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Research Article

Basic Rules of Amyloid A Deposition in Rheumatoid Arthritis - A Postmortem Clinicopathologic Study of 161 Autopsied Patients

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Abstract

The authors summarize the basic rules of amyloid deposition on different tissue structures of eight organs in 34 RA patients with systemic (secondary) AA amyloidosis, highlighted with amyloid deposition in the gastrointestinal tract.

Keywords: *Rheumatoid Arthritis; Systemic AA Amyloidosis; Gastrointestinal Amyloid Deposition*

Background

Systemic AA amyloidosis (sAAa) is one of the main and most insidious complications of rheumatoid arthritis (RA).

Amyloidosis is a progressive cumulative process, in its early stage only a few structures in some organs are affected, and in later stages of the disease increasingly more will be involved [1,2].

Objectives of the Study

The aim of this study was to detect the amount and increase of amyloid A deposits on different tissue structures of various organs in patients with clinically diagnosed rheumatoid arthritis (RA).

Patients and Methods

The amyloid A deposits were assessed in eight organs (kidneys, heart, pancreas, GI tract, liver, lungs, skin and brain) of 161 autopsy patients (females 116, average age 64.95 years, range 16-87, average disease duration 14.79 years, onset of RA 50.19; males 45, average age 66.27 years, range 19-88, average disease duration 13.46 years at death, onset of RA 52.57).

Amyloid A was specified histologically according to Romhányi [3] by a modified, more sensitive Congo red staining [4].

The amount of amyloid A deposition was determined by semi-quantitative, visual estimation on a 0 to 3 plus scale, based on the number of involved blood vessels and tissue structures in various organs per light microscopic field (x40 objective of an Olympus BX51) [1].

Results and Discussion

Systemic AA amyloidosis (sAAa) complicated RA in 34 (21.12%) of 161 patients (females 29, average age 64.34 years, range 32-83, average disease duration 15.70 years, onset of RA 48.56; males 5, average age 51.20 years, range 19-88, average disease duration 14.75 years at death, onset of RA 53.94).

Tissue blocks of stomach, small and/or large intestine of gastrointestinal tract (GI tract) were available in 31 (91.17% of 34, and 19.25% of 161) patients with sAAa.

In 2 (6,45%) of 31 RA patients with sAAa there was no amyloid A deposition in the GI tract; this was considered a "latent" stage of gastrointestinal AA amyloidosis (giAAa); the amount of AA deposits was: 0.00.

In 13 (41.94%) of 31 patients amyloid A deposits were mild (< 0.65). in 13 (41.94%) severe, and in further 3 (9.68%) patients extremely severe (> 1.5).

Amyloid A protein deposition did not start at the same time on different tissue structures of various organs, but subsequently the amount of deposited amyloid A protein increased simultaneously on all tissue structures of all investigated organs (Figures, table 1 and 2).

The prevalence and amount of AA deposits on different tissue structures of various organs ran basically parallel to each other, and the tendency was the same in all patients.

The amounts of deposited amyloid A protein varied, but the proportion of deposits on different tissue structures of various organs was basically constant, independent of the stage of amyloidosis (Figures, table 1 and 2).

Figure 1 and table 1 demonstrate the progressive deposition of amyloid A in eight organs, arranged according to their decreasing severity in % of the total number of surgical specimens.

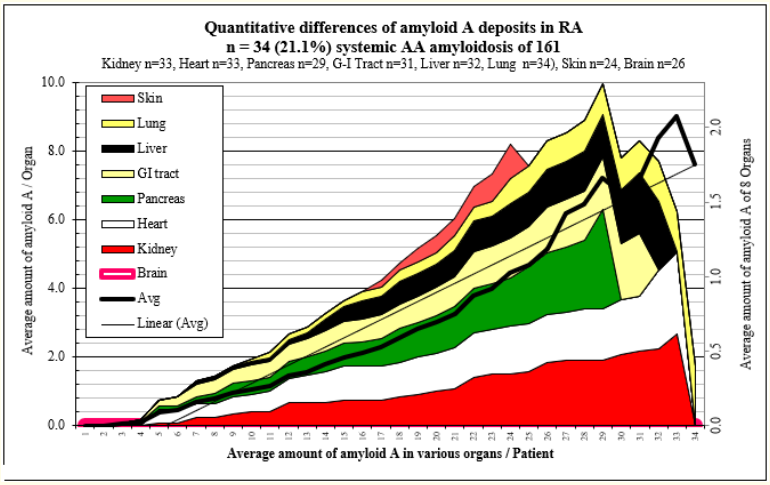

Figure 1

	Kidney	Heart	Pancreas	GI tract	Liver	Lung	Skin	Brain	Av/8 organs
Prevalence %	87,879	87,879	89,655	93,548	81,25	73,529	33,333	0	94,118
Severity %	32,998	32,424	28,046	24,785	20,025	14,3	5,833	0	24,713

Table 1

Figure 2 and table 2 demonstrate the progressive deposition of amyloid A on the blood vessels and different tissue structures of the GI tract, arranged according to their decreasing severity in % of the total number of surgical specimens.

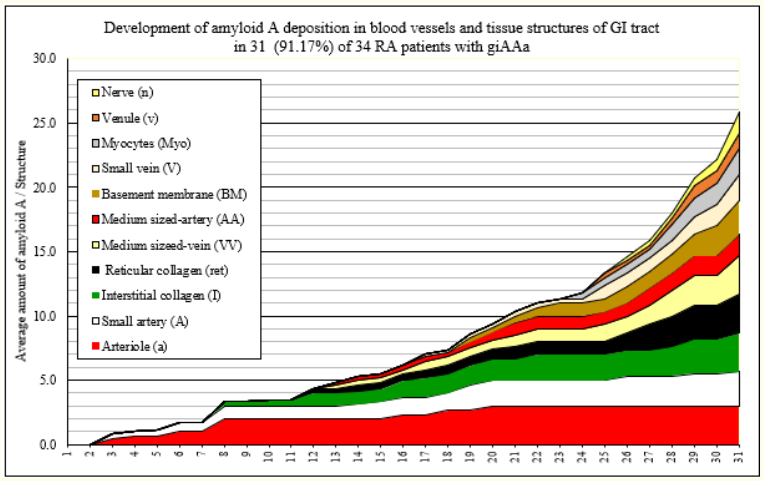

Figure 2

	Vaginal Cerclage[a] n = 81	Abdominal Cerclage[a] n = 15	P-value	History Indicated Cerclage n = 42	Ultrasound Indicated Cerclage n = 41	P-value
Mean age ± SD (years)	32.9 ± 5.1	33.1 ± 3.9	p = 0.875	33.7 ± 5.6	32.1 ± 4.1	p = 0.143
Median BMI (IQR)	27.1 (20.15-34.05)	26.5 (19.9-33.1)	p = 0.428	29 (23.2-34.8)	26.5 (18.3-34.7)	p = 0.353
Ethnicity White Asian Black	 63 (77.8%) 12 (14.8%) 6 (7.4%)	 15 (100.0%) 0 0	p = 0.129	 30 (71.4%) 7 (16.7%) 5 (11.9%)	 35 (85.4%) 5 (12.2%) 1 (2.4%)	p = 0.185
Smoker	11 (13.6%)	3 (20.0%)	p = 0.454^	4 (9.5%)	7 (17.1%)	p = 0.350^
Previous cervical surgery	30 (37.0%)	12 (80.0%)	p < 0.001	9 (21.4%)	23 (56.1%)	p < 0.013
Parity Nulliparous Multiparous	 24 (29.6%) 57 (70.4%)	 8 (53.3%) 7 (46.7%)	p = 0.133^	 9 (21.4%) 33 (78.6%)	 16 (39.0%) 25 (61.0%)	p = 0.098^

Previous MTL	31 (38.3%)	4 (26.7%)	p = 0.391	23 (54.8%)	12 (29.3%)	p = 0.019
Previous PPROM	30 (37.0%)	4 (26.7%)	p = 0.563^	20 (47.6%)	13 (31.7%)	p = 0.180^
Previous sPTL	35 (43.2%)	2 (13.3%)	p = 0.041^	20 (47.6%)	16 (39.0%)	p = 0.509^
Previous Cerclage	24 (29.6%)	3 (20.0%)	p = 0.545^	24 (57.1%)	2 (4.8%)	p < 0.001^

Table 2: *Maternal demographics and prior pregnancy history for abdominal and vaginal cerclages, and history and ultrasound indicated cerclages.*

SD: Standard Deviation, BMI: Body Mass Index, IQR: Interquartile Range, MTL: Mid Trimester Loss, PPROM: Preterm Pre-Labor Rupture of Membranes, sPTL: Spontaneous Preterm Labor.

[a]All values are counts for each variable unless otherwise noted.

^Fisher's Exact Test.

Mild and severe amyloid A deposition in the GI tract ran basically parallel and showed a linear growth curve; development of giAAa was continuously steady, except at the end stage of the disease, when it was exponential.

Mild or severe amyloidosis progressed at the same rate; only the amount of amyloid A deposits was different (Figure 3).

The speed of amyloid deposition was practically the same with mild and severe giAAa in patients, based on the different production of the precursor, in other words, on the activity of RA [4].

Figure 3 demonstrates the quantitative differences of amyloid A deposits of GI tract in 31 RA patients with AA amyloidosis.

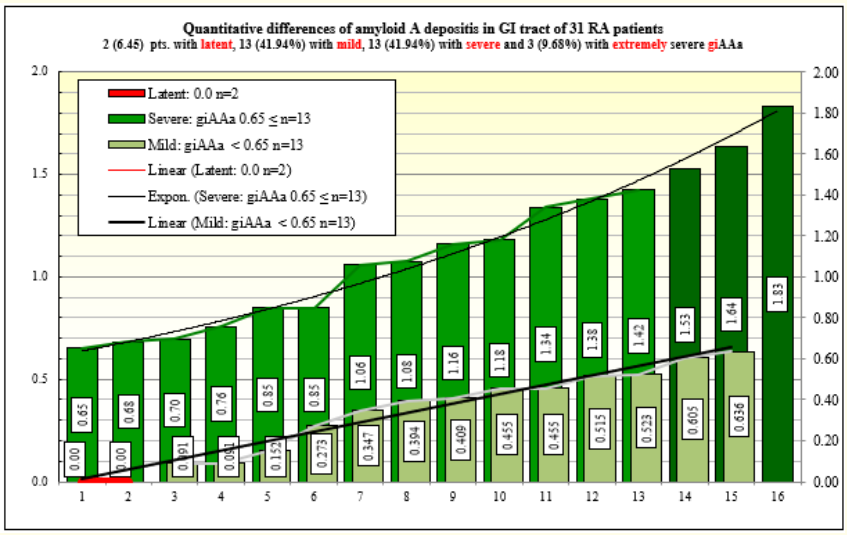

Figure 3

Figure 4 and 5 demonstrate the early and late stages of AA deposits on different tissue structures of the pancreas.

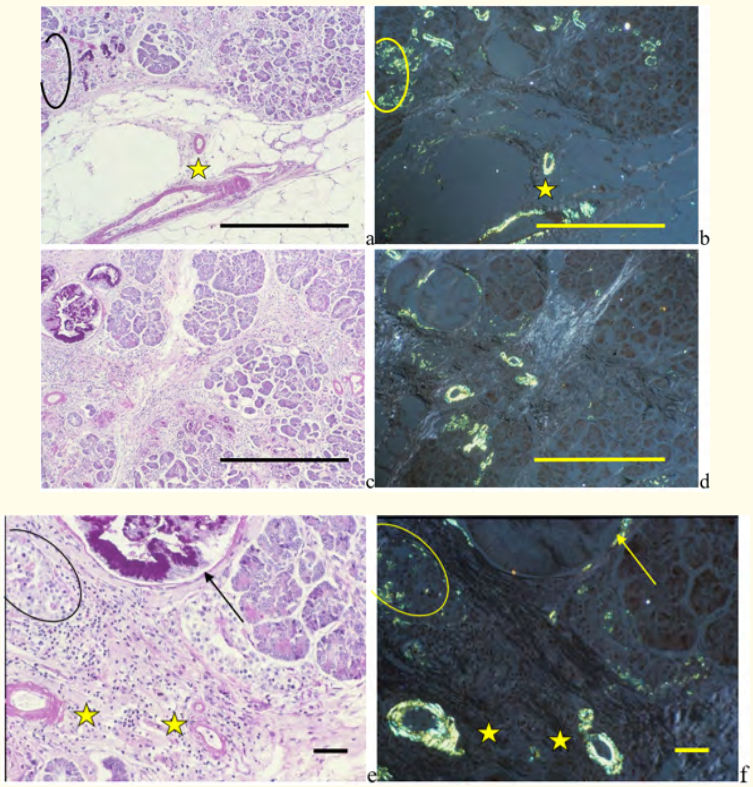

Figure 4a-4f: *(Pr. n0/y: 43/1985). Rheumatoid arthritis, pancreas, systemic secondary AA amyloidosis combined with minimal IAPP deposits (ellipses).*

Early stage of pancreatic AA amyloidosis (average amount of amyloid A protein deposit / patients: 0.841).

AA amyloidosis is a progressive and cumulative processes, involving in the early stages only a few structures, and increasingly more in later stages of the disease.

AA deposits are present only within the walls of arterioles (yellow stars), and minimal deposits along the basement membrane of pancreatic duct (BM) (arrow); the venules and other tissue structures are spared.

The constant relationship between amyloid A deposits on different tissue structures allows an indirect estimation of deposited amyloid in currently not investigated tissue structures.

(a) PAS, scale bar: 1250 [µm], magnification: ×50; (b) Congo red staining, without alcoholic differentiation, covered with gum Arabic, and viewed under polarized light, same as (a) scale bar: 1250 [µm], magnification: ×50; (c) PAS, scale bar: 1250 [µm], magnification: ×50; (d) Congo red staining, viewed under polarized light, same as (c) scale bar: 1250 [µm], magnification: ×50; (e) PAS, same as (c) scale bar: 125 [µm], magnification: ×125; (f) Congo red staining, viewed under polarized light, same as (e) scale bar: 125 [µm], magnification: ×125.

Abbreviations

PAS: Periodic Acid Schiff Reaction; Pr. n0/y: Protocol Number/Year; IAPP: Islet Amyloid Polypeptide; AA: Amyloid A Protein.

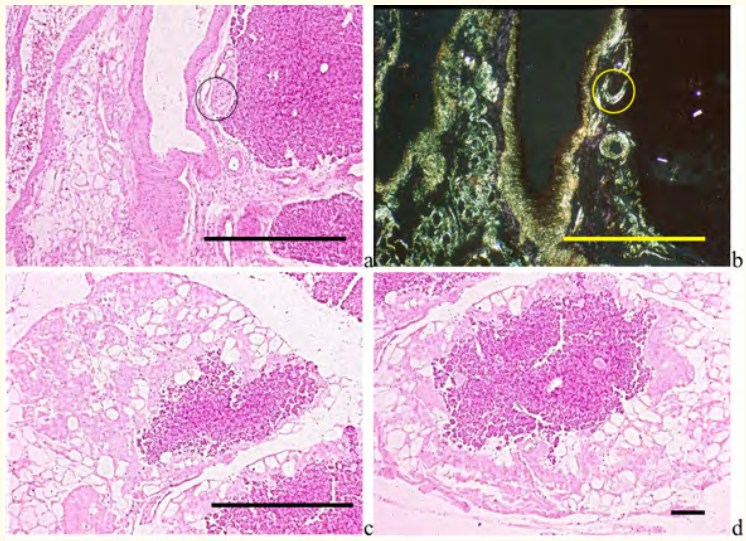

Figure 5a-5d: *(Pr. n0/y: 181/1980). Rheumatoid arthritis, pancreas, systemic secondary AA amyloidosis.*

Late (terminal) stage of pancreatic AA amyloidosis, with massive amyloid A protein deposits (average amount of amyloid A protein deposit/patients: 2.900).

Amyloid A deposits on nerves and nerve sheets (ellipses) represent a late stage of AA amyloidosis, with massive involvement of other structures of pancreas.

(a) HE, scale bar: 1250 [µm], magnification: ×50; (b) Congo red staining, without alcoholic differentiation, covered with gum Arabic, and viewed under polarized light, same as (a) scale bar: 1250 [µm], magnification: ×50; (c) HE, atrophic pancreatic glands, surrounded with massive amyloid A deposits on interstitial and reticulin fibers, scale bar: 1250 [µm], magnification: ×50; (d) HE, same as (c) scale bar: 125 [µm], magnification: ×125.

Abbreviations

HE: Hematoxylin-Eosin; AA: Amyloid A Protein.

Figure 6 and 7 demonstrate the advanced stage of AA deposits in the heart and kidneys.

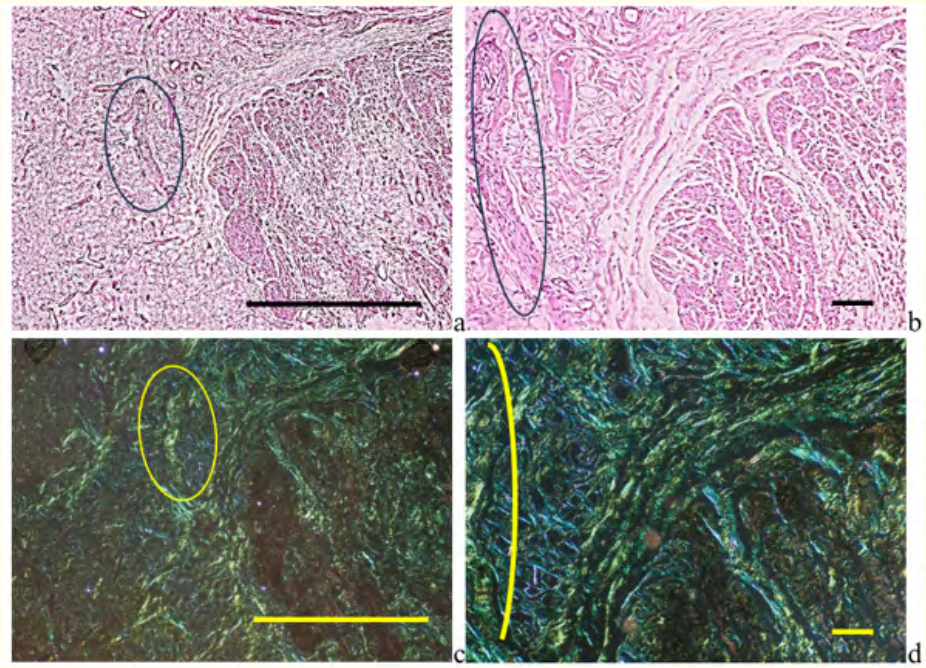

Figure 6a-6d: *(Pr. n0/y: 181/1980). Rheumatoid arthritis, heart, systemic secondary AA amyloidosis.*

Advanced stage of cardiac AA amyloidosis (average amount of amyloid A protein deposit / patients: 1.500).

AA amyloidosis is a progressive and cumulative processes, involving in the early stages only a few structures in some organs, and increasingly more in later stages of the disease. The involved nerves and nerve sheets (ellipses) represent an advanced stage of cardiac AA amyloidosis.

Usually, the kidneys, the heart, and the pancreas are involved with dominant amyloid A deposits compared to the other organs.

The constant relationship between amyloid A deposits in various organs allows an indirect estimation of deposited amyloid in other, currently not investigated organs.

(a) HE, scale bar: 1250 [µm], magnification: ×50; (b) HE, same as (a) scale bar: 125 [µm], magnification: ×125; (c) Congo red staining, without alcoholic differentiation, covered with gum Arabic, and viewed under polarized light, same as (a) scale bar: 1250 [µm], magnification: ×50; (d) same as (c) scale bar: 125 [µm], magnification: ×125.

Abbreviations

HE: Hematoxylin-Eosin; AA: Amyloid A Protein.

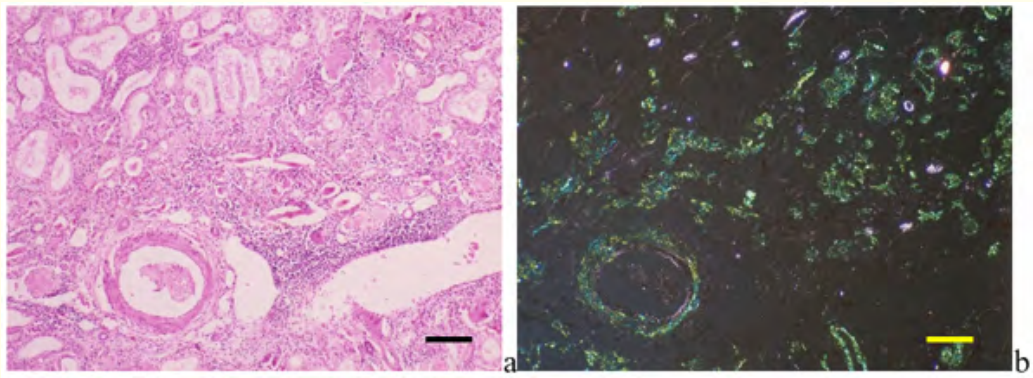

Figure 7a and 7b: *(Pr. n0/y: 181/1980). Rheumatoid arthritis, kidney, systemic secondary AA amyloidosis.*

Advanced stage of renal AA amyloidosis (average amount of amyloid A protein deposit / patients: 1.917).

AA amyloidosis is a progressive and cumulative processes, involving in the early stages only some organs, and increasingly more in later stages of the disease.

Usually, the amyloid A protein deposits are more abundant in the kidneys, heart, and pancreas, compared to the other organs.

The constant relationship between amyloid A deposits in various organs allows an indirect estimation of deposited amyloid in other, currently not investigated organs.

(a) HE, scale bar: 125 [µm], magnification: ×125; (b) Congo red staining, without alcoholic differentiation, covered with gum Arabic, and viewed under polarized light, same as (a) scale bar: 125 [µm], magnification: ×125.

Abbreviations

HE: Hematoxylin-Eosin; AA: Amyloid A Protein.

Conclusion

Amyloid A deposition starts usually on the most frequently involved tissue structures of the most frequently affected organs, characterized by more massive deposits [1].

The steady, constant, and gradual (consistently linear) accumulation of amyloid A on different tissue structures of various organs may be related to the systemic circulation, and determined by blood supply of the organs.

The constant ratio between amyloid A deposits on different tissue structures or in various organs approximately indicates the amounts of amyloid depositions in other, not evaluated structures and organs.

The constant relationship between amyloid A deposits on different tissue structures of various organs allows an indirect estimation of deposited amyloid in currently not investigated tissue structures or organs as well.

This indirect correlation may be of clinical significance.

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