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Research Article

Changing Characteristics of Rheumatoid Arthritis during the Last Third of the 20th Century - A Postmortem Clinicopathologic Study of 237 Autopsy Patients

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Abstract

The characteristics of rheumatoid arthritis (RA) can change over time.

This has happened during the last third of the 20th century and noted by the changes of incidence and mortality of autoimmune vasculitis, AA amyloidosis, acute bacterial septic infection, and purulent arthritis.

New drugs, a consequent therapeutic strategy and patient awareness play an important role in improving the patient's life expectancy and quality of life, but RA cannot be cured today despite our therapeutic efforts and the introduction of new drugs.

Keywords: *Changing Characteristics; Rheumatoid Arthritis; Autoimmune Vasculitis; AA Amyloidosis; Acute Bacterial Septic Infection; Purulent Arthritis*

Abbreviations

RA: Rheumatoid Arthritis; ACR: American College of Rheumatology; AV: Autoimmune (Rheumatoid) Vasculitis; AAa: Systemic AA Amyloidosis; AbSI: Acute Bacterial Septic Infection with Lethal Outcome (Only Fatal Septic Infections were Considered); PA: Purulent Septic Arthritis; HE: Hematoxylin Eosin Staining; PAS: Periodic Acid Schiff Reaction; SD: Standard Deviation; NS: Not Significant; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; DMARDs: Disease-Modifying Antirheumatic Drugs

Introduction

The characteristics of rheumatoid arthritis (RA) change over time, partly because of treatment and partly for other reasons.

The number of fatal cases decreased (especially cardiovascular mortality), disease activity became more moderate, and destructive forms occurred less commonly, presumably due to biological therapy, a stricter treatment strategy and increased patient awareness [1,2].

There is no doubt that the "early diagnosis, treatment, ... biological therapies have transformed the outlook for many patients with rheumatoid arthritis" [3], but is this really the case, and is it true in the long run or permanently?

Objective of the Study

The changing characteristics of RA were investigated to assess the possible impact of steroids and basic therapy on the incidence and mortality of autoimmune vasculitis (AV), AA amyloidosis (AAa), acute bacterial septic infection with lethal outcome (AbSI), and purulent arthritis (PA).

Autopsy population

The data of two hundred and thirty-seven (237) patients with rheumatoid arthritis (RA), who died at the National Institute of Rheumatology and Physiotherapy (ORFI) in the last third of the 20th century (1969 - 2000) [4] were analyzed.

The patients with the clinical diagnosis of RA fulfilled the criteria of the American College of Rheumatology (ACR) [5].

The patients' history and protocols were clinically controlled by the co-author Ágnes Apáthy rheumatologist, neurologist, the autopsies and histopathologic reports were reviewed by Miklós Bély, pathologist.

Methods

Incidence (presence) of autoimmune vasculitis AV, AAa, AbSI, and PA was confirmed histologically, based on a detailed evaluation of twelve organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) [6].

Fatal and non-fatal cases of AV and AAa were determined on data of autopsy and clinical protocols. In the case of septic infection (with or without PA), only fatal septic infections were considered.

AA amyloid deposition in different tissue structures of various organs was diagnosed histologically according to Romhányi [7] by a modified, more sensitive Congo red staining [8]. The types of AAa deposits were identified by immunohistochemical [9] and histochemical methods [10-12].

The average incidence and mortality of AV, AAa, AbSI and PA was calculated in percentage of the number of RA patients, who died during four periods of time (8-8-8-8 years) covering 32 years (1969 - 2000).

Severity of AV or AAa 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 of a x40 lens of Olympus BX51 polarizing microscope [6].

Semi-objective score system of "severity":

- "0" - no AV or AA amyloid deposits.
- "1" - Sporadic, AV or minimal amyloid deposits on blood vessels or different tissue structures.
- "2" - Less than five involved blood vessel or tissue structures.
- "3" - Five or more involved blood vessel or 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.

Statistics

Demographics of different patient cohorts were evaluated with the Student (Welch) T-test comparing the age, sex, onset of RA, and duration of disease at the time of death with or without AV, AAa, AbSI, and PA [13].

The p cutoff for significance was < 0.05.

Comparing two types of data, the most severe criteria of excel calculator were used; two-tailed distribution ("2"), and non-equal variation ("not homoscedastic -3").

The mean age of the patients was variable (between minimal and maximal value of age), and the mean (average) severity of AV, and the mean amount of the AA deposits showed a "normal distribution"; typical bell-shaped curve of Gauss.

The correlation existing between different patient cohorts were calculated with Pearson's chi-squared ($\chi 2$) test [13].

Results

AV complicated RA in 48 (20,53%) of 237 patients, and led to death in 23 (47,91%) of 48 patients; there was a very strong positive relationship between AV (n = 48) and fatal AV (n = 23) (c = 1.0, $\chi^{2 = 94,9022, p < 0.000)}$.

AAa complicated RA in 49 (20,68%) of 237 patients, and led to death in 20 (40,82%) of 48 patients; there was a very strong positive relationship between AAa (n = 49) and fatal AAa (n = 20) (c = 1.0, $\chi^{2 = 78,6077, p < 0.000)}$.

AbSI complicated RA in 31 (13,08% of 237) patients, it was associated with PA in 15 (6,33% of 237, 48,39% of 31), and was not in 16 (6,75% of 237, 51,61% of 31) patients.

PA did not exist without fatal AbSI; there was a very strong positive relationship between SI (n = 31) and PA (n = 15) (c = 1.0, $\chi^{2 = 98,4071,}$ p < 0.000).

Demographics of patients with AV, AAa, AbSI and/or PA

Table 1 summarizes demographics, onset and duration of disease of the total population (n = 237), with (n = 48) and without AV (n = 128), with (n = 34) and without AAa (n = 127), with (n = 31) and without AbSI (n = 206) or with (n = 15) and without PA (n = 16).

Sex	Number of autopsies	Mean age in years at death ± SD	Range of age (in years)	Mean age at onset of disease ± SD	Disease duration (in years) ± SD
RA patients (total)	**237**	**66,18 ± 13,27**	**16- 88**	**51,00 ± 16,76**	**14,69 ± 10,76**
Female	171	66,12 ± 13,05	16 - 88	50,21 ± 16,18	15,43 ± 11,12
Male	66	66,30 ± 13,92	19 - 88	53,08 ± 18,20	12,75 ± 9,57
With AV	**48 of 237**	**67,38 ± 11,76**	**32 - 88**	**55,02 ± 16,24**	**12,89 ± 11,14**
Female	30	67,67 ± 13,32	32 - 88	54,26 ± 15,72	14,33 ± 10,45
Male	18	66,89 ± 8,89	53 - 83	56,17 ± 17,41	10,72 ± 12,09
Without AV	**189 of 237**	**65,87 ± 13,63**	**16 - 88**	**49,70 ± 16,77**	**15,27 ± 10,61**
Female	141	65,79 ± 13,01	16 - 88	48,92 ± 16,05	15,80 ± 11,33
Male	48	66,08 ± 8,89	19 - 88	52,12 ± 18,88	13,62 ± 7,87

With fatal AV	**23 of 48**	**63,43 ± 11,04**	**32 - 88**	**52,32 ± 16,92**	**12,55 ± 12,51**
Female	14	64,21 ± 13,22	32 - 82	53,54 ± 14,45	13,15 ± 9,99
Male	9	62,22 ± 6,96	53 -72	50,56 ± 20,79	11,67 ± 16,12
Without fatal AV	**25 of 48**	**71,00 ± 11,42**	**34 - 88**	**57,61 ± 15,50**	**13,22 ± 9,94**
Female	16	70,69 ± 13,06	34 - 88	54,93 ± 17,33	15,43 ± 11,11
Male	9	71,56 ± 8,40	59 - 83	61,78 ± 11,86	9,78 ± 7,00
With AAa	**49 of 237**	**63,14 ± 15,36**	**19 - 88**	**46,00 ± 18,36**	**± 9,85**
Female	39	64,33 ± 12,41	32 - 88	45,72 ± 16,90,	17,89 ± 10,65
Male	10	58,50 ± 24,04	19 - 88	47,11 ± 24,56	14,33 ± 5,10
Without AAa	**188 of 237**	**66,97 ± 12,62**	**16 - 88**	**52,61 ± 15,95**	**13,89 ± 10,95**
Female	132	66,66 ± 13,25	36 - 88	51,65 ± 15,62,	14,65 ± 11,26
Male	56	67,70 ± 11,02	19 - 88	54,77 ± 16,66	12,40 ± 10,17
With fatal AAa	**20 of 49**	**57,40 ± 18,56**	**19 - 88**	**40,68 ± 20,36**	**18,05 ± 10,03**
Female	13	60,46 ± 13,57	32 - 79	40,77 ± 17.59	19,69 ± 11,36
Male	7	51,71 ± 25,77	19 - 88	40,50 ± 27,39	14,50 ± 5,50
Without fatal AAa	**29 of 49**	**67,10 ± 11,44**	**34 - 88**	**49,88 ± 16,05**	**16,54 ± 9,87**
Female	132	66,27 ± 11,57	34 - 88	48,52 ± 16,21	16,87 ± 10,35
Male	3	74,33 ± 8,50	68 - 84	60,33 ± 12,01	14,00 ± 5,29
With AbSI*	**31 of 237**	**62,45 ± 9,01**	**41 - 83**	**49,59 ± 12,39**	**13,00 ± 8,92**
Female	22	61,50 ± 9,83	41 - 83	49,53 ± 13,35,	12,32 ± 9,32
Male	9	64,78 ± 6,53	52 - 71	49,75 ± 10,58	14,63 ± 8,25
Without AbSI	**206 of 237**	**66,73 ± 13,74**	**16 - 88**	**51,24 ± 17,42**	**14,98 ± 11,04**
Female	150	66,85 ± 13,43	16 - 88	50,32 ± 16,65	15,95 ± 11,43
Male	56	66,41 ± 14,88	19 - 88	53,70 ± 19,32	12,40 ± 9,85
With PA	**15 of 31**	**59,47 ± 7,28**	**46 - 71**	**44,08 ± 10,88**	**16,38 ± 10,73**
Female	10	58,20 ± 7,05	46 - 68	42,88 ± 11,59,	16,63 ± 12,12
Male	5	62,00 ± 7,84	52 - 71	46,00 ± 10,61	16,00 ± 9,38
Without PA	**16 of 31**	**65,25 ± 9,79**	**41 - 83**	**54,71 ± 11,79**	**9,86 ± 5,56**
Female	12	64,25 ± 11,20	41 - 83	54,36 ± 12,86,	9,18 ± 5,29
Male	4	68,25 ± 1,71	66 - 70	56,00 ± 8,54	12,33 ± 7,02

Table 1: *Sex, mean age with SD, range, onset and disease duration (in years) of 237 RA patients with and without AV, AAa, AbSI or PA including fatal and non-fatal cases of AV and AAa.*

Glossary to table 1: RA: Rheumatoid Arthritis; AV: Systemic Autoimmune Vasculitis; SV: Systemic Septic Vasculitis; AAa: Systemic AA Amyloidosis; AbSI: Acute Bacterial Septic Infection with Lethal Outcome; PA: Purulent Septic Arthritis; SD: Standard Deviation.

**In the case of AbSI (with or without PA), only the fatal septic infection was considered.*

Relationship between the overall RA population and patient groups with AV, AAa, AbSI or PA

When comparing age, sex, onset and duration of RA at death, there was no significant difference in survival time, onset or duration of RA between the overall population (n = 237) and AV patients (n = 49) ($p < 0.527$, $p < 0.143$), $p < 0.331$), neither in women ($p < 0.557$, $p < 0.232$, $p < 0.624$) nor in men ($p < 0.830$, $p < 0.527$, $p < 0.527$), AAa patients (n = 48) ($p < 0$, 200, $p < 0.101$, $p < 0.141$), neither in women ($p < 0.418$, $p < 0.159$, $p < 0.229$) nor in men ($p < 0.340$, $p < 0.503$, $p < 0.472$) or among AbSI patients. (n = 31) ($p < 0.046$, $p < 0.603$, $p < 0.376$), neither in women, ($p < 0.053$, $p < 0.841$, $p < 0.195$), nor in men ($p < 0.588$, $p < 0.474$, $p < 0.571$); except in life expectancy of AbSI patients, who died earlier compared to the overall population (62.45 years versus 66.18 years, $p < 0.046$).

Relationship between patient groups with and without AV, AAa, AbSI or PA

There was no significant difference in survival time (mean age at death), onset or duration of RA between patients with (n = 48) and without AV (n = 189) ($p < 0,439$, $p < 0.062$, $p < 0.211$), neither in women ($p < 0.480$, $p < 0.125$, $p < 0.525$) nor in men ($p < 0.794$, $p < 0.443$, $p < 0.367$), with (n = 49) and without AAa (n = 188) ($p < 0,109$, $p < 0.034$, $p < 0.062$), neither in women ($p < 0.305$, $p < 0.072$, $p < 0.119$) nor in men ($p < 0.263$, $p < 0.394$, $p < 0.408$), except for the RA onset, with (n = 23) and without AbSI (n = 25) ($p < 0$, 025, $p < 0.553$, $p < 0.310$), neither in women ($p < 0.028$, $p < 0.814$, $p < 0.139$) nor in men ($p < 0.585$, $p < 0.418$, $p < 0.511$), except for survival time in AbSI patients, and women with AbSI (n = 31) and with PA (n = 15) ($p < 0,234$, $p < 0.163$, $p < 0.336$), neither in women ($p < 0.292$, $p < 0.213$, $p < 0.388$) nor in men ($p < 0.522$, $p < 0.551$, $p < 0.795$) with (n = 15) and without PA (n = 16) ($p < 0,071$, $p < 0.022$, $p < 0.066$), neither in women ($p < 0.140$, $p < 0.059$, $p < 0.138$) nor in men ($p < 0.151$, $p < 0.202$, $p < 0.555$), except for the onset of RA.

RA started earlier in AAa patients than in those without AAa (46.00 years vs 52.61 years, $p < 0.034$), and the duration of RA was also longer (17.18 years vs 13.89 years), but this difference was not significant (NS - $p < 0.062$).

AbSI patients died earlier than those without AbSI (62.45 years vs 66.73 years, $p < 0.025$), as did women (61.50 years vs 66.85 years, $p < 0.028$); the differences were significant.

RA started earlier in patients with PA than in those without PA (44.08 years vs 54.71 years, $p < 0.022$), and duration of RA was also longer (16.38 years vs 9.86 years), but this difference was not significant (NS - $p < 0.066$).

Relationship between patient groups with and without fatal outcome of AV and AAa

There was no significant difference between in the onset or duration of RA in patients with fatal AV (n = 23) and without fatal AV (n = 25) ($p < 0.281$, $p < 0.843$), in either women ($p < 0.822$, $p < 0.580$) or men ($p < 0.184$, $p < 0.753$), and between patients with fatal AAa (n = 20) and non-fatal AAa (n = 29) ($p < 0.112$, $p < 0.617$), in women ($p < 0.040$, $p < 0.467$) or men ($p < 0.176$, $p < 0.901$), except for the onset of RA in women.

Patients with fatal AV (64.43 years vs. 71.00 years, $p < 0.024$) or fatal AAa (57.40 years vs. 67.10 years, $p < 0.046$) died earlier than those with non-fatal AV or AAa.

AV, AAa, AbSI and PA (with or without fatal outcome) developed in both sexes, and at any time in the course of RA (Table 1 and 2).

Table 2 summarizes the relationship between demographic data, onset and duration of RA ("p" correlation values) between the total population (n = 237) and patients with AV, AAa or AbSI (with and without PA), furthermore between patients with (n = 48) and without AV (n = 189 /237), with (n = 49) and without AAa (n = 188/237), with (n = 31) and without AbSI (n = 206/237), moreover between patients with (n = 15) and without PA (n = 16/31).

Patient cohorts with RA	Age	Onset of RA	Duration of RA
RA patients n = 237 (total) versus pts. with AV n = 48 of 237	**0,527**	**0,143**	**0,331**
Female n = **171** of 237 versus n = 30 of 48	0,557	0,232	0,624
Male n = 66 of 237 versus n = 18 of 48	0,830	0,527	0,527
With AV n = 48 of 237 vs without AV n = 189 of 237	**0,439**	**0,062**	**0,211**
Female n = 30 of 48 versus n = 141 of 189	0,480	0,125	0,525
Male n = 18 of 48 versus n = 48 of 189	0,794	0,443	0,367
With fatal AV n = 23 of 48 vs without fatal AV n = 25 of 48	**0,024**	**0,281**	**0,843**
Female n = 14 of 23 versus n = 16 of 48	0,190	0,822	0,580
Male n = 9 of 23 versus n = 9 of 48	**0,021**	0,184	0,753
RA patients n = 237 (total) versus pts. with AAa n = 49 of 237	**0,200**	**0,101**	**0,141**
Female n = 171 of 237 versus n = 39 of 49	0,418	0,159	0,229
Male n = 66 of 237 versus n = 10 of 49	0,340	0,503	0,472
With AAa n = 49 of 237 vs without AAa n = 188 of 237	**0,109**	**0,034**	**0,062**
Female n = 39 of 49 versus n = 132 of 188	0,305	0,072	0,119
Male n = 19 of 49 versus n = 56 of 188	0,263	0,394	0,408
With fatal AAa n = 20 of 49 vs without fatal AAa n = 29 of 49	**0,046**	**0,112**	**0,617**
Female n = 13 of 20 versus n = 26 of 29	0,140	**0,040**	0,467
Male n = 7 of 20 versus n = 3 of 29	0,072	0,176	0,901
RA patients n = 237 (total) versus pts. with AbSI n = 31 of 237	**0,046**	**0,603**	**0,376**
Female n = 171 of 237 versus n = 22 of 31	0,053	0,841	0,195
Male n = 66 of 237 versus n = 9 of 31	0,588	0,474	0,571
With AbSI n = 31 of 237 vs without AbSI n = 206 of 237	**0,025**	**0,553**	**0,310**
Female n = 22 of 31 versus n = 150 of 206	**0,028**	0,814	0,139
Male n = 9 of 31 versus n = 56 of 206	0,585	0,418	0,511
With AbSI n = 31 of 237 vs PA n = 15 of 31	**0,237**	**0,163**	**0,336**
Female n = 22 of 31 versus n = 10 of 15	0,292	0,213	0,388
Male n = 9 of 31 versus n = 5 of 15	0,522	0,551	0,795
With PA n = 15 of 31 vs without PA n = 16 of 31	**0,071**	**0,022**	**0,066**
Female n = 10 of 15 versus n = 12 of 16	0,140	0,059	0,138
Male n = 5 of 15 versus n = 4 of 16	0,151	0,202	0,555

Table 2: *Statistical correlations ("p" values of significance) between female and male RA patients with and without AV, AAa, AbSI or PA.*

Mean age, onset and duration of RA, incidence and mortality of AV, AAa, AbSI and/or PA in four groups of patients during the last third of the 20th century

Table 3 summarizes the mean age, onset and duration of RA, furthermore incidence and mortality of AV, AAa, AbSI, and PA in autopsy patients who died during the last third of the 20th century covering 32 years (1969 - 2000).

Number of autopsied patients - overall, RA, AAa, AbSI, and PA population	1969-1976 n = 65	1977-1984 n = 50	1985-1992 n = 72	1993-2000 n = 50	∑ n = 237 Avg. of Avg's
Demographics of RA patients (n = 237)					
Mean age of patients in overall population (Avg)	65,32	66,14	66,46	66,92	66,21
Onset of RA in overall population (Avg)	48,10	49,41	52,74	51,48	50,43
Duration of RA in overall population (Avg)	14,83	15,93	13,45	15,44	14,91
Autoimmune vasculitis (AV)					
Mean age of RA patient with AV (Avg)	57,00	72,00	69,61	67,87	66,62
Onset of RA with AV (Avg)	49,20	56,33	58,65	50,86	53,76
Duration of RA in AV patients (Avg)	12,60	15,67	10,96	15,57	13,70
RA patients with AV (n = 48)	7	3	23	15	48
RA patients with fatal vasculitis (n = 23)	4	1	14	4	23
RA patients without fatal vasculitis (n = 25)	3	2	9	11	25
RA patients without AV (n = 189)	58	47	49	35	189
Total number of RA patients (n = 237)	65	50	72	50	237
Incidence of AV in (%) of patients	10,77	6,00	31,94	30,00	20,25
Fatal AV in % of patients	6,15	2,00	19,44	8,00	9,70
Non-fatal AV in % of patients	4,62	4,00	12,50	22,00	10,55
AA amyloidosis (AAa)					
Mean age of RA patient with AAa (Avg)	56,71	59,56	66,06	64,80	61,78
Onset of RA with AAa (Avg)	46,50	45,44	48.94	42,43	33,59
Duration of RA in AAa patients (Avg)	12,00	14,11	17,11	20,71	15,98
RA patients with AAa (n = 49)	7	9	18	15	49
RA patients with fatal AAa (n = 15)	4	3	6	2	15
RA patients without fatal AAa (n = 34)	3	6	12	13	34
RA patients without AAa (n188)	58	41	54	35	188
Total number of RA patients (n = 237)	65	50	72	50	237
Incidence of AAa in (%) of patients	10,77	18,00	25,00	30,00	20,68
Fatal AAa in % of patients	6,15	6,00	8,33	4,00	6,33
Non-fatal AAa in % of patients	4,62	12,00	16,67	26,00	14,35

Fatal acute bacterial septic infection (AbSI)					
Mean age of RA patient with fatal SI (Avg)	61,29	61,33	61,13	65,57	62,33
Onset of RA with fatal SI (Avg)	39,67	52,86	47,50	58,50	49,63
Duration of RA in fatal SI patients (Avg)	19,83	7,71	13,63	11,50	13,17
RA patients with fatal AbSI (n = 31)	7	9	8	7	31
RA patients without fatal AbSI (206)	58	41	64	43	206
Total number of RA patients	65	50	72	50	237
Incidence of fatal AbSI in % of patients	10,77	18,00	11,11	14,00	13,08
Incidence of RA without fatal AbSI in % of patients	89,23	82,00	88,89	86,00	86,92
Fatal AbSI with purulent arthritis (PA)					
Mean age of RA patient with PA (Avg)	61,00	58,75	62,20	61,00	62,33
Onset of RA with PA (Avg)	37,33	52,86	45,20	54,50	49,63
Duration of RA in PA patients (Avg)	23,67	7,71	17,00	14,00	13,17
RA patients with PA (n = 15)	3	4	5	3	15
RA patients without PA (n = 222)	62	46	67	47	222
Total number of RA patients	65	50	72	50	237
Incidence of PA in % of patients	4,62	8,00	6,94	6,00	6,33
Incidence of RA in % of patients without PA	95,38	92,00	93,06	94,00	93,67

Table 3: *Incidence and mortality of AV, AAa, AbSI, and PA in patients who died between 1969 and 2000.*

Remarks to table 2: The data correspond to the era of medication with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and/or disease-modifying antirheumatic drugs (DMARDs): Following the introduction of biological therapies (in the period after 2000), the number of autopsies decreased dramatically, so we no longer have reliable data on changes of RA and/or on the effectiveness of biologic drugs and other targeted therapies.

Incidence and mortality of AV, AAa, AbSI and PA was calculated in percentage of RA patients who died during four periods of time (8-8-8-8 years) covering 32 years (1969 - 2000).

Abbreviations: RA: Rheumatoid Arthritis; AV: Systemic Autoimmune Vasculitis; SV: Systemic Septic Vasculitis; AAa: Systemic AA amyloidosis; AbSI: Acute Bacterial Septic Infection with Fatal Outcome; PA: Purulent septic Arthritis; Avg. of Avg's: Average of Averages.

Differences in mean age, onset and duration of RA were not significant between four group of patients with AV, AAa, AbSI or PA; these complications occurred at any time during RA.

Exceptional differences were in mean age of patient groups, who died between 1969-1976 and 1977-1984 (65.32 years versus 66.14 years, $p < 0.025$), and in onset of RA between 1969-1976 and 1993-2000 (48.10 years vs. 51.48 years, $p < 0.021$); during these periods the patients lived longer and RA started later, approaching the turn of the century (Table 4).

Statistical correlations ("p" values of significance) between four groups of patients with AV, AAa, AbSI, and PA are listed in table 4.

The patients died in four periods of time (8-8-8-8 years) during the last third of the 20th century (1969 - 2000).

Relationship between	Overall population			AV			AAa			AbSI			PA		
Four patient groups	Age	Onset	Duration	Age	Onset	Duration	Age	Onset	Dura-tion	Age	Onset	Duration	Age	Onset	Dura-tion
1969-1976 vs. 1977-1984	0,765	0,587	0,847	0,025	0,299	0,634	0,713	0,895	0,691	0,804	0,092	0,05	0,229	0,669	0,298
1969-1976 vs. 1985-1992	0,637	0,182	0,438	0,05	0,203	0,887	0,143	0,583	0,339	0,929	0,271	0,378	0,785	0,519	0,589
1969-1976 vs. 1993-2000	0,494	0,359	0,806	0,106	0,821	0,621	0,211	0,506	0,11	0,340	0,021	0,164	1,000	0,241	0,447
1977-1984 vs. 1985-1992	0,908	0,297	0,205	0,26	0,791	0,447	0,338	0,617	0,532	0,929	0,413	0,154	0,024	0,539	0,206
1977-1984 vs. 1993-2000	0,750	0,550	0,841	0,278	0,401	0,986	0,461	0,732	0,142	0,303	0,357	0,199	0,445	0,274	0,466
1985-1992 vs. 1993-2000	0,838	0,696	0,338	0,673	0,210	0,265	0,815	0,3400	0,316	0,224	0,014	0,611	0,892	0,356	0,645

Table 4: *Statistical correlations ("p" values of significance) between four groups of patients during the last third of the 20th century.*

Incidence and mortality of AV and AAa in four groups of patients during the last third of the 20th century

Incidence of AV and AAa increased during the last third of the 20th century.

The increment of AV and AAa was mainly due to the non-fatal cases.

The rate of fatal AAa fell by more than one third from 6.15% to 4.0% (34.95%) by the turn of the century, presumably due to controlled RA activity and effectively controlled inflammation.

However, the incidence of fatal AV increased by nearly one third from 6.15% to 8.0% (30.08%), which may be an indirect sign that RA cannot be cured with our current therapeutic options, at most the quality of life of the patients can be improved (Table 3 and figure 1).

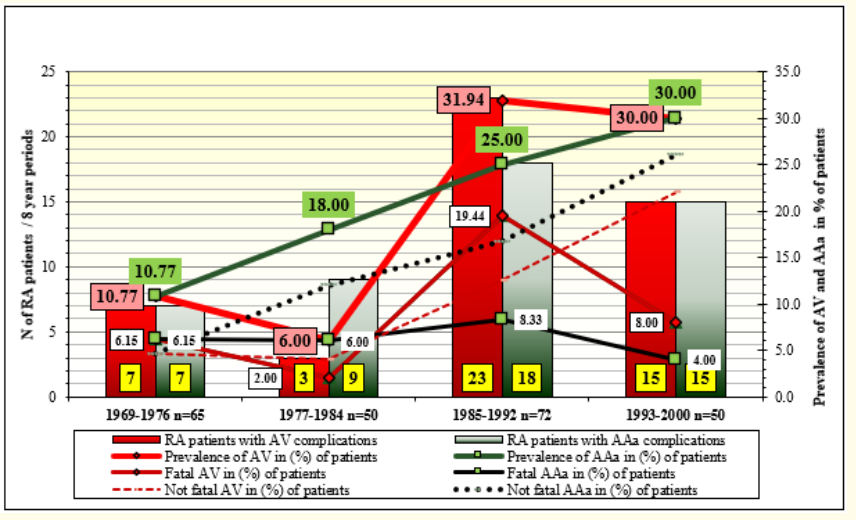


Figure 1: *The changing features of AV and AAa in the last third of the 20th century.*

Legends to figure 1: The rate of lethal AAa fell by more than one third from 6.15% to 4.0%, and the incidence of fatal AV increased by nearly one third 6.15% to 8.0% by the turn of the century.

Remarks: "Incidence" of AV or AAa concerns the presence of vascular inflammation or amyloid A deposits in various organs of our autopsy population, and conveys information about the risk of complications.

Presence of AV or AAa was histologically confirmed by the presence of vascular inflammation, and amyloid A on blood vessels of different calibers or on different tissue structures analyzed in 12 organs of each patient [3].

"Severity" of AV designates density of inflamed blood vessels, and "severity" of AAa means different amounts of AA deposition on blood vessels or on different tissue structures of various organs.

The incidence of fatal AbSI and PA increased during the last third of the 20th century.

The incidence of fatal AbSI increased by nearly one third from 10.77% to 14.0% (29.99%), and the incidence of PA increased by a similar rate (nearly one third - 29.87%) from 4.62% to 6.0% of cases.

The increment may be explained by the longer life span, associated with gradually decreased responsiveness of ageing patients (not excluding the role of repeated intraarticular injections (Table 3 and figure 2).

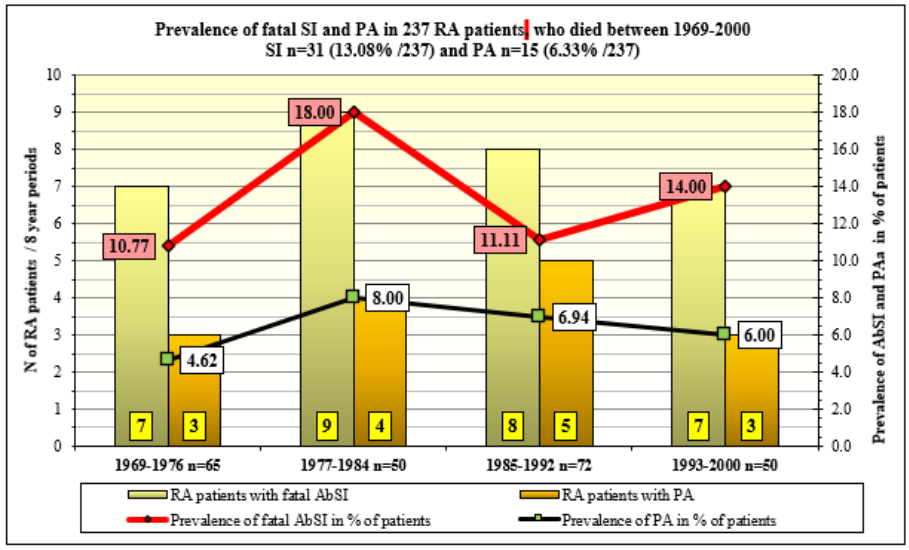


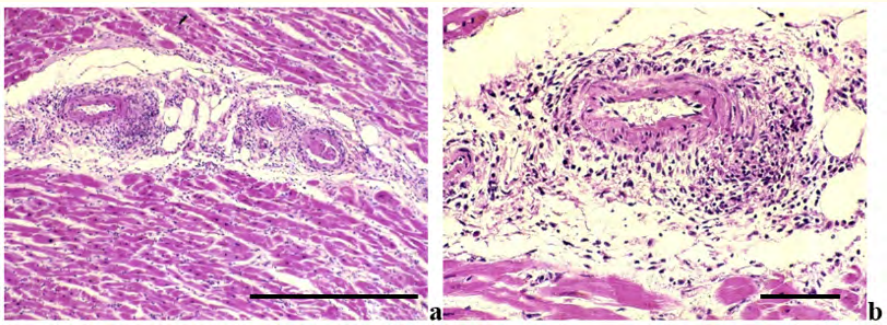
Figure 2: *The changing features of AbSI and PA during the last third of the 20th century.*

Legends to figure 2: The rate of fatal AbSI increased from 10.77% to 14.0%, and the rate of PA fell from 4.62% to 8.0% by the turn of the century. The increment may be related to longer life span, and declining immune reactivity of the elderly RA patients.

Histological images

Original magnifications of all figures correspond to the 24x36 mm transparency slide; the correct height: width ratio is 2:3. The printed size may be different; therefore, the original magnifications are indicated.

Figure 3 and 4 demonstrate moderate non-specific, and fatal fibrinoid necrotic autoimmune vasculitis of the heart in RA.



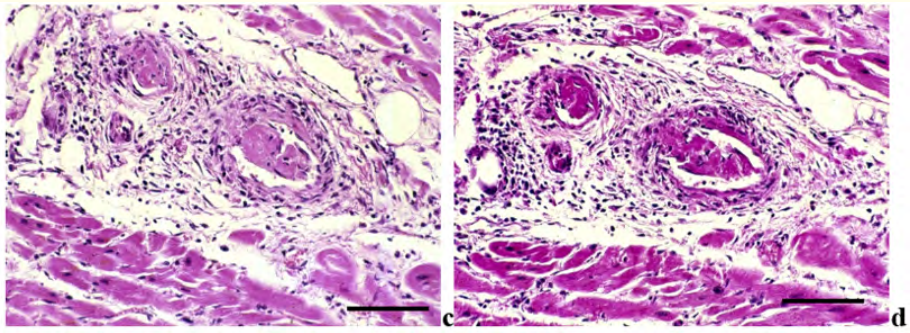


Figure 3a-3d: *RA, heart, arteriole, moderate non-specific AV.*

Adjacent arterioles with sectorial accentuated leuko-lymphocytic infiltration and intraluminal thrombus.

(a) Arteriole, HE, scale bar: 1250 [µm], magnification: x50.

(b) Same as (a), cale bar: 125 [µm], magnification: x125.

(c) Same as (a), cale bar: 125 [µm], magnification: x125.

(d) Same as (a), PAS, scale bar: 125 [µm], magnification: x125.

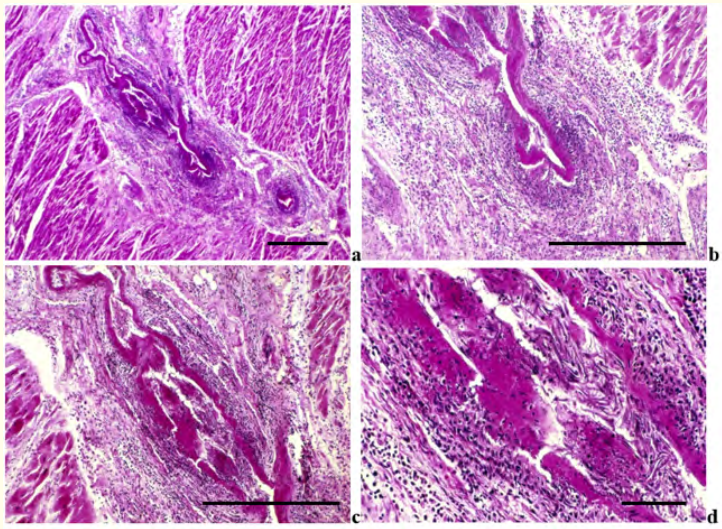


Figure 4a-4d: *RA, heart, small artery, fatal fibrinoid necrotic AV.*

Fibrinoid necrosis of the blood vessel walls is accompanied with non-specific leuco-lymphocytic infiltration.

(a) Small artery, PAS, scale bar: 1250 [µm], magnification: x20.

(b) Same as (a), scale bar: 1250 [µm], magnification: x50.

(c) Same as (a), scale bar: 1250 [µm], magnification: x50.

(d) Same as (c) scale bar: 125 [µm], magnification: x125.

Figure 5-7 demonstrates the early, late and terminal stages of AA deposits on different tissue structures of adrenal glands.

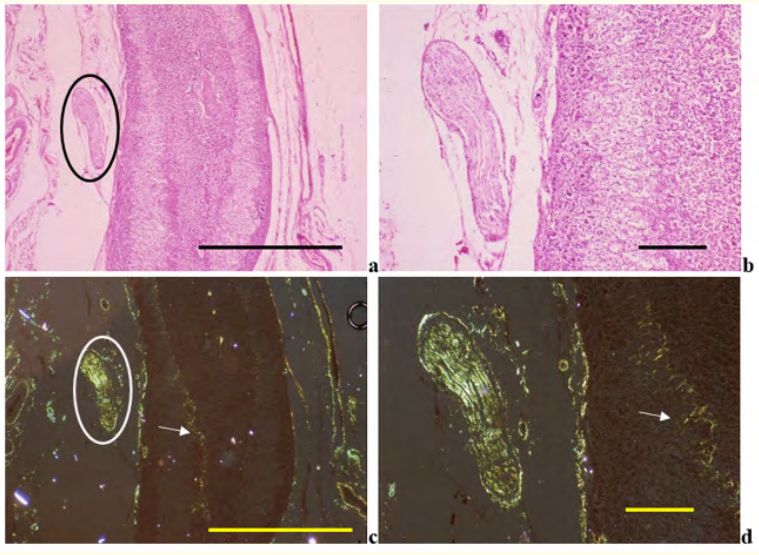


Figure 5a-5d: *RA, AAa, adrenal gland and periadrenal fat tissue with peripheral nerve.*

Massive AA amyloid deposits are along the axons and on the nerve sheets (ellipses).

Incipient cortical amyloid deposition is within the reticular zone of the adrenal cortex (arrow).

(a) HE, scale bar: 1250 [μm], magnification: x50.

(b) Same as (a), scale bar: 125 [μm], magnification: x125.

(c) Congo red staining, without alcoholic differentiation, covered with gum Arabic, and viewed under polarized light, same as (a), scale bar: 1250 [μm], magnification: x50.

(d) Same as (c), scale bar: 125 [μm], magnification: x125.

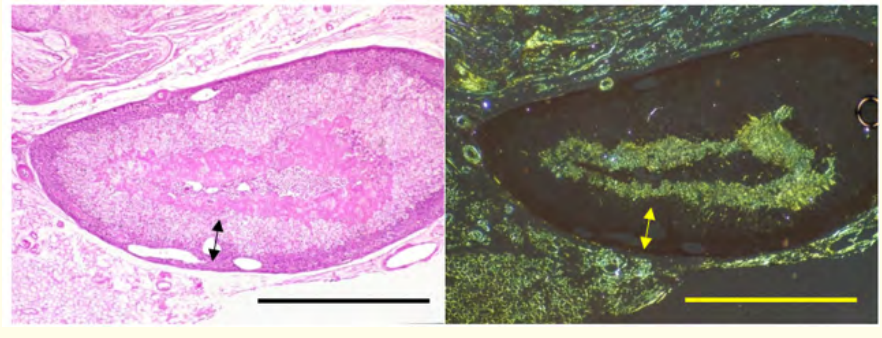


Figure 6a and 6b: *RA, AAa, adrenal gland and periadrenal fat tissue.*

Massive AA amyloid deposits are in periadrenal fat tissue, and advanced stage of cortical amyloid deposition is within the reticular zone of the adrenal cortex; fascicular and glomerular zones appear intact (arrows).

(a) PAS, scale bar: 1250 [μm], magnification: x50.

(b) Congo red staining, without alcoholic differentiation, covered with gum Arabic, and viewed under polarized light, same as (a), scale bar: 1250 [μm], magnification: x50.

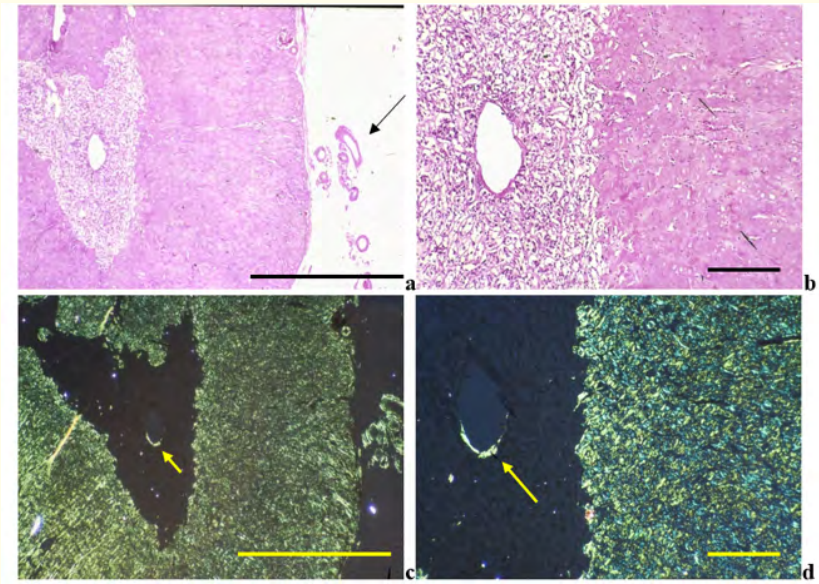


Figure 7a-7d: *RA, AAa, adrenal gland and periadrenal fat tissue with arterioles and venules (black arrow).*

Terminal stage of cortical amyloid deposition involving the reticular, fascicular and glomerular zones.

(a) PAS, scale bar: 1250 [µm], magnification: x50.

(b) Same as (a), scale bar: 125 [µm], magnification: x125.

(c) Sectorial AA amyloid deposit in a venule wall of medullary region of adrenal gland (yellow arrow), Congo red staining, without alcoholic differentiation, covered with gum Arabic, and viewed under polarized light, same as (a), scale bar: 1250 [µm], magnification: x50.

(d) Same as (c), scale bar: 125 [µm], magnification: x125.

Figure 8-11 demonstrate the PA in the knee joint.

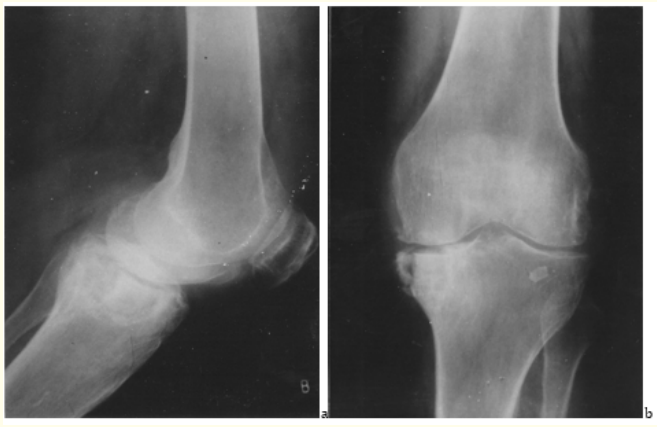


Figure 8a and 8b: *RA, knee joint, purulent arthritis. (a) Latero-lateral X-Ray photograph, (b) Postero-anterior X-Ray photograph.*

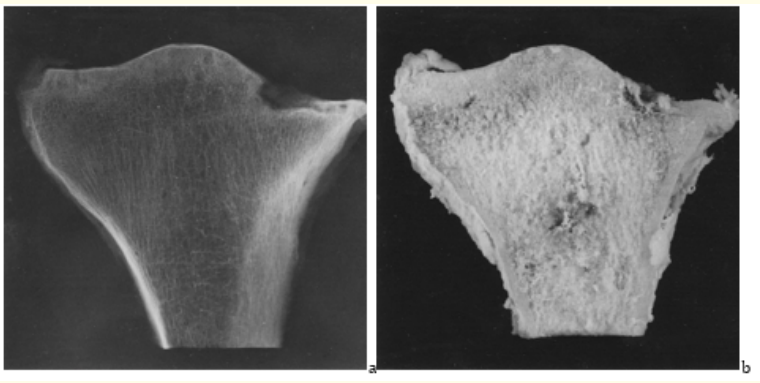


Figure 9a and 9b: *RA, knee joint, purulent arthritis. (a) Horizontal shift of tibia, (b) same as (a), contact X-photograph.*

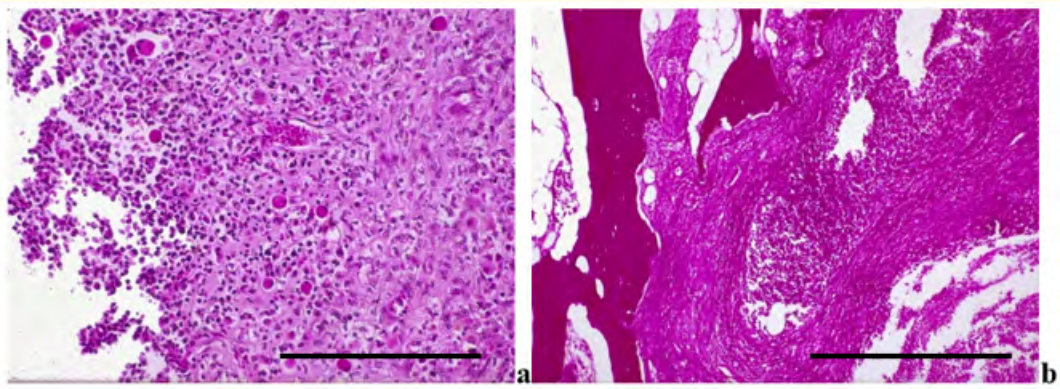


Figure 10a and 10b: *RA, knee joint, purulent arthritis.*

(a) Synovial membrane, purulent inflammation of synovial membrane, HE, scale bar: 1250 [µm], magnification: x50.

(b) Subchondral bone, osteomyelitis, HE, scale bar: 1250 [µm], magnification: x50.

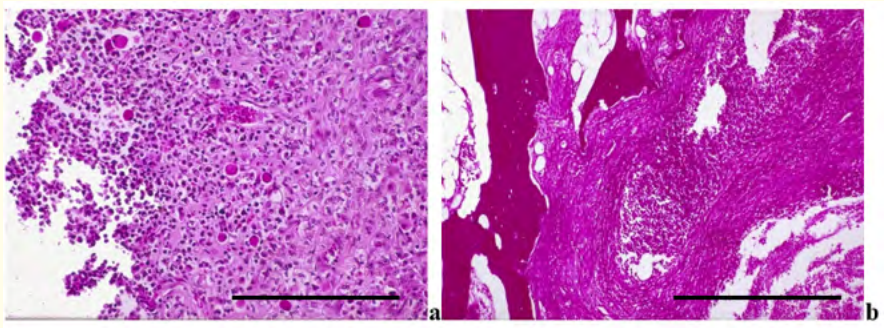


Figure 11a and 11b: *RA, knee joint, purulent arthritis and purulent skeletal muscle (phlegmonous myositis).*

(a) HE, x50, scale bar: 1250 [µm], magnification: x50.

(b) same as (a), HE, scale bar: 125 [µm], magnification: x125.

Discussion

Our data indicate undoubted changes in the incidence and mortality of RA complications (AV, AAa, AbSI, PA) during the last third of the 20th century.

Has RA really changed or are the changes due to the gradually introduced corticosteroids and DMARDs to the NSAIDs? Today we do not know.

In any case, it can be stated that controlled inflammatory activity has reduced the severity of AAa, and supports the influence of therapy on RA.

The increase in moderate cases of AAa may be related to the older age of patients, to impaired renal function, and gradually decreasing elimination of amyloid precursors.

The decline of estimated glomerular filtration rate has been stated in association with increased RA activity in the USA [14].

According to Myasoedova., *et al*. (2020) the RA improved; the number of RF positive patients decreased [15].

The increase in the number of fatal AV suggests that RA has not fundamentally improved indeed a possible worsening of the underlying disease (of the immunologic reactivity) may have occurred.

It can be concluded that RA cannot be cured still today despite all of our therapeutic efforts and the introduction of new drugs.

New drugs, consequent therapeutic strategy, and patient awareness play an important role in the above-mentioned changes, are essential for the patients' life prospects and ameliorate their quality of life.

The value of this study is limited by the randomly taken tissue samples. The incidence and severity of AV or AAa may be misleading especially in early stages of complications, in case of sporadic inflammation of blood vessels or minimal amyloid deposits.

With high-dose, effective antibiotic treatment of generalized septic infection, tissue signs of inflammation may be absent and only toxic signs of sepsis (tissue necrosis) may be seen on histopathological examination ("sepsis sine sepsi").

Conclusion

The face of RA has changed in the last third of the 20th century, but the underlying disease can currently not be cured despite the introduction of new drugs.

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