panlobular (plobBM) of the lung
- Nerve (n) in the lung
- **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.

Results

sAAa complicated RA in 34 (23.13%) of 147 patients. Branches of pulmonary and bronchial blood vessels of different calibers and various tissue structures of the lungs were involved in 25 (73.53% of 34, 17.01% of 147) cases; pAAa was histologically excluded in 9 (26.47% of 34) of 34 cases.

There was a very strong positive relationship between sAAa (n = 34) and pAAa (n = 25) ($c = 1.0$, $\chi^2 = 94.9728$, $p < 0.0000$).

PurBr or BrPn were associated with RA in 18 (12.23%), InfPn in 5 (3.4%), OblPn in 2 (1.4%), RhPn in 3 (2.1%) of 147 patients (only the fatal cases were considered). IPn - characterized by interstitial cellular infiltration with or without edema, fibrinoid deposition, with or without fibrosis, and with or without correspondent pleuritis was present in 35 (23.8% of 147) patients; IPn alone was not fatal in our cohort and contributed to death only in association with cardiac, circulatory or cardio-respiratory insufficiency.

In table 1 are summarized the demographics, onset and duration of disease of total population (n = 147), with (n = 34) and without (n = 113) sAAa, with (n = 25) and without (n = 9) amyloid A deposits in the lungs, with (n = 18) and without (n = 129) PurBr or BrPn, with (n = 3) and without (n = 144) RhPn, with (n = 2) and without (n = 145) OblPn, furthermore with (n = 35) and without (n = 112) IPn.

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 or duration of RA between patient cohorts with sAAa (n = 34) compared to the total population (n = 147) ($p < 0.27$, $p < 0.29$, $p < 0.44$), neither between females ($p < 0.76$, $p < 0.51$, $p < 0.52$) and males ($p < 0.33$, $p < 0.54$, $p < 0.70$), with (n = 34) and without sAAa (n = 113) ($p < 0.16$, $p < 0.17$, $p < 0.32$), neither between females ($p < 0.68$, $p < 0.37$, $p < 0.39$) and males ($p < 0.27$, $p < 0.49$, $p < 0.67$), with sAAa (n = 34) and with pAAa (n = 25) ($p < 0.88$, $p < 0.93$, $p < 0.99$), neither between females ($p < 0.99$, $p < 0.98$, $p < 0.98$) and males ($p < 1.00$, $p < 1.00$, $p < 1.00$) or between patient cohorts with (n = 25) and without pAAa (n = 9) ($p < 0.60$, $p < 0.78$, $p < 0.99$), neither between females ($p < 0.99$, $p < 0.95$, $p < 0.96$); the males were not involved by pAAa, significance was not calculated.

Amyloidosis developed in both sexes, and at any time in the course of the disease (Table 1 and 2).

Sex	Number of autopsies	Mean age in years at death ± SD	Range (in years)	Mean age at onset of disease ± SD	Disease duration (in years) mean ± SD
RA patients (Total)	147	65.63 ± 12.44	16 - 88	51.52 ± 16.63	14.06 ± 10.34
Female	104	65.10 ± 11.74	16 - 87	50.82 ± 15.45	14.29 ± 10.38
Male	43	66.91 ± 13.89	19 - 88	53.31 ± 19.24	13.49 ± 10.23
With sAAa	34 of 147	62.41 ± 15.59	19 - 88	47.61 ± 18.04	15.58 ± 9.36
Female	29	64.34 ± 11.07	32 - 83	48.56 ± 15.25	15.70 ± 9.88
Male	5	51.20 ± 28.18	19 - 88	41.25 ± 30.07	14.75 ± 4.44
Without sAAa	113 of 147	66.60 ± 11.14	16 - 87	52.79 ± 15.94	13.56 ± 10.59
Female	75	65.39 ± 11.98	16 - 87	51.78 ± 15.43	13.67 ± 10.52
Male	38	68.97 ± 8.78	52 - 87	54.87 ± 16.74	13.32 ± 10.74
With pAAa	25 of 34	61.72 ± 17.16	19 - 88	47.14 ± 20.11	15.59 ± 9.77
Female	20	64.35 ± 11.62	32 - 83	48.44 ± 16.86	15.78 ± 10.59
Male	5	51.20 ± 28.18	19 - 88	41.25 ± 30.07	14.75 ± 4.44
Without pAAa	9 of 34	64.33 ± 9.74	44 - 82	48.78 ± 11.38	15.56 ± 8.27
Female	9	64.33 ± 9.74	44 - 82	48.78 ± 11.38	15.56 ± 8.27
Male	0	-	-	-	-
With purBr or BrPn	18 of 147	71.17 ± 6.12	61 - 83	52.14 ± 15.32	19.43 ± 12.23
Female	11	70.27 ± 6.90	61 - 83	48.11 ± 16.01	22.33 ± 12.76
Male	7	72.57 ± 4.27	64 - 79	59.40 ± 10.67	14.20 ± 9.13
Without purBr or BrPn	129 of 147	64.86 ± 12.89	16 - 88	51.44 ± 16.78	13.38 ± 0.88
Female	93	64.48 ± 12.04	16 - 87	51.12 ± 15.36	13.39 ± 9.68
Male	36	65.81 ± 14.82	19 - 82	52.30 ± 20.14	13.37 ± 10.39
With OblPn	2 of 147	58.50 ± 8.50	50 - 67	40.50 ± 4.50	18.00 ± 13.00
Female	2	58.50 ± 8.50	50 - 67	40.50 ± 4.50	18.00 ± 13.00
Male	0	-	-	-	-
Without OblPn	145 of 147	65.73 ± 12.46	16 - 88	51.69 ± 16.69	13.09 ± 10.28
Female	102	65.23 ± 11.76	16 - 87	51.06 ± 15.33	14.19 ± 10.29
Male	43	66.91 ± 13.89	19 - 88	53.31 ± 19.24	13.49 ± 10.23
With InfPn	5 of 147	68.00 ± 7.80	55 - 78	59.63 ± 15.18	7.13 ± 7.60
Female	5	68.00 ± 7.80	55 - 78	59.63 ± 15.18	7.13 ± 7.60
Male	0	-	-	-	-
Without InfPn	142 of 147	65.55 ± 12.56	16 - 88	51.25 ± 16.61	14.28 ± 10.34
Female	99	64.95 ± 11.80	16 - 87	50.42 ± 15.34	14.60 ± 10.37
Male	43	66.91 ± 13.89	19 - 88	53.31 ± 19.24	13.49 ± 10.23
With RhPn	3 of 147	61.67 ± 2.62	58 - 64	53.67 ± 3.30	8.00 ± 3.56
Female	2	63.50 ± 0.50	63 - 64	54.00 ± 4.00	9.50 ± 3.50
Male	1	58.00 ± 0.00	58	53.00 ± 0.00	5.00 ± 0.00
Without RhPn	144 of 147	65.72 ± 12.55	16 - 88	51.46 ± 16.82	14.20 ± 10.41
Female	102	65.13 ± 11.85	16 - 87	50.75 ± 15.60	14.38 ± 10.45
Male	42	67.12 ± 13.99	19 - 88	53.32 ± 19.52	13.74 ± 10.27

With IPn	35 of 147	63.63 ± 14.43	19 - 87	48.32 ± 18.12	13.94 ± 10.37
Female	23	62.83 ± 10.73	32 - 87	46.52 ± 13.78	15.67 ± 12.28
Male	12	65.17 ± 19.58	19 - 87	52.10 ± 24.45	10.30 ± 6.86
Without IPn	112 of 147	66.33 ± 11.66	16 - 88	52.58 ± 15.96	14.16 ± 10.39
Female	82	65.76 ± 11.86	16 - 84	51.94 ± 15.64	14.04 ± 10.10
Male	30	67.87 ± 10.91	32 - 88	54.46 ± 16.71	14.50 ± 11.20

Table 1: *Sex, mean age with SD, range, onset and disease duration (in years) of 147 RA patients complicated by or associated with sAAa, pAAa and lung diseases.*

Glossary to table 1: *RA: Rheumatoid Arthritis; sAAa: Systemic AA Amyloidosis; pAAa: Pulmonary AA Amyloidosis (amyloid A deposits in the lungs); purBr: Purulent Bronchitis or Bronchiolitis; BrPn: Bronchopneumonia; InfPn: Infarct Pneumonia; OblPn: Obliterative Pneumonia; IPn: Interstitial Pneumonia; SD: Standard Deviation.*

The prevalence of purBr or BrPn was higher in elderly patients in comparison to the total population (n = 147) or to the patient cohorts without purBr or BrPn (n = 129). There was no significant difference in survival time, onset and duration of disease between RA patients with and without OcclPn, InfPn, RhPn or IPn; these complications or associated diseases developed in both sexes, and at any time in the course of the disease.

The relationship ("p" values of correlation) of demographics, onset and duration of disease between RA patients with and without sAAa or pAAa are summarized in table 2.

RA patients (Lung) n = 147	Age	Onset of disease	Disease duration
RA n = 147 versus with sAAa n = 34 of 147	p < 0.273	p < 0.286	p < 0.436
Female n = 104 of 147 versus n = 29 of 34	p < 0.755	p < 0.509	p < 0.524
Male n = 43 of 147 versus n = 5 of 34	p < 0.330	p < 0.541	p < 0.697
with sAAa n = 34 vs. without sAAa n = 113 of 147	p < 0.157	p < 0.166	p < 0.323
Female n = 29 of 34 versus n = 75 of 113	p < 0.680	p < 0.370	p < 0.391
Male n = 5 of 34 versus n = 38 of 113	p < 0.277	p < 0.493	p < 0.671
with sAAa n = 34 vs. with pAAa n = 25 of 34	p < 0.877	p < 0.931	p < 0.997
Female n = 29 of 34 versus n = 20 of 34	p < 0.999	p < 0.983	p < 0.982
Male n = 5 of 34 versus n = 5 of 34	p < 1.000	p < 1.000	p < 1.000
with pAAa n = 25 vs. without pAAa n = 9 of 34	p < 0.600	p < 0.785	p < 0.992
Female n = 20 of 25 versus n = 9 of 9	p < 0.997	p < 0.954	p < 0.955
Male n = 5 of 25 versus n = 0 of 9	-	-	-

Table 2: *The statistical correlations ("p" values of significance) between female and male RA patients with and without sAAa or pAAa.*

Glossary to table 2: *RA: Rheumatoid Arthritis; sAAa: Systemic AA Amyloidosis; pAAa: Pulmonary AA Amyloidosis (Amyloid A deposits in the lungs).*

Table 3 and figure 1 summarize the quantitative differences of amyloid A deposits in the lungs of 34 RA patients.

In 9 (26.47%) of 34 RA patients with sAAa there was no amyloid A deposition in the lungs, these represent a latent stage of pulmonary amyloidosis (the amount of amyloid A deposits was: 0.00).

In 11 (32.35%) of 34 RA patients with pAAa, the average amount of amyloid A deposits of the lungs were less than < 0.4 and were regarded as "mild"; in 14 (41.18%) of 34 patients were more than 0.4 ≤, and were considered as "severe" (Table 3).

	Pr n⁰/	Sex	a	I	BM-Br	BM-Lob	A	AA	BmPlob	V	ret	v	VV	n	Avg	CoD	Cl+/Cl-
1	45/74	f	0	0	0	0	0	0	0	0	0	0	0	0	0	cAAa	
2	162/78	f	0	0	0	0	0	0	0	0	0	0	0	0	0		
3	76/79	f	0	0	0	0	0	0	0	0	0	0	0	0	0		
4	90/85	f	0	0	0	0	0	0	0	0	0	0	0	0	0		
5	243/87	f	0	0	0	0	0	0	0	0	0	0	0	0	0	cAAa	
6	240/88	f	0	0	0	0	0	0	0	0	0	0	0	0	0		
7	306/90	f	0	0	0	0	0	0	0	0	0	0	0	0	0	rAAa	Cl+
8	287/91	f	0	0	0	0	0	0	0	0	0	0	0	0	0	cAAa	
9	183/92	f	0	0	0	0	0	0	0	0	0	0	0	0	0		
10	155/87	f	1	0	0	0	0	0	0	0	0	0	0	0	0,083		
11	395/76	f	1	1	0	0	0	0	0	0	0	0	0	0	0,167	cAAa	
12	266/78	f	0	1	0	1	0	0	0	0	0	0	0	0	0,167		
13	430/80	f	1	1	0	0	0	0	0	0	0	0	0	0	0,167	cAAa	
14	322/81	f	1	0	0	0	1	0	0	0	0	0	0	0	0,167	cAAa	
15	226/85	f	1	0	1	0	0	0	0	0	0	0	0	0	0,167		
16	342/86	m	1	1	0	0	1	0	0	0	0	0	0	0	0,25	rAAa	
17	245/88	f	1	1	0	0	1	0	0	0	0	0	0	0	0,25	cAAa	
18	232/74	m	1	1	1	0	1	0	0	0	0	0	0	0	0,333	rAAa	Cl+
19	367/75	f	1	1	1	0	1	0	0	0	0	0	0	0	0,333	cAAa	
20	39/76	f	1	1	1	1	0	0	0	0	0	0	0	0	0,333	rAAa	
21	80/80	f	1	1	1	1	0	1	0	0	0	0	0	0	0,417	rAAa	Cl+
22	265/80	f	0	1	0	2	1	1	0	0	0	0	0	0	0,417	rAAa	Cl+
23	V/T	f	2	0	2	0	1	0	0	0	0	0	0	0	0,417	rAAa	
24	203/88	f	2	1	2	2	1	1	0	0	0	0	0	0	0,75	rAAa	
25	52/92	f	2	2	1	0	2	1	0	0	0	0	0	1	0,75		
26	73/87	f	2	1	1	2	2	0	0	1	0	1	0	0	0,833	rAAa	Cl+
27	101/90	f	2	1	2	2	0	1	0	1	1	0	0	0	0,833	rAAa	
28	237/70	f	2	2	2	2	2	1	0	0	0	0	0	0	0,917	rAAa	
29	137/76	f	2	2	2	2	1	0	1	0	1	0	0	0	0,917	rAAa	Cl+
30	255/83	f	2	1	2	2	2	1	0	0	1	0	0	0	0,917	rAAa	Cl+
31	174/88	f	2	2	2	2	2	1	0	0	0	0	0	0	0,917	rAAa	
32	43/85	m	2	2	2	2	2	2	1	0	1	0	0	0	1,167	rAAa	
33	53/87	m	2	2	2	2	2	1	1	1	0	1	0	0	1,167	rAAa	Cl+
34	181/80	m	3	3	3	3	2	1	3	2	0	0	1	0	1,75	rAAa	Cl+
	Count		34	34	34	34	34	34	34	34	34	34	34	34	34	25	9
	Sum		36	29	28	26	25	12	6	5	4	2	1	1	14,58		
	Avg		1,059	0,853	0,824	0,765	0,735	0,353	0,176	0,147	0,118	0,059	0,029	0,029	0,429		

	SD		0,886	0,821	0,936	0,987	0,828	0,544	0,576	0,436	0,327	0,239	0,171	0,171	0,445		
	0 value		11	13	17	20	17	23	30	30	30	32	33	33	9		
	+ value		23	21	17	14	17	11	4	4	4	2	1	1	25		
	Prevalence %		67,647	61,765	50	41,176	50	32,353	11,765	11,765	11,765	5,882	2,941	2,941	73,529		
	Severity%		35,294	28,431	27,451	25,49	24,51	11,765	5,882	4,902	3,922	1,961	0,98	0,98	14,297		

Table 3: *Prevalence and extent of amyloid A deposits in lungs of 34 RA patients with sAAa arranged according to the increasing values of average amounts of amyloid A deposits/patient (horizontal lines) and A deposits/structure (vertical columns).*

Remarks to table 3: *Pr n0/y: Protocol number/year; CoD: Cause of Death: rAAa: Uremia due to massive amyloid A deposition in the kidneys with renal insufficiency (n = 17), cAAa: Lethal outcome exclusively caused by cardiac amyloidosis (n = 3) (430/80, 322/81, 45/74); cAAa: Cardiac amyloidosis only contributed to the death (n = 5) (243/87, 287/91, 367/75, 395/76, 245/88); 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); BM: Basement Membrane; (BM-Br): Peribronchial; BM-Lob: Perilubular; BM-pLob: Panlobular; n: Nerve.*

In patients with mild and severe pAAa, the amyloid A deposition in the lungs after an early latent stage ran basically parallel, and showed a linear growth curve; development of pAAa was continuously steady, except for the end stage of the disease with extremely severe amyloid A deposits (Table 3 and figure 1).

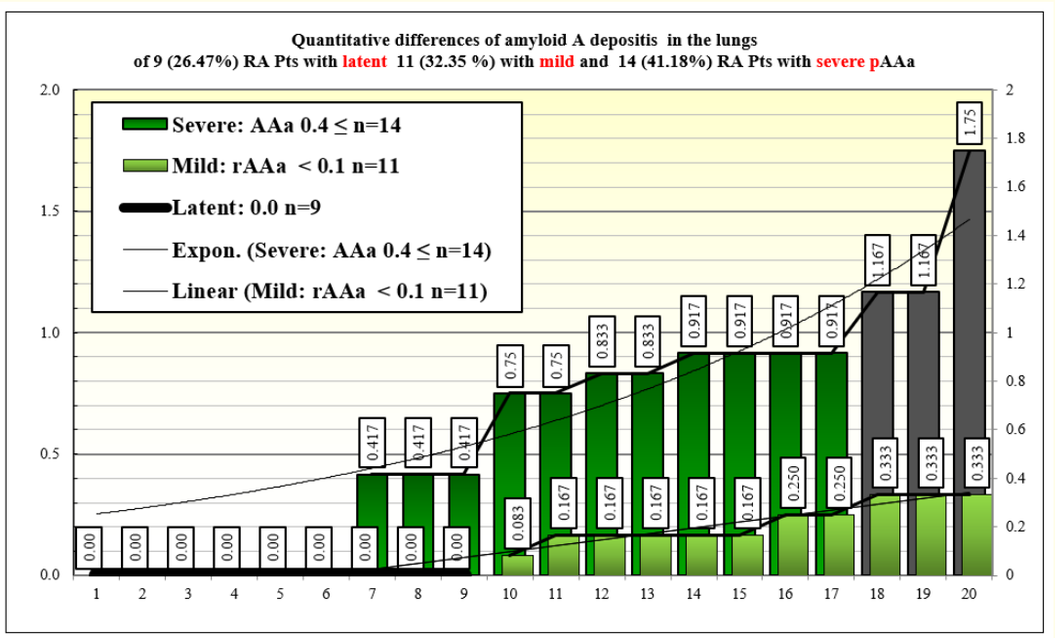

Figure 1: *Mean amount of amyloid A of the lungs in early, advanced, late and end stages of pAAa according to increasing "severity" ("average amount of amyloid A deposits/patient").*

Legend to figure 1: Cohort of 34 RA patients with pAAa. In 9 (26.47 %) of 34 RA patients complicated with sAAa there was no amyloid A deposition in the lungs, these represent a latent stage of pulmonary amyloidosis (the amount of amyloid A deposits was: 0.00); in 11 (32.35 %) patients with mild amyloidosis the amount of amyloid A deposits was: 0.083 - 0.333, and in 14 (41.18 %) patients with severe pulmonary amyloid A deposition the amount of amyloid A deposits was: 0.417 - 1.75 (Table 3). In the last 3 of these 14 patients with severe pAAa the amyloid A deposition was extremely severe and exceeded the average amount of 1.0, these represent the terminal (end) stage of pulmonary amyloidosis. The increment with mild and severe pAAa showed a basically linear growth curve, representing the same rate of amyloid A deposition, except in 3 patients with extremely severe pAAa; in these the increment was exponential.

The prevalence and amount of amyloid A deposits in different tissue structures of the lung run parallel to each other. The frequently involved tissue structures showed marked deposits of amyloid. Deposits were less striking in less frequently involved tissue structures.

Differences were only found for perilobular basement membrane and small arteries, in which the sequence was inverse (Table 3 and figure 2).

Quantitative differences (prevalence and extent) of amyloid A deposits in different tissue structures of lungs with pAAa are summarized in figure 2.

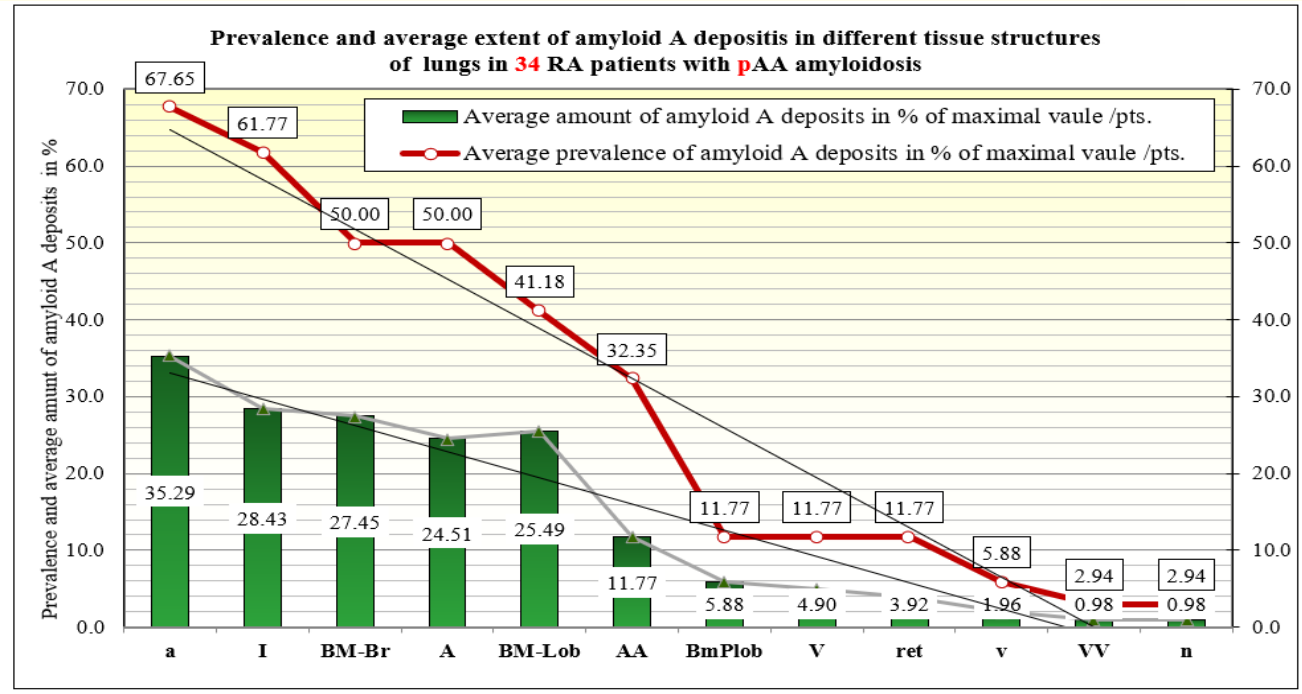

Figure 2: *Prevalence and extent of amyloid A deposits in different tissue structures of the lungs (in % of maximal value/patients). Legend to figure 2: Prevalence and amount of amyloid A deposits in different tissue structures of the lungs changed basically parallel except the perilobular basement membranes (BM-Lob), and small arteries (A) in which it was inverse (Table 3).*

Detectable amounts of amyloid A deposits in different tissue structures of the lungs did not appear simultaneously. In the early stage of pAAa there were histologically detectable amyloid deposits only in a few structures (arterioles, interstitial collagen fibers, peribronchial basement membranes), and in advanced stages more structures (small arteries, perilobular basement membranes, medium size arteries) were involved. In other structures of the lungs (diffuse panlobular involvement of basement membranes, small veins, reticulin fibers, venules, medium size veins, and nerves) deposits were seen only in late stages of amyloidosis (with massive involvement of the former figure 3).

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 different structures of the lung (according to prevalence) are demonstrated in figure 3.

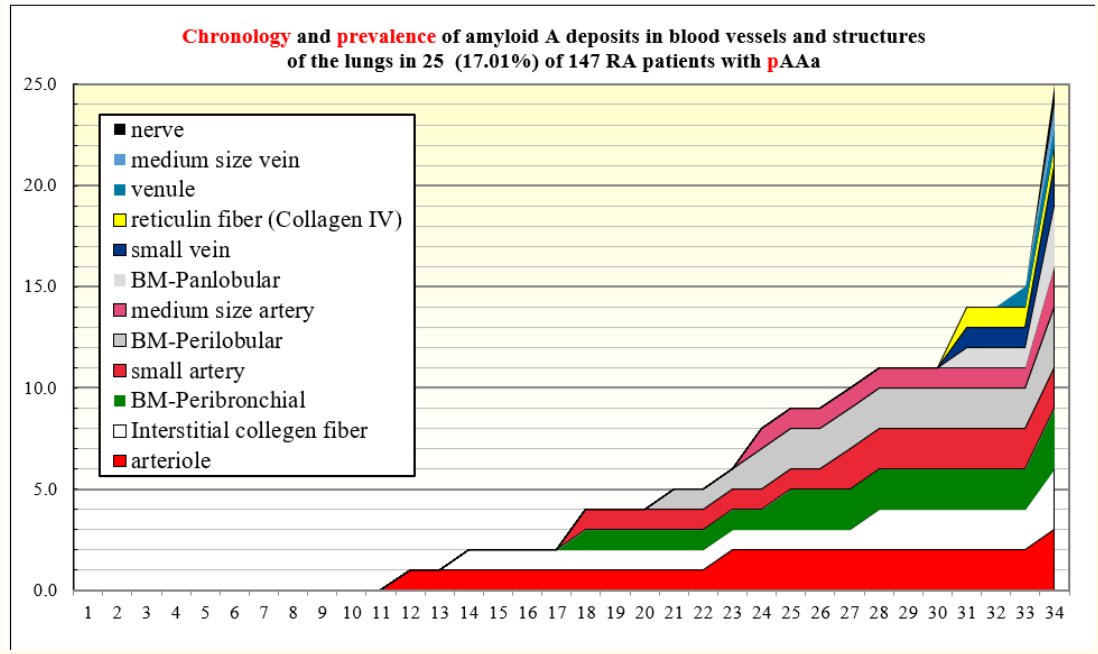

Figure 3: *Chronology of amyloid A deposition in different structures of the lungs in 25 (73.53%) of 34 RA patients with pAAa arranged according to the decreasing values of prevalence of amyloid A deposits/structure.*

Legend of figure 3: Amyloid A deposits in different tissue structures of the lungs arranged according to their increasing prevalence. Amyloid A deposition did not start at the same time in different tissue structures of the lungs. The amount of amyloid A deposits in different tissues increased simultaneously, the rate was constant and independent of the stage of amyloidosis.

The quantitative differences of amyloid A deposits in six organs in 34 of 147 RA patients are summarized in table 4 and figure 4.

	f/m	Pr n⁰/y	Kidney	Heart	Pancr	Liver	Lung	Brain	Avg	Total	Avg %	CoD	Cl+/-
1	f	155/87	0,000	0,000	0,000	0,000	0,083	0,000	0,014	0,083	0,461		
2	f	240/88	0,000	0,000	0,100	0,000	0,000	0,000	0,017	0,100	0,556		
3	f	76/79	0,250	0,000	*	0,000	0,000	0,000	0,050	0,250	1,667		
4	f	243/87	0,000	0,400	0,100	0,000	0,000	0,000	0,083	0,500	2,778	cAAa	
5	f	287/91	0,083	0,500	0,400	0,000	0,000	0,000	0,164	0,983	5,461	cAAa	
6	f	183/92	0,667	0,000	0,500	0,111	0,000	0,000	0,249	1,495	8,306		
7	f	266/78	0,333	0,500	*	0,111	0,167	0,000	0,249	1,495	8,306		
8	f	430/80	0,417	0,600	0,200	0,111	0,167		0,256	1,278	8,520	cAAa	
9	f	226/85	0,417	0,400	0,400	0,111	0,167		0,278	1,111	9,258		
10	f	395/76	0,250	1,200	0,000	0,111	0,167	0,000	0,288	1,728	9,600	cAAa	
11	f	162/78	0,083	1,100	0,550	0,111	0,000	0,000	0,307	1,844	10,244		
12	f	306/90	0,750	0,800	0,400	*	0,000	0,000	0,390	1,950	13,000	rAAa-U	Cl+
13	f	45/74	0,000	1,400	0,800	0,444	0,000	0,000	0,441	2,644	14,689	cAAa	
14	m	342/86	0,750	1,100	0,300	0,333	0,250	0,000	0,447	2,234	14,893	rAAa-U	

15	f	80/80	0,750	0,400	*	0,667	0,417	0,000	0,456	2,733	15,183	rAAa-U	Cl+
16	f	52/92	0,667	1,000	0,650	0,000	0,750	0,000	0,511	3,067	17,039		
17	f	322/81	0,833	0,700	1,000	0,556	0,167	0,000	0,543	3,256	18,089	cAAa	
18	f	203/88	0,667	1,000	0,700	0,167	0,750	0,000	0,547	3,284	18,244	rAAa-U	
19	f	39/76	1,500	0,400	1,200	0,667	0,333	0,000	0,683	4,100	22,778	rAAa-U	
20	f	90/85	0,917	1,400	0,100	1,778	0,000	0,000	0,699	4,195	23,306		
21	f	265/80	1,500	1,400	0,000	0,889	0,417	0,000	0,701	4,206	23,367	rAAa-U	Cl+
22	f	245/88	1,000	1,500	1,100	0,556	0,250	0,000	0,734	4,406	24,478	cAAa	
23	f	V/T	*	1,300	*	1,111	0,417	0,000	0,930	5,578	30,989	rAAa-U	
24	m	232/74	1,833	1,300	0,600	1,000	0,333		0,943	2,828	31,422	rAAa-U	Cl+
25	f	367/75	2,167	0,900	1,400	0,778	0,333	0,000	0,970	5,822	32,344	cAAa	
26	m	43/85	1,083	1,000	1,350	1,222	1,167		1,013	5,066	33,773	rAAa-U	
27	f	137/76	1,583	1,400	1,000	*	0,917	0,000	1,044	6,261	34,783	rAAa-U	Cl+
28	f	73/87	1,417	1,600	1,300	1,111	0,833	0,000	1,087	6,523	36,239	rAAa-U	Cl+
29	f	174/88	1,917	1,000	1,800	0,889	0,917		1,225	4,900	40,833	rAAa-U	
30	f	237/70	2,250	*	*	1,222	0,917	0,000	1,303	7,817	43,428	rAAa-U	
31	f	101/90	1,917	2,400	2,000	0,667	0,833	0,000	1,375	8,250	45,833	rAAa-U	
32	f	255/83	2,083	1,600	1,650	2,000	0,917		1,463	4,389	48,767	rAAa-U	Cl+
33	m	53/87	2,667	2,300	1,900	1,000	1,167		1,807	9,034	60,227	rAAa-U	Cl+
34	m	181/80	1,917	1,500	2,900	1,556	1,750		1,925	9,623	64,153	rAAa-U	Cl+
Count			33	33	29	32	34	26	34			25	9
Sum			32,67	32,10	24,40	19,28	14,59	0,00	23,19				
Average			0,990	0,973	0,841	0,602	0,429	0,000	0,682				
SD			0,783	0,611	0,724	0,567	0,445	0,000	0,506				
0 values n			4	4	3	6	9	26	0				
+ values n			29	29	26	26	25	0	34				
Prevalence %			87,88	87,88	89,66	81,25	73,53	0,000	100,00				
Severity %			33,00	32,42	28,05	20,08	14,30	0,000	22,736				
	Sex	Pr n^0/y	Kidney	Heart	Pancr	Liver	Lung	Brain	Avg	Total	Avg %	CoD	Cl+/-

Table 4: *Average amount of amyloid A deposits in different organs of 34/147 RA patients with sAAa arranged according to the increasing values of average amounts of amyloid A deposits/patient (horizontal lines) and amyloid A deposits/organ (vertical columns).*

Remarks to table 4: *Pr n /year: Number of autopsy protocol/year; CoD: Cause of death: rAAa-U: Uremia due to massive amyloid A deposition in the kidneys with consecutive renal insufficiency (n = 17), cAAa: Lethal outcome exclusively caused by cardiac amyloidosis (n = 3); cAAa: Contribution of cardiac amyloidosis to the death (n = 5); Cl+: Clinically recognized; Cl- : Clinically not recognized; f: Female; m: Male; Avg: Average; SD: Standard Deviation; *: Tissue blocks were not available.*

In the lungs the amyloid A deposition (pAAa) started later than systemic amyloid A deposition in other organs of RA patients with sAAa. Development of sAAa and pAAa was steady and showed consistently a linear growth curve. In the terminal stage of the disease the increment in various organs (sAAa) and in the lung (pAAa) was exponential.

Amyloid A deposition in the lungs (pAAa) compared to other organs of RA patients (sAAa) is demonstrated on figure 4.

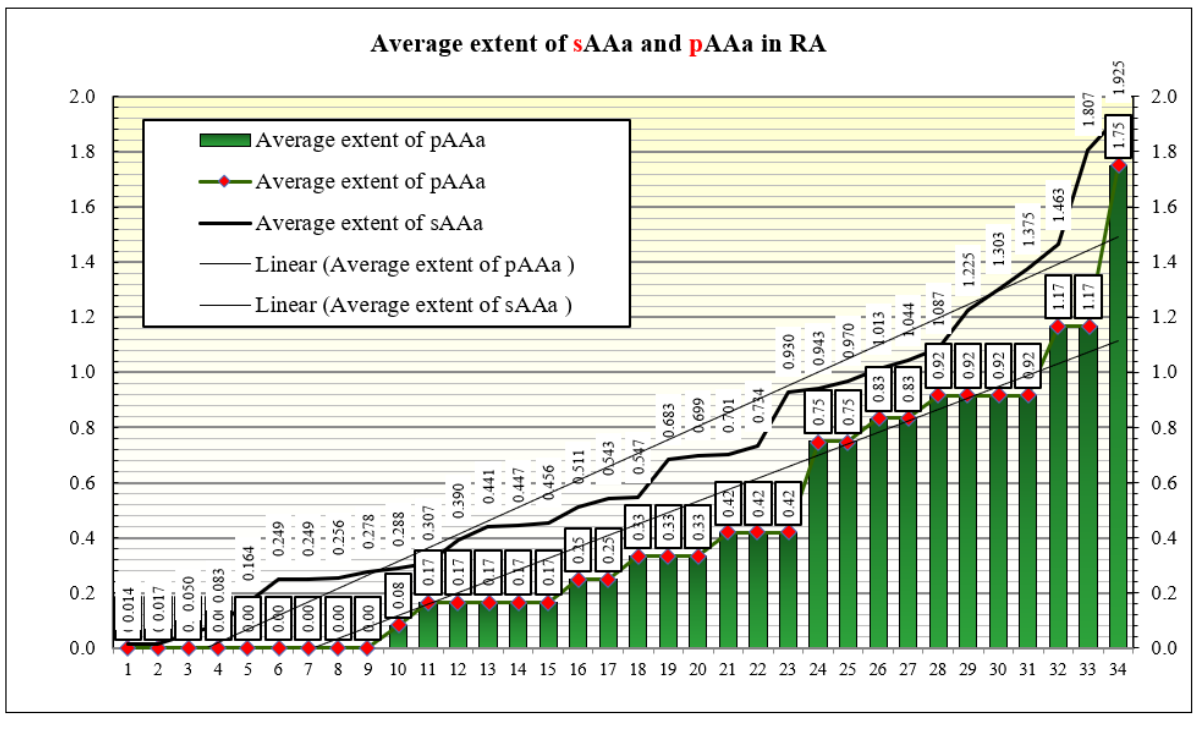

Figure 4: *Cohort of 34 RA patients with sAAa and pAAa according to increasing "severity" ("average amount of amyloid A deposits/patient").*

Legend to figure 4: "Average amount of amyloid A deposits/patient" with sAAa of six organs and pAAa at death according to increasing values of amyloid A deposits. The sAAa showed basically a linear growth curve, except in the terminal stage of the disease, in which the increment was exponential. The amount of amyloid A deposits in lungs (pAAa) increased gradually after a latent stage and showed basically a lineal growth curve like the systemic amyloid A deposition. The advanced stage of pAAa was characterized by an intensive amyloid A deposition, and the late (terminal) stage by an abrupt exponential increment of amyloid A.

sAAa (n = 34) was associated with purBr or BrPn in 2 (11.11%) of 18, and with IPn in 14 (34.29%) of 35 patients.

pAAa (n = 25) was associated with purBr or BrPn in 1 (5.55%) of 18, and with IPn in 12 (34.29%) of 35 patients.

The coincidence (overlap) between sAAa or pAAa and InfPn was in 1 (20.0%) of 5, OblPn in 2 (100.0%) of 2, RhPn in none (0.0%) of 3 patients.

sAAa did not influenced the prevalence of purBr or BrPn ($c^* = -0.4504$, $\chi^2 = 0.9850$, $p < 0.32$), InfPn ($c^* = -0.0954$, $\chi^2 = 0.1374$, $p < 0.71$), RhPn ($c^* = -1.0$, $\chi^2 = 0.0719$, $p < 0.79$) or OblPn ($c = 1.0$, $\chi^2 = 3.0683$, $p < 0.08$) (asterisk indicates negative value of association's coefficient).

The relationship between pAAa and purBr or BrPn ($c^* = -0.0906$, $\chi^2 = 1.8933$, $p < 0.29$), InPn ($c = 0.1028$, $\chi^2 = 0.1800$, $p < 0.67$) or RhPn ($c^* = -1.0$, $\chi^2 = 0.0003$, $p < 0.98$) was not significant, moreover the negative association's coefficients indicate inverse relationships.

There was a significant and positive correlation between sAAa and IPn (c = 0.5082, χ^2 = 7.3538, p < 0.007) or between pAAa and lPn (c = 0.5978, χ^2 = 9.7171, p < 0.002), furthermore between pAAa and OblPn (c = 1, χ^2 = 4.8313, p < 0.03).

In table 5 the statistical links are summarized between sAAa (n = 34) or pAAa (n = 25) and coexisting complications or associated diseases in 147 RA patients.

The prevalence of complications or associated diseases in 147 RA pts with or without sAAa	The coexistent complications or associated diseases in RA pts with sAAa (n = 34)	The statistical links between sAAa and complication or associated disease in 147 RA pts	The co-existent complications or associated diseases in RA pts with pAAa (n = 25)	The statistical links between pAAa and complication or associated disease in 147 RA pts
purBr or BrPn: n = 18 (12.24 %) of 147	purBr or BrPn: n = 2 (11.1 %) of 18	c*: -0.4504 χ^2 = 0.9850, p < 0.32	purBr or BrPn: n = 1 (5.55 %) of 18	c*: -0.5906 χ^2 = 1.0933, p < 0.295
InfPn: n = 5 (3.4 %) of 147	InfPn: n = 1 (20.0 %) of 5	c*: -0.0954 χ^2 = 0.1374, p < 0.71	InfPn: n = 1 (20.0 %) of 5	c: 0.1028 χ^2 = 0.1800, p < 0.61
OblPn: n = 2 (1.4 %) of 147	OblPn: n = 2 (100.0 %) of 2	c: 1.000 χ^2 = 3.0683, p < 0.079	OblPn: n = 2 (100.0 %) of 2	**c: 1.0000** χ^2 = 4.8313, p < 0.028
RhPn: n = 3 (2.1 %) of 147	RhPn: n = 0 (0.0 %) of 3	c*: -1.0 χ^2 = 0.0719, p < 0.78	RhPn: n = 0 (0.0 %) of 3	c*: -1.0 χ^2 = 0.0003, p < 0.99
IPn: n = 35 (23.8 %) of 147	IPn: n = 14 (40.0 %) of 35	**c: 0.5082** χ^2 = 7.3538, p < 0.007	IPn: n = 12 (34.28 %) of 35	**c: 0.5978** χ^2 = 9.7171, p < 0.002

Table 5: *The influence of sAAa or pAAa on the prevalence of coexistent complications or associated diseases in 147 RA patients.*

Glossary and legend to table 5: *c: Association coefficient; *: Asterisk indicates negative value of association's coefficient (inverse relationship between sAAa or pAAa and complications or associated disease of the lungs in 147 RA patients).*

Bold indicates significant value.

There was a significant and positive correlation.

Between pAAa and prevalence of OblPn (c = 1, c^2 = 4.8313, p < 0.03) and Between sAAa and IPn (c = 0.5082, c^2 = 7.3538, p < 0.007) or pAAa and IPn (c = 0.5978, c^2 = 9.7171, p < 0.002).

Amyloid A deposits in the lungs are demonstrated in figure 5-8.

Original magnifications correspond to the 24x36 mm transparency slide; the correct height: width ratio is 3:2. The printed size may be different; therefore, it is necessary to indicate the original magnifications.

Discussion

Amyloidosis syndromes are systemic or localized disorders characterized by the extracellular deposition of chemically heterogeneous fibrillar proteins [12-14]. To date 36 distinct precursor proteins have been identified in humans [14,15]. Pulmonary amyloidosis may be a part of systemic amyloidosis or localized (isolated) one [16].

The most common form of pulmonary amyloidosis is the systemic primary AL or AH amyloidosis (Amyloid Light chain or Heavy chain amyloidosis) [17]. AL or AH amyloidosis is characterized by immunoglobulin light chain-λ (Lλ) or light chain-κ (Lκ) deposition or by im-

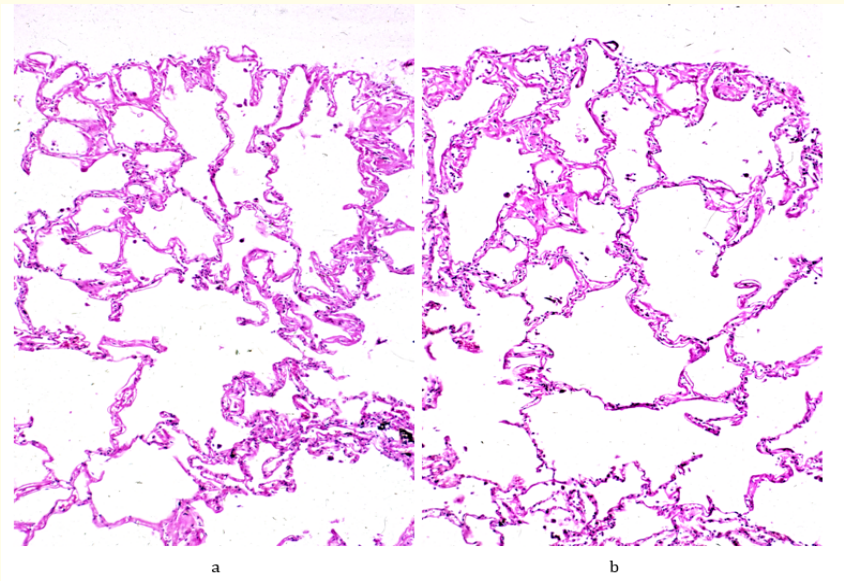

Figure 5a and 5b: *Rheumatoid arthritis, lung, early stage of pAA. Amyloid deposited within interstitial reticular and collagen fibers, and along alveolar basal membranes. (a) HE, x 50, (b) same as (a) x125.*

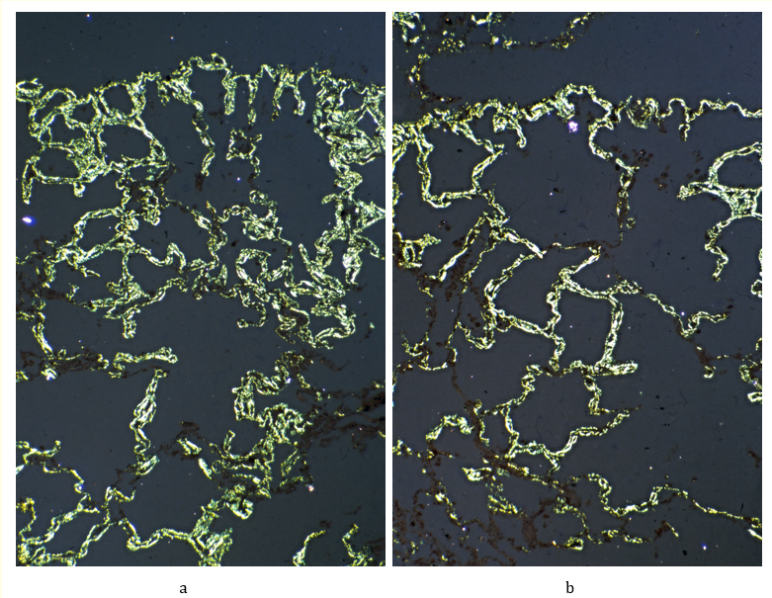

Figure 6a and 6b: *Rheumatoid arthritis, lung, early stage of pAA. Same as figure 5a-5b, Congo red staining, without alcoholic differentiation, covered with gum arabic. Viewed under polarized light (a) x50 (b) x125.*

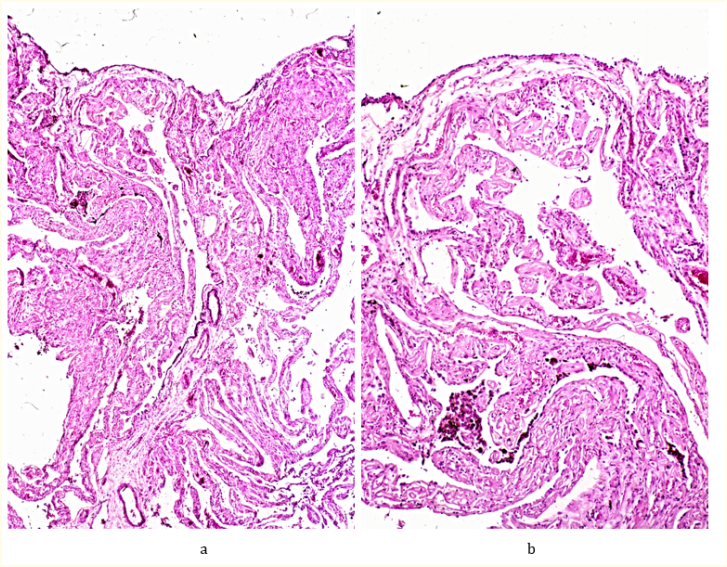

Figure 7a and 7b: *Rheumatoid arthritis, lung, late stage of pAA. Massive secondary amyloid deposition within widened interstitial areas of the lung along reticular, collagen fibres, and alveolar basal membranes. (a) HE, x 50, (b) same as (a) x125.*

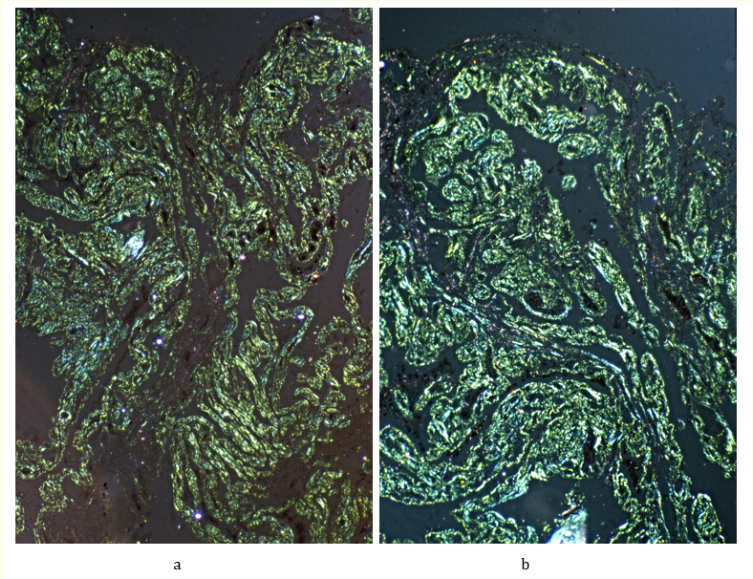

Figure 8a and 8b: *Rheumatoid arthritis, lung, late stage of pAA. Same as figure 7a-b, Congo red staining, without alcoholic differentiation, covered with gum arabic. Viewed under polarized light (a) x50 (b) same as (a) x125.*

munoglobulin heavy chain deposition of IgG, IgA, IgM or IgD classes. AL or AH amyloidosis is associated with myeloma, B-cell dyscrasia or Waldenstrom's macroglobulinemia [18].

Localized (nodular) form of AL λ-, or AL κ-chain amyloidosis (Amyloid Light λ-, or κ-chain amyloidosis) is characterized by isolated immunoglobulin light chain-λ (Lλ) or light chain-κ (Lκ) deposition, and caused by isolated (solitary) plasmacytoma or B-cell dyscrasia.

Systemic (secondary, reactive) AA amyloidosis (Amyloid A amyloidosis) with amyloid A deposition occurs in a wide spectrum of chronic inflammatory diseases [19-21], such as chronic microbial infections: tuberculosis, leprosy, fibrocystic lung diseases, bronchiectasis, lung abscess, chronic osteomyelitis, chronic xanthogranulomatous pyelonephritis, chronic mesenteric lymphadenitis, decubitus, etc. chronic reactive inflammatory diseases: ankylosing spondylitis, psoriatic arthropathies, Reiter's syndrome, etc. autoimmune (inflammatory) diseases: rheumatoid arthritis, juvenile chronic arthritis, adult Still's disease, systemic lupus erythematodes, progressive systemic sclerosis, Crohn's disease, ulcerative colitis, polymyositis, polymyalgia rheumatica or giant-cell arteritis (GCA), etc., and in association with chronic cachectic diseases or malignancies: renal cell carcinoma, ovarian carcinoma, hepatocellular adenoma, bronchial carcinoma, Hodgkin's disease, cardiac (atrial) myxoma, etc.

Three forms of pulmonary amyloidosis are distinguished by the traditional regional approach [22]: nodular pulmonary amyloidosis (caused by isolated solitary plasmocytoma or B-cell dyscrasia), diffuse alveolar-septal, and tracheobronchial amyloidosis (as manifestations of primary AL, AH, senile, secondary AA or other forms of systemic amyloidosis).

Assording to our data amyloid A deposition is more widespread and does not affect only the alveolar-septal or peribronchial regions. All tissue structures of the lungs may be involved including blood vessels of different calibers, etc.

Amyloid A deposition is a progressive, cumulative process, initially involving only a few structures, and increasingly more in later stages of the disease [12,23,24].

Development of mild and severe amyloidosis represent different aspects of the same process, based on the linear growth course of amyloid A deposition (Figure 2). Mild and severe deposition of amyloid A is determined basically by the production of precursors. 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 genetic and/or other factors.

Prevalence and severity of amyloid A deposits in different tissue structures of the lungs signify different aspects of the same pathological process which usually run parallel to each other (Figure 3). Amyloid A deposition starts in the most frequently involved structures of the most frequently involved organs (Figure 3) [12,23,24]. Chronological approach of amyloid A deposition in different tissue structures of the lungs allows an indirect assessment of the stage of pAAa.

The main complications of RA such as sAAa, and amyloid A deposition in different tissue structures of the lungs (pAAa) may influence the prevalence, clinical course and symptoms of lung diseases. Knowledge of these relationships is important to estimate the relative danger they potentially represent. The significant correlation between sAAa or pAAa and IPn propose a positive influence of amyloid A deposition on IPn. The role of sAAa may be indirect on lung diseases based on the strong positive relationship between sAAa and pAAa. The significant correlation between pAAa and OblPn seems to be more direct. The statistically not significant correlations between sAAa or pAAa and purBr or BrPn, InfPn and RhPn suggest that these are independent entities which are not influenced by sAAa or pAAa.

From a prognostic point of view, amyloid A deposition in the lungs did not prove to be a very serious, life-threatening complication of RA. It can be asymptomatic or may present nonspecific symptoms such as progressive dyspnea, cough, wheezing and rarely respiratory failure [17], by blocking gas exchange in alveolar structures [16].

Conclusion

Systemic AAa (sAAa) is related to the cardiovascular system, and pulmonay AAa (pAAa) is connected with it. In sAAa the amyloid A deposition in the lungs starts after a latent stage. Systemic or pulmonary amyloid A deposition is a progressive and cumulative process, involving in its early stage only a few structures in the lungs, and increasingly more in later stages of the disease. Amyloid A deposition starts in the most frequently involved structures of the lungs with more massive deposits. The chronology of amyloid A deposition allows an indirect assessment of the stage of pAAa, which may have a prognostic value in biopsies.

sAAa or pAAa may develop in both sexes, and at any time in the course of RA. According to our study interstitial pneumonia (IPn) is influenced by sAAa or pAAa. The relatiomship between pAAa and obliterative pneumonia (OblPn) seems to be more direct. Lung diseases, such as purulent bronchitis or bronchiolitis (purBr), bronchopneumonia (BrPn), infarctpneumonia (InfPn), rheumatoid pneumonia (RhPn) are independent entities.

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