Demographics and Predictive Clinical-Laboratory Parameters of Systemic and Cardiac Vasculitis of Autoimmune Origin - A Postmortem Clinicopathologic Study of 161 Rheumatoid Arthritis Patients

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Abstract

Background: In the general population the incidence of systemic rheumatoid vasculitis of autoimmune origin (sAV) has decreased in the last decades, but remained a serious complication of rheumatoid arthritis (RA) associated with a poor prognosis and significant mortality. The heart is more frequently involved by coronary vasculitis of autoimmune origin (cAV) in comparison with other organs of RA patients.

Aim of the Study: The aim of this study was to determine the prevalence of sAV and cAV in RA, and to assess the predictive clinical laboratory parameters for sAV and cAV.

Patients and Methods: One hundred sixty one (161) non- selected autopsy patients with RA were studied. RA was confirmed clinically according to the criteria of the American College of Rheumatology.

The presence of vasculitis was confirmed histologically reviewing an extensive histological material of 12 organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain). Tissue samples of heart were available for histologic evaluation in 138 of 161 patients.

The correlations were determined by the Student (Welch) t-probe, comparing the age, sex of patients, onset of RA, duration of disease, and laboratory parameters at the last hospitalization: with and without sAV and cAV.

Results and Conclusions: The risk of sAV or cAV is higher in elderly female RA patients than in RA patients who did not have vasculitis (p < 0.002, resp. p < 0.010). The chance of survival of female patients with sAV is lower than for RA patients who do not have vasculitis (p < 0.052); the disease duration in patients with cAV is shorter than in patients without sAV, but this difference is not significant (p < 0.17 - NS).

Comparing the age, sex, onset of RA, and duration of disease at the time of death we found no significant difference between patients with sAV (n = 33) and cAV (n = 21), neither between females or males; sAV and cAV may complicate RA in both sexes, and at any time in the course of the disease.

The classic clinical-laboratory parameters mentioned in the pertinent literature and analyzed in our study (Latex, BUN, creatinin, albumin, alfa-2 globulin, CRP, Waaler-Rose, RBC, and ESR) with or without significant differences, are not sufficient to predict vasculitis. They are related to the basic activity of RA or to the actual intensity of inflammatory processes of the disease. We found no significant differences in classic laboratory parameters between patient cohorts with sAV or cAV and without sAV, which were suitable for indication of existing vasculitis.

Keywords: Rheumatoid Arthritis; Systemic and Coronary Vasculitis of Autoimmune Origin; Laboratory Parameters

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Abbreviations

sAV: Systemic Vasculitis of Autoimmune Origin; cAV: cardiac (coronary) Vasculitis of Autoimmune Origin; RA: Rheumatoid Arthritis; ARA: American College of Rheumatology; H-E: Hematoxylin-Eosin Staining; PAS: Periodic Acid Schiff Reaction; ESR: Erythrocyte Sedimentation Rate; CRP: C Reactive Protein; BUN: Blood Urea Nitrogen; RBC: Red Blood Cells; WBC: White Blood Cells; LDH: Lactate Dehydrogenase; GPT: Glutamic- Pyruvic-Transaminase; GGT: Gamma-Glutamyl-Transpeptidase; SD: Standard Deviation

Introduction

In the general population the incidence of systemic rheumatoid vasculitis of autoimmune origin (sAV) has decreased in the last decades [1,2], but remained a serious complication of rheumatoid arthritis (RA) associated with a poor prognosis and significant mortality [1-6].

In the RA autopsy population the prevalence of sAV is between 10 - 25% [7-21]. The heart is more frequently involved by coronary vasculitis of autoimmune origin (cAV) in comparison with other organs of RA patients [22].

Aim of the Study

The aim of this study was to determine the prevalence of sAV and cAV in RA, and to assess the predictive clinical laboratory parameters for sAV and cAV.

Patients and Methods

At the National Institute of Rheumatology 9475 patients died between 1969 and 1992; among them 161 with RA and all of them were autopsied [23].

RA was confirmed clinically according to the criteria of the American College of Rheumatology (ACR) [24].

The presence of vasculitis was confirmed in a detailed review of extensive histological material in agreement with the recommendations of the Consensus Conference (2013) [25], Scott., *et al.* (1981) [3], and Schilling and Fassbender (1988) [26]. From each patient a total of 50-100 tissue blocks of 12 organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) were studied microscopically.

Tissue samples of heart were available for histologic evaluation in 138 of 161 patients.

The correlations were determined by the Student (Welch) t-probe [27], comparing the age, sex of patients, onset of RA, duration of disease, and laboratory parameters (Latex, Waaler-Roose values, ESR, CRP, serum albumin/globulin ratio, serum electrophoresis (albumin, alpha-1-globulin, alpha-2-globulin, beta-globulin, gamma-globulin), RBC, hemoglobin, WBC, systolic and diastolic blood pressure, blood urea nitrogen (BUN), serum creatinine, serum potassium and sodium values, urine specific gravity, proteinuria, urine sediment (RBC, WBC), serum bilirubin, LDH, GPT, GGT, blood sugar, and diastase values) at the last hospitalization: with and without sAV and cAV.

Immunological parameters (immunoglobulins, immunocomplexes, antineutrophil cytoplasmic antibodies - ANCAs, complements, cytokines s, etc. were not analyzed.

The relationship between sAV and cAV was analyzed by Pearson's chi-squared (χ^2) test [27].

Glossary of definitions

- **"Prevalence" of vasculitis:** Concerns the presence of inflammatory infiltration and structural changes in blood vessels of different calibers.
- **Systemic vasculitis of autoimmune origin (sAV):** sAV was defined as one of the basic manifestations of RA determined in 12 organs [23,28], excluding other causes of vasculitis, like hypertension, diabetes mellitus, tumors, septic infections, etc.

  Prevalence of sAV concerns the average prevalence of vasculitis determined in 12 organs of RA patients.
- **Cardiac vasculitis of autoimmune origin (cAV):** Means the prevalence of vasculitis in the heart of RA patients involving coronary blood vessels of different caliber.

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Size of blood vessels [29]

- Arteriole (a): No internal or external elastic membrane, < 500 micrometers in diameter.
- Small artery (A): Only internal elastic membrane present, vessels 500 - 1000 micrometers in diameter.
- Medium size artery (AA): Internal and external elastic membrane are present - vessel > 1000 micrometers in diameter.
- Venule (v), small vein (V), medium size vein (VV): Accompanying (a), (A) or (AA).

Results

sAV complicated RA in 33 (21.18%) of 138 patients, and the cardiac blood vessels (branches of coronary arteries and arterioles - cAV) were involved in 21 (63.64%) of these 33 patients; coronary veins and venules were spared by vasculitis of autoimmune origin in our autopsy population (Figures 4-7). In 12 (36.36%) of 33 patients vasculitis was not found in the heart.

sAV was associated with cAV in all of 21 (63.64% of 33) patients; the relationship between sAV and cAV was strong and positive (association's coefficient = 0.8626, χ^2: 37.614; p < 0.0000).

Demographics, onset and duration of disease complicated by sAV and cAV are summarized in table 1 and figures 1.1-1.5.

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	161	65.32 ± 12.95	16- 88	50.83 ± 16.96	14.43 ± 10.51
Female	116	64.95 ± 11.79	16 - 87	50.19 ± 15.70	14.79 ± 10.65
Male	45	66.29 ± 15.50	19 - 88	52.57 ± 19.88	13.46 ± 10.08
RA pts heart	138 of 161	65.10 ± 12.72	16- 88	51.18 ± 16.79	14.25 ± 10.51
Female	100	64.78 ± 12.03	16 - 84	50.64 ± 15.81	14.44 ± 10.58
Male	38	65.95 ± 14.33	19 - 88	52.74 ± 19.22	13.71 ± 10.29
With sAV*	33 of 138	67.18 ± 10.64	32 - 83	56.94 ± 14.63	11.68 ± 10.34
Female	20	66.95 ± 11.11	32 - 82	58.50 ± 9.52	10.89 ± 7.59
Male	13	67.54 ± 9.86	32 - 83	54.77 ± 19.42	12.77 ± 13.16
Without sAV*	105 of 138	64.45 ± 13.24	16 - 88	49.38 ± 17.02	15.05 ± 10.44
Female	80	64.24 ± 12.19	16 - 84	48.45 ± 16.19	15.38 ± 11.02
Male	25	65.12 ± 16.12	19 - 88	52.64 ± 19.30	13.91 ± 7.0
With cAV	21 of 33	66.33 ± 11.97	32 - 82	56.58 ± 16.85	12.00 ± 11.70
Female	13	66.92 ± 13.62	32 - 82	59.27 ± 10.36	11.64 ± 7.23
Male	8	65.25 ± 8.48	53 - 78	52.88 ± 22.42	12.50 ± 15.91
Wtihout cAV	12 of 33	68.67 ± 7.55	58 - 83	57.50 ± 10.16	11.17 ± 7.68
Female	7	67.00 ± 2.83	63 - 71	59.75 ± 9.85	9.25 ± 7.56
Male	5	71.00 ± 10.79	58 - 83	53.00 ± 9.25	15.00 ± 6.36

Table 1: Sex, mean age with SD, range, onset and disease duration (in years) of RA patients with or without sAV (n = 33) and cAV (n = 21) of 138 RA patients.

Glossary to table 1

RA: Rheumatoid Arthritis; sAV: Systemic Vasculitis of Autoimmune Origin; cAV: Cardiac Vasculitis of Autoimmune Origin; SD: Standard Deviation

* - there is a minimal difference in data of the current table in comparison with the previously published one [28], because of an error.

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There was no significant difference in survival time, onset or duration of RA between patient cohorts of 161 and 138 patients (p < 0.882, p < 0.865, p < 0.887), neither between female (p < 0.918, p < 0.844, p < 0.817) and male patients (p < 0.918, p < 0.972, p < 0.920) (Tables 1-2 and Figure 1.1).

Comparing the age, sex, onset of RA, and duration of disease at the time of death there was no significant difference between patients with sAV (n = 33) and cAV (n = 21) (p < 0.797, p < 0.941, p < 0.924), neither between female (p < 0.995, p < 0.849, p < 0.801) and male patients (p < 0.601, p < 0.855, p < 0.970) (Table 1-2 and Figure 1.1).

Comparing the age, sex, onset of RA, and duration of disease at the time of death, RA started significantly later in patients with sAV in comparison without sAV (56.94 years versus 49.38, p < 0.021); this difference was especially expressed in women (58.50 years versus 48.45, p < 0.002,), who died notable earlier (10.89 years versus 15.38, p< 0.052.
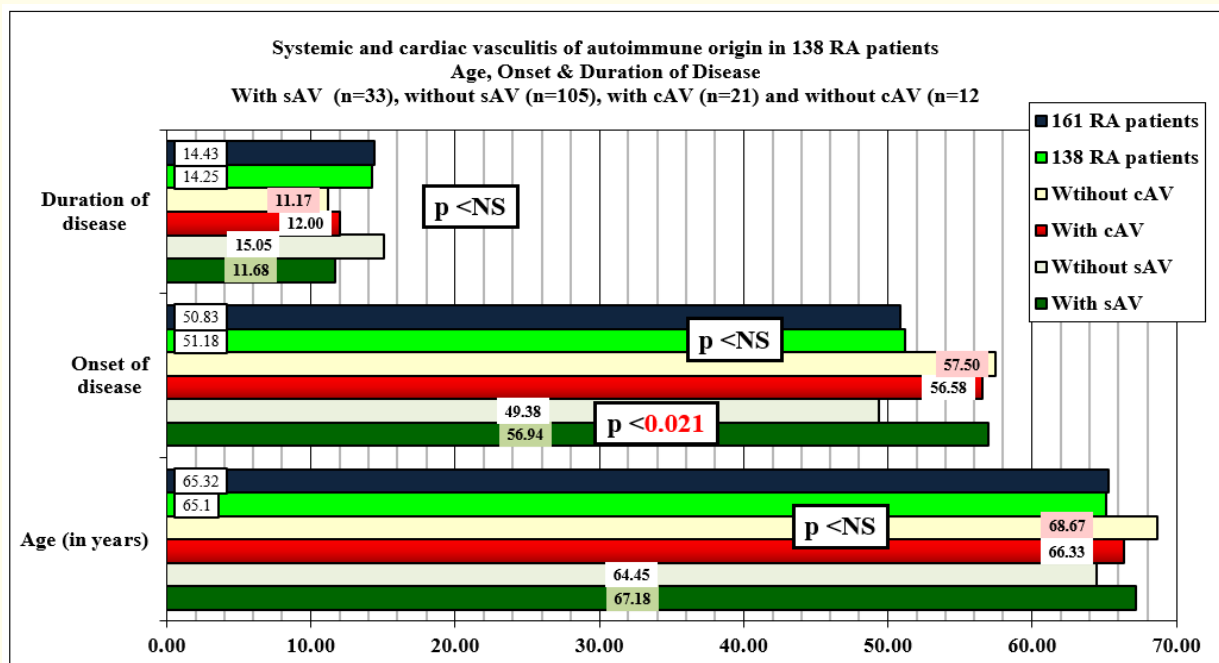

Figure 1.1: *Demographics, onset and duration of 161 and 138 RA in patients with sAV (n = 33) or cAV (n = 21) and without sAV (n = 105) or cAV (n = 12).*
Comparing the age, sex, onset of RA, and duration of disease at the time of death there was no significant difference in survival time, onset and duration of disease between 161 and 138 patients, with cAV or without cAV. sAV started significantly later in comparison without sAV (56.94 years versus 49.38, p < 0.021).

Demographics, onset and duration of disease of RA patients with sAV (n = 33 of 138) and without sAV (n = 105 of 138) are summarized in figures 1.2a-d and 1.3a-d.
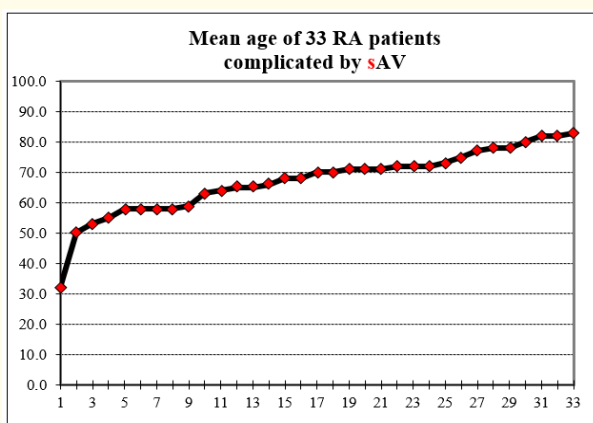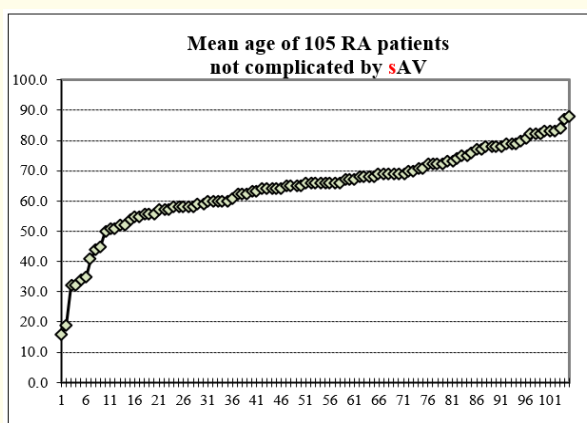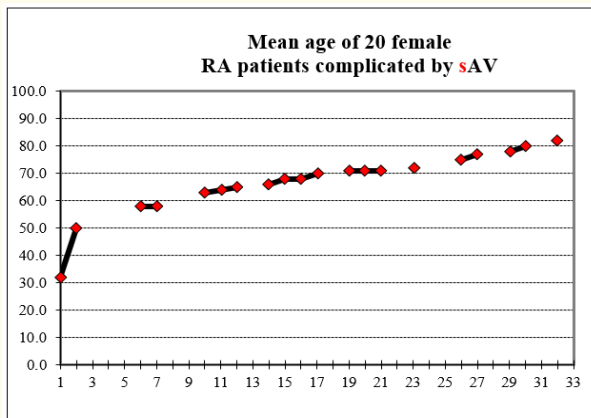

Figure 1.2a

Figure 1.3a

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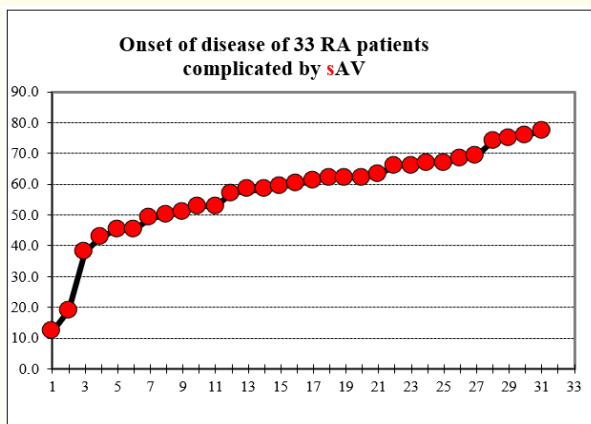
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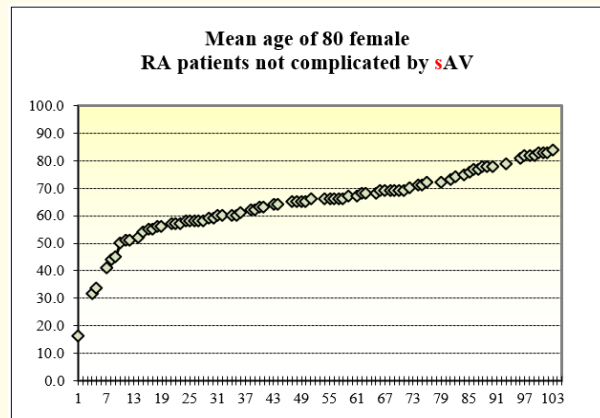
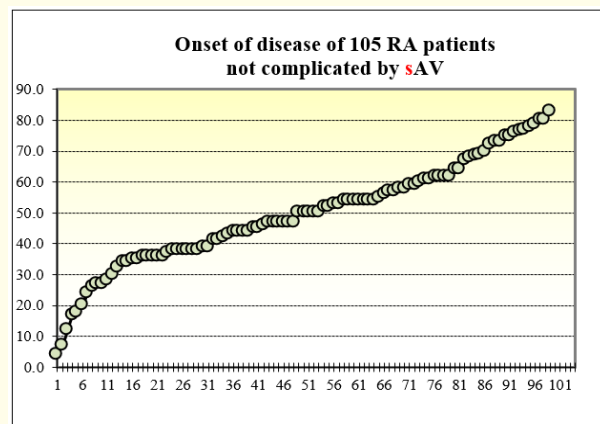*Figure 1.2b*

Figure 1.3b

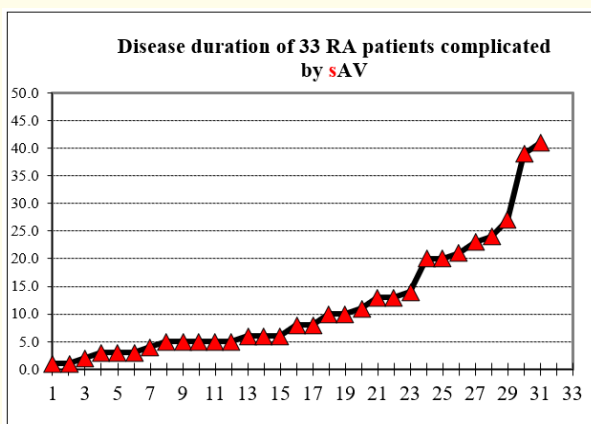*Figure 1.2c*

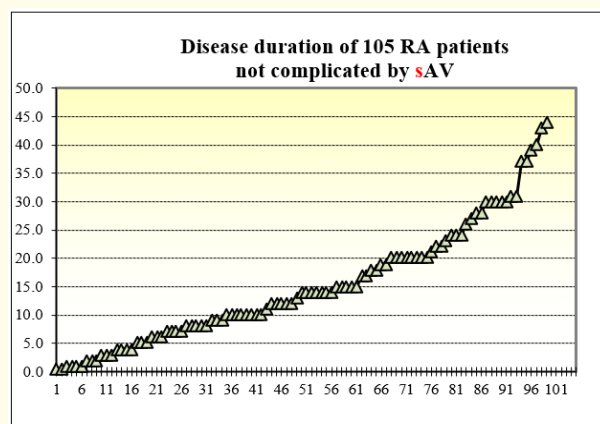*Figure 1.3c*

Figure 1.2d

Figure 1.3d

Figure 1.2a-d-1.3a-d: There was no significant difference in survival time (a), onset (c) and duration of disease (d) between RA patients with sAV (n = 33) and without sAV (n = 105) except onset of RA (56.94 years versus 49.38; p < 0.021) see: 1.2c and 1.3c.

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Demographics, onset and duration of disease of RA patients with cAV (n = 21 of 33) and without cAV (n = 12 of 33) are summarized in figures 1.4a-c and 1.5a-c.
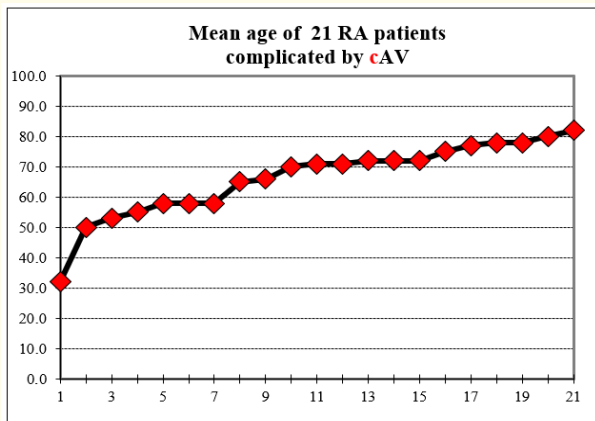
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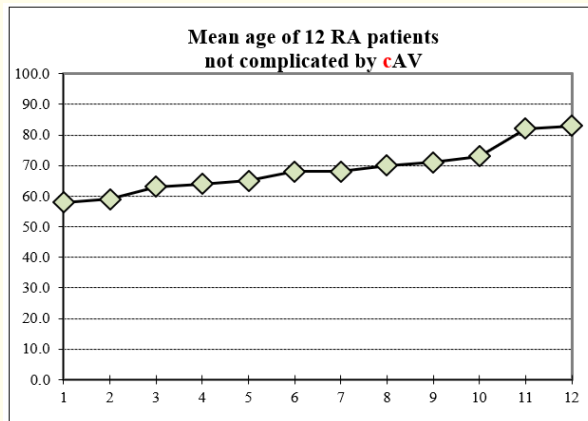
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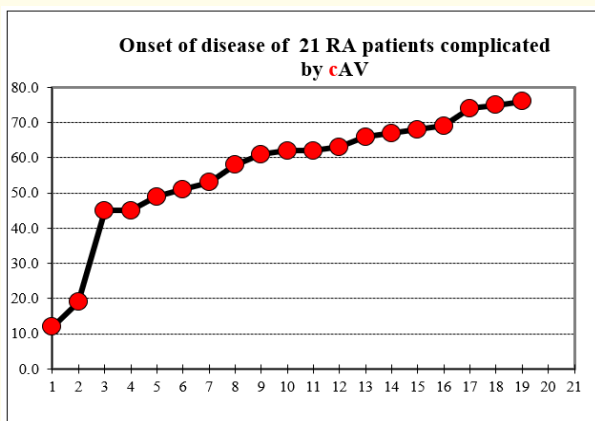
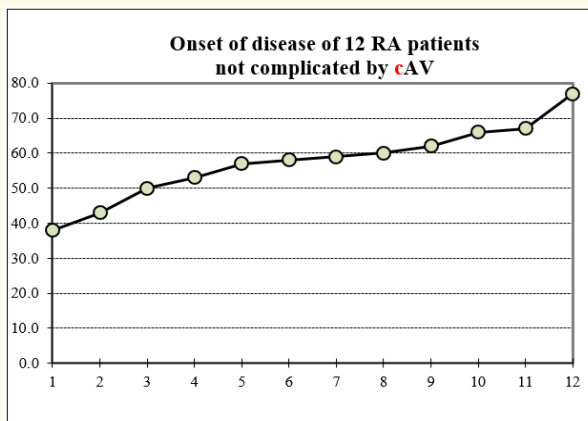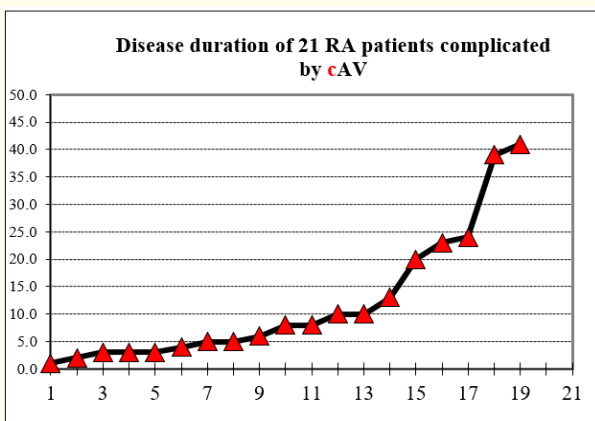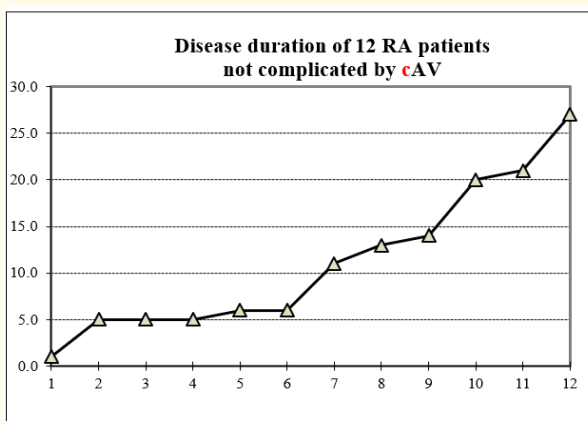*Figure 1.4b*

Figure 1.5b

Figure 1.4c

Figure 1.5c

Figure 1.4a-c-1.5a-c: *There was no significant difference in survival time (a), onset (b) and duration of disease (c) between RA patients with cAV (n = 21) and without cAV (n = 12), neither females nor males.*

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RA started significantly later (58.50 years versus 48.45 at onset of disease; p < 0.002) in female patients complicated by sAV (n = 20), and led significantly earlier to death (within 10.89 years versus 15.38; p < 0.052) in comparison with female patients without sAV (n = 80) (Tables 1-2).

The mean age of RA female patients with cAV (n = 13) was significantly higher at onset of disease (59.27 years versus 48.45; p < 0.010), and the female patients with cAV died earlier (within 11.64 years versus 15.38; p < 0.170 - NS) compared to the female patients without sAV (n = 80), but this latter difference was not significant (Tables 1 and 2).

RA patients n = 161 - available heart n = 138	Age	Onset of disease	Disease duration
RA pts. n = 161 versus pts. with available heart n = 138	p < 0.88	p < 0.86	p < 0.89
Female n = 116 of 161 versus n = 100 of 138	p < 0.91	p < 0.84	p < 0.81
Male n = 45 of 161 versus n = 38 of 138	p < 0.91	p < 0.97	p < 0.92
with sAV n = 33 of 138 vs without sAV n = 105 of 138	p < 0.23	p < 0.021	p < 0.12
Female n = 20 of 33 versus n = 80 of 105	p < 0.35	p < 0.002	p < 0.052
Male n = 13 of 33 versus n = 25 of 105	p < 0.58	p < 0.76	p < 0.78
with sAV n = 33 versus with cAV n = 21	p < 0.79	p < 0.94	p < 0.92
Female n = 20 of 33 versus n = 13 of 21	p < 0.99	p < 0.84	p < 0.80
Male n = 13 of 33 versus n = 8 of 21	p < 0.60	p < 0.85	p < 0.97
with cAV n = 21 of 33 versus without sAV n = 105 of 138	p < 0.53	p < 011	p < 0.31
Female n = 13 of 21 versus n = 80 of 105	p < 0.53	p < 0.010	p < 0.17
Male n = 8 of 21 versus n = 25 of 105	p < 0.98	p < 0.98	p < 0.82
with cAV n = 21 of 33 versus without cAV n = 12 of 33	p < 0.51	p < 0.85	p < 0.81
Female n = 13 of 21 versus n = 7 of 12	p < 0.98	p < 0.92	p < 0.52
Male n = 8 of 21 versus n = 5 of 12	p < 0.39	p < 0.99	p < 0.73

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

Glossary to table 2

RA: Rheumatoid Arthritis; sAV: Systemic Vasculitis of Autoimmune Origin; cAV: Cardiac Vasculitis of Autoimmune Origin

There were no significant differences between laboratory parameters of 161 and 138 RA patients, and there were no significant differences between laboratory parameters of 33 RA patients with sAV, and 21 with cAV.

Mean values of pertinent clinical laboratory parameters of RA patients with sAV (n = 33) at death with "p"values of correlation in comparison without sAV (n = 105) and with the total population of patients (n = 138) are shown in table 3 and figures 3.1-3.2.

Parameters ± SD	Normal range	With sAV n = 33	Without sAV n = 105	p < n = 33 vs n = 105 RA pts	Total n of patients 138	p < n = 33 vs 138 RA pts
Latex - 1-4+	0+	3.76 ± 0.57	3.18 ± 1.24	0.001	3.32 ± 1.14	0.004
BUN - mmol/l	2.00 - 8.90 mmol/l	8.94 ± 3.78	12.28 ± 11.57	0.020	11.44 ± 11.29	0.036
Creatinin - μ mol/l	62 - 106 μmol/l	79.97 ± 31.36	144.70 ± 113.7	0.00017	127.92 ± 103.20	0.001
albumin - g/l	35 - 50 g/l	29.11 ± 5.3	30.93 ± 7.08	0.266 - NS	30.48 ± 6.73	0.372 - NS
afa 2 globulin - %	7,4 - 12.6 %	13.94 ± 2.86	13.21 ± 3.31	0.311 - NS	13.37 ± 3.23	0.413 - NS
CRP - mg/l	0.00 - 5.00 mg/l	354.00 ± 890.2	445.2 ± 786.8	0.696 - NS	425.52 ± 811.1	0.755 - NS
Waaler-Rose titres	less than 1:160	457.10 ± 881.8	473.5 ± 1053.0	0.944 - NS	468.3 ± 1002.0	0.958 - NS
RBC - T/l	4.50 - 5.90 T/l	3.96 ± 0.55	3.687 ± 0.73	0.061 - NS	3.76 ± 0.69	0.146 - NS
ESR - mm/h	≤ 15 - 20 mm/h	80.94 ± 33.3	77.49 ± 36.62	0.632 - NS	78.33 ± 35.87	0.706 - NS

Table 3: Mean values of pertinent clinical laboratory parameters with sAV (n = 33) at death with "p" values compared those to without sAV (n = 105) and to the total population of RA patients (n = 138).

Glossary to table 3 (Significantly different links are in red)

RA: Rheumatoid Arthritis; sAV: Systemic Vasculitis of Autoimmune Origin (average value of prevalence in 12 organs); BUN: Blood Urea Nitrogen; CRP: C Reactive Protein; RBC: Red Blood Cells; ESR: Erythrocyte Sedimentation Rate; SD: Standard Deviation

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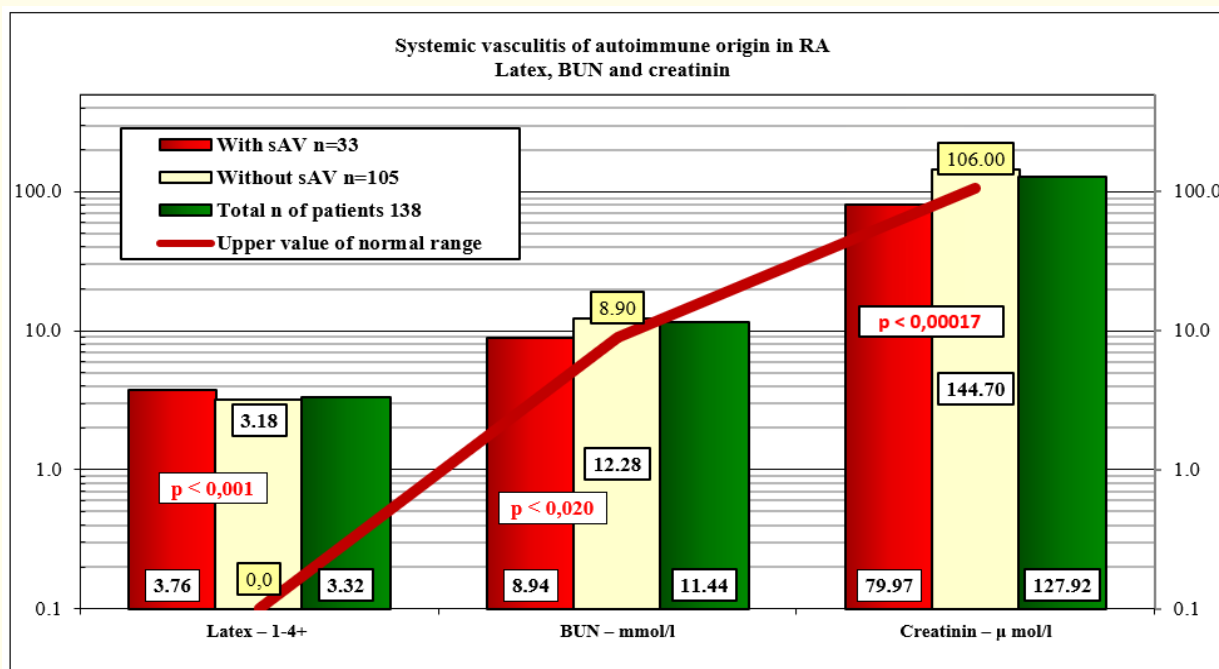
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Figure 3.1: The patients with sAV (n = 33) had significantly higher values of Latex fixation compared to the normal titres or to patients without sAV (n = 105), and to the total population (n = 138).
BUN and creatinin values of RA patients with sAV (n = 33) were near the normal range of laboratory parameters, but significantly decreased compared to patients without sAV (n = 105) or to the total population (n = 138) (Table 3).
The "p" values of correlation represent differences between with and without sAV of RA patients.
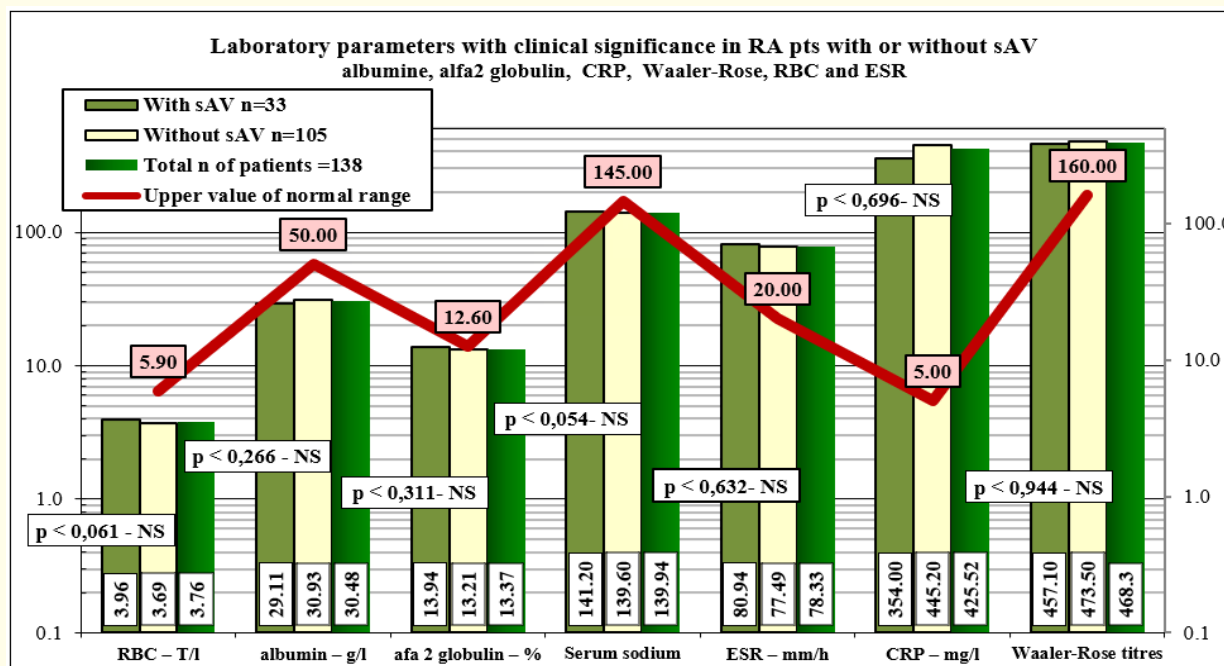
Figure 3.2: The patients with sAV were anemic with lower levels of serum albumin, sodium and with increased sedimentation rate (ESR), and had higher levels of alfa2 globuline, CRP values and Waaler-Rose titres compared to the normal range of laboratory parameters.
There was no significant difference between patient cohorts with and without sAV or in comparison with the total population.
The "p" values of correlation represent the differences between RA patients with and without sAV (Table 3).

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Mean values of pertinent clinical laboratory parameters of RA patients with cAV (n = 21) at death with "p"values of correlation in comparison without sAV (n = 105) and with the total population of patients (n = 138) are shown in table 4 and figures 4.1-4.2.

Parameters ± SD	Normal range	With cAV n = 21	Without sAV n = 105	p < n = 21 vs n = 105 RA pts	Total n of patients 138	p < n = 21 vs 138 RA pts
Latex - 1-4+	0+	3.667 ± 0.67	3.18 ± 1.24	0.024	3.32 ± 1.14	0.080
BUN - mmol/l	2.00 - 8.90 mmol/l	8.50 ± 3.36	12.28 ± 11.57	0.011	11.44 ± 11.29	0.020
Creatinin - μ mol/l	62 - 106 μmol/l	71.94 ± 30.35	144.70 ± 113.70	0.00009	127.92 ± 103.20	0.00036
Serum sodium	135 - 145 mmol/l	142.1 ± 1.80	139.60 ± 4.88	0,003	139.94 ± 4.57	0,005
Albumin - g/l	35 - 50 g/l	27.10 ± 3.70	30.93 ± 7.08	0,023	30.48 ± 6.73	0,034
afa 2 globulin - %	7,4 - 12.6%	14.98 ± 2.24	13.21 ± 3.31	0,033	13.37 ± 3.23	0,046
CRP - mg/l	0.00 - 5.00 mg/l	88.00 ± 61.66	445.2 ± 786.80	0,00047	425.52 ± 811.10	0,00028
Waaler-Rose titres	less than 1:160	440.7 ± 968.7	473.5 ± 1053.0	0.908 - NS	468.3 ± 1002.0	0.919 - NS
RBC - T/l	4.50 - 5.90 T/l	3.967 ± 0.53	3.687 ± 0.73	0.108 - NS	3.76 ± 0.69	0.215 - NS
ESR - mm/h	≤ 15-20 mm/h	78.84 ± 36.36	77.49 ± 36.62	0.886 - NS	78.33 ± 35.87	0.956 - NS

Table 4: *Mean values of pertinent clinical laboratory parameters with cAV (n = 21) at death with "p" values compared to the patients without sAV (n = 105) and to the total population (n = 138).*

Glossary to table 3 (Significantly different links are in red)

RA: Rheumatoid Arthritis; cAV: Coronary Vasculitis of Autoimmune Origin; BUN: Blood Urea Nitrogen; CRP: C Reactive Protein; RBC: Red Blood Cells; ESR: Erythrocyte Sedimentation Rate; SD: Standard Deviation
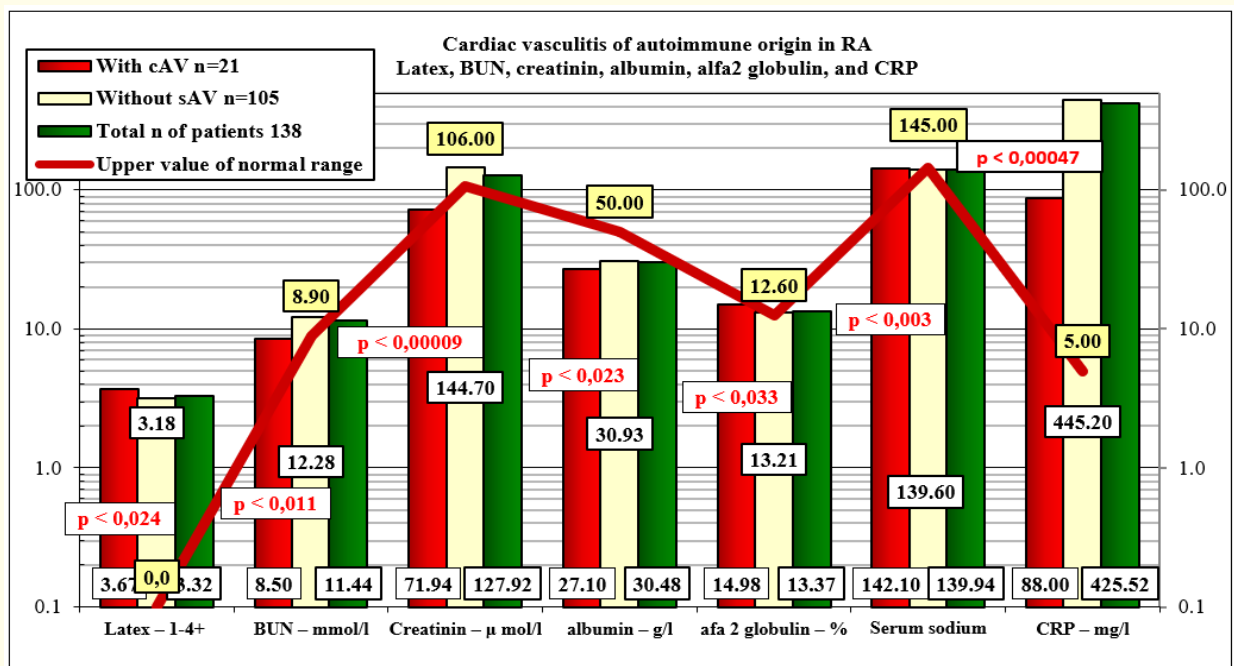
Figure 4.1: *The patients with cAV (n = 21) had significantly higher values of Latex fixation compared to the normal range of titres or to patients without sAV (n = 105), and to the total population (n = 138).*

The level of serum sodium was lower, than the normal level and was significantly higher in comparison without sAV (n = 105), and with the total population (n = 138).

BUN, creatinin and albumin values of RA patients with cAV (n = 21) were near to the upper values of normal range, and were significantly decreased in comparison without sAV (n = 105) or with the total population (n = 138) (Table 4).

The patients with cAV (n = 21) had elevated alfa2 globulin and CRP values in comparison with the normal range of laboratory parameters. Alfa2 globulin significantly increased and CRP significantly decreased compared those to the patients without sAV (n = 105) or to the total population (n = 138). The "p" values of correlation represent the differences between with cAV and without sAV of RA patients.

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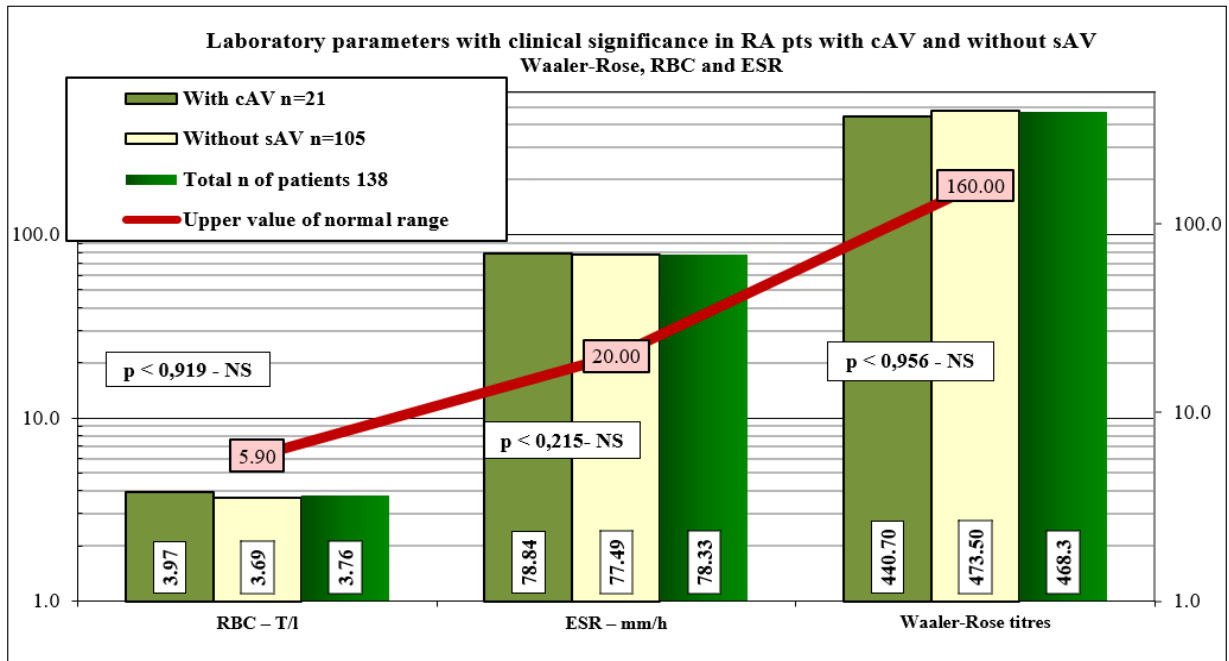
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Figure 4.2: The patients with cAV were anemic, with increased ESR, and had higher levels of Waaler-Rose titres compared to the normal range of laboratory parameters, but these differences were not significant in comparison with the patients without sAV (n = 105) or with the total population of RA patients (n = 138) (Table 3).

The acute-subacute-subchronic-chronic stages of non-specific cAV (Figure 4), in combination with fibrinoid necrosis (Figure 5) or granulomatous transformation of vessel walls (Figure 6) existed side by side in blood vessels of different caliber (Figure 7). Figures 3-7 demonstrate the fundamental histology of cAV.

The printed size may be different, therefore it is necessary to indicate the original magnifications corresponding to a fixed size; the original magnification corresponds to the 24x36 mm transparency slide - the correct height: width ratio is 2:3.
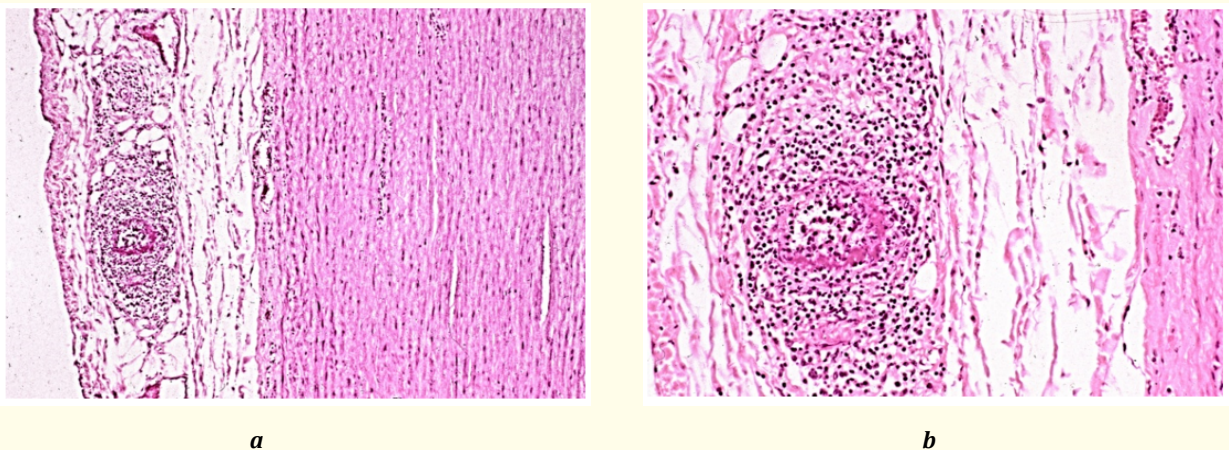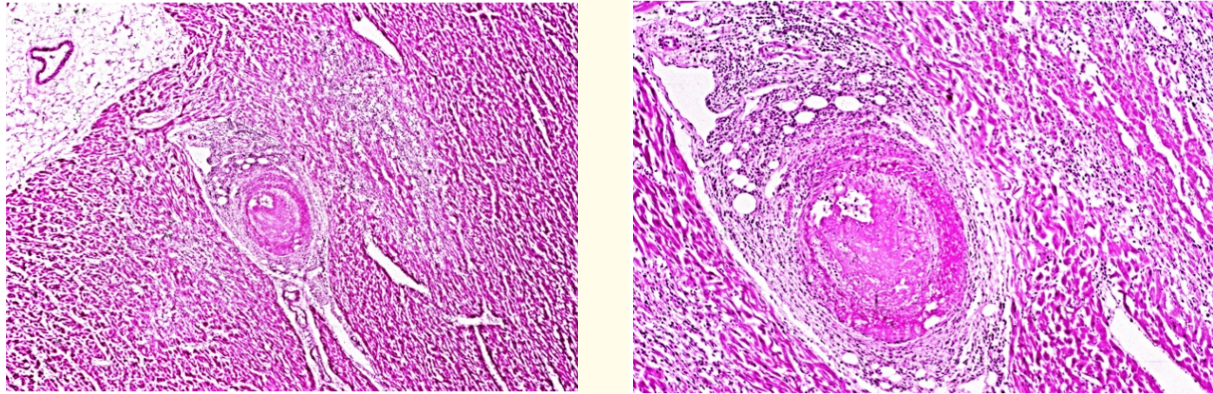

a *b*

Figure 4a-4b: Rheumatoid arthritis, heart, subepicardial arteriole. Acute non-specific vasculitis.
(a) Hematoxylin-Eosin staining (H-E), x50, (b) same as (a) x125.

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a   *b*

Figure 5a-5b: *Rheumatoid arthritis, heart, intramural small artery. Subacute-subchronic fibrinoid necrotic thrombovasculitis.*
(a) Hematoxylin-Eosin (H-E), x20, (b) same as (a) x50.
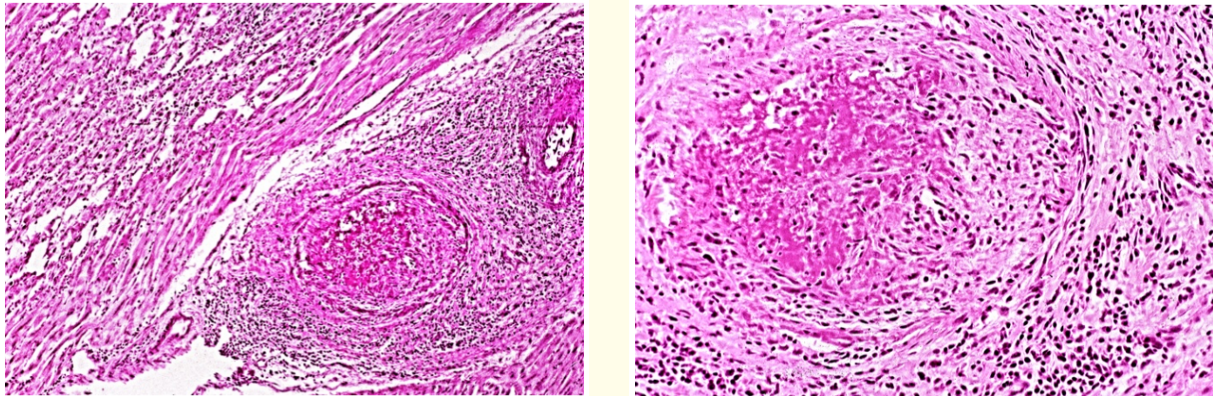
a   *b*

Figure 6a-6b: *(Same field of Figure 7c in different deepness). Rheumatoid arthritis, heart, intramural small artery. Subacute-subchronic granulomatous thrombovasculitis.*
(a) H-E, x125, (b) same as (a) x200.

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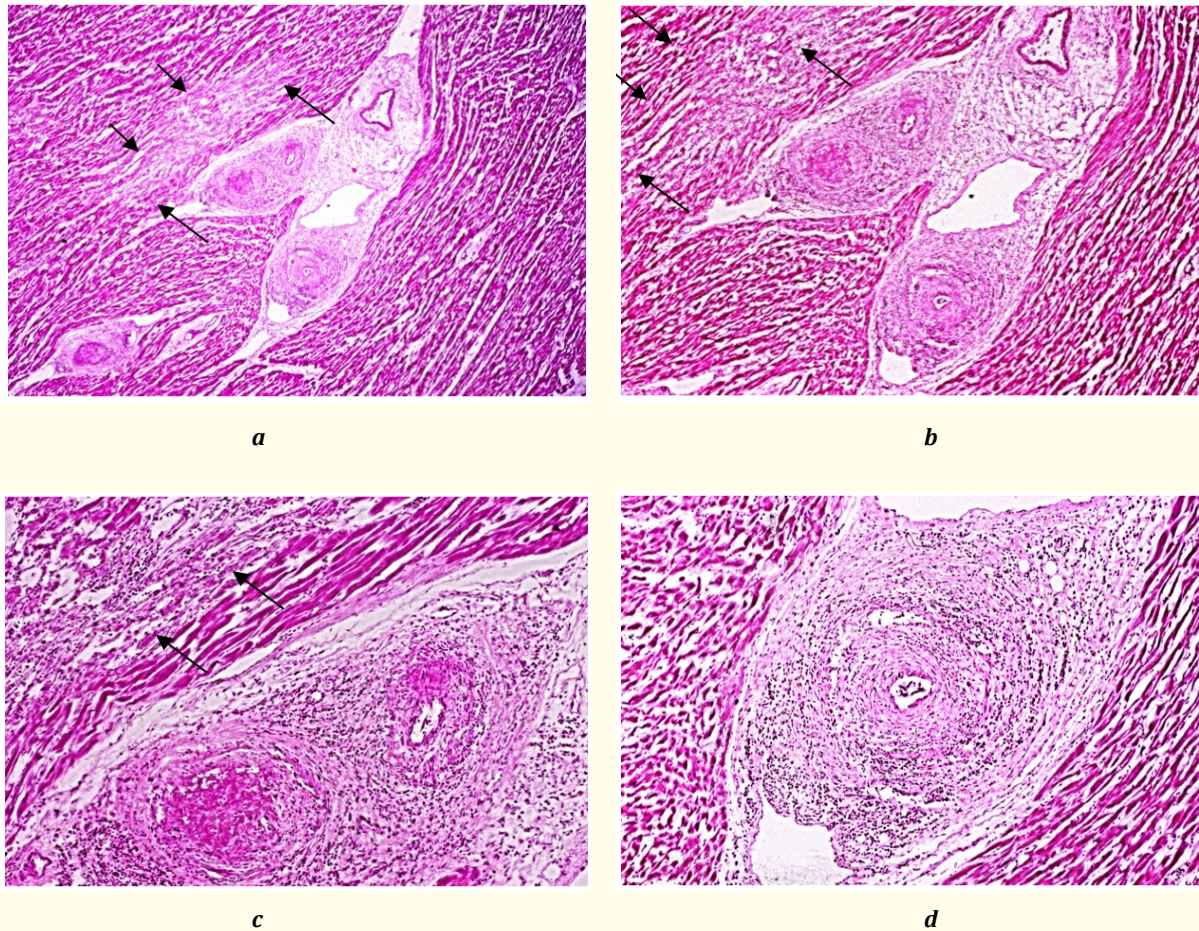
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Figure 7a-7d: Rheumatoid arthritis, heart, intramural small arteries, arterioles and accompanying veins with incipient myocardiocytolysis (focal microinfarct of the myocardium - arrows).
Different stages of non-specific, fibrinoid necrosis and granulomatous vasculitis exists side by side in blood vessels of different caliber.
(a) H-E, x20, (b) same as (a) x50, (c-d) same as (a) x125.

Discussion

sAV is a basic complication of RA, and cAV is closely associated with it; the relationship was very strong and positive (association's coefficient = 0.8626, χ^2 = 37.614, p < 0.0000).

According to Vollertsen's data the survival of RA patients with rheumatoid vasculitis decreased compared those to the age- and sex-matched Upper Middle Western (normal) population [30].

They found no difference in survival between patients with vasculitis and the patients with classic rheumatoid arthritis [30] like us; in our autopsy population there was no significant difference in mean age of patients with and without sAV or cAV (Tables 1 and 2).

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The lack of significant difference in average age, onset or duration of RA between female and male patients with sAV and with cAV indicating that sAV or cAV may develop in both sexes and at any time in the course of the disease (Table 2, 3rd section).

According to Vollertsen and Conn (1990) the most common laboratory findings of rheumatoid vasculitis are the elevated ESR, increased CRP level, anemia, thrombocytosis, hypoalbuminemia, and a positive rheumatoid factor [31]. In Nikolaisen and coworkers' study (2005) the cut-off titres for rheuma factor by Waaler-Rose haemagglutination test was 1:160 [32].

Laboratory values mentioned by Vollertsen and Conn (1990) were elevated and accompanied with hypoalbuminemia in our patient cohort's with sAV as well, compared those to the normal range of parameters, but probable because of the limited number of patients and/or the high values of SDs, the differences were not significant between patient cohorts with and without sAV or in comparison to the total population.

Patients with cAV showed significant differences regarding the incriminated albumin (p < 0.023) or CRP (p < 0.00047) values, compared to patients with sAV or to the total population (albumin p < 0.034, CRP p < 0.000287).

In contrast with these we found a very strong and consequent difference between patient cohorts with and without sAV regarding the Latex (p < 0.001), BUN (p < 0.020), and creatinin (p < 0.00017) values, and in comparison with the total population (Latex p < 0.004, BUN p < 0.036, and creatinin p < 0.001).

The differences were similarly strong and consequent comparing the patients with cAV and without sAV (Latex p < 0.024, BUN p < 0.011, and creatinin p < 0.00009), and in comparison with the total population (Latex p < 0.080 - NS, BUN p < 0.020, and creatinin p < 0.00036).

Furthermore the patients with cAV had a significantly lower level of albumin (p < 0.023) and serum sodium (p < 0.003) and significantly higher level of CRP (p < 0.00047) and alfa2 globulin (p < 0.033), compared to patients without sAV (n = 105) or to the total population (n = 138 - albumin p < 0.034, serum sodium (p < 0.005, CRP p < 0.00028, and alfa2 globulin p < 0.046).

Renal involvement in rheumatoid vasculitis has been considered unusual in earlier studies, but according to several recent reports this may be more common than previously recognized [31]. The higher values of BUN (12.28 mmol/l) and the elevated creatinin level (144.70 µmol/l) in patients without sAV compared to the normal range (BUN 12.28 versus 2.00 - 8.90 mmol/l and creatinin 144.70 µmol/l versus 62 - 106 µmol/l) argue against the role of vasculitis in restricted renal function.

The significantly lower values of BUN (8.94 mmol/l) and creatinin (79.97 µmol/l) in patients with sAV compared to patients without sAV (BUN 12.28 mmol/l and creatinin 144.70 µmol/l) or to the total population (BUN 11.44 mmol/l and creatinin 127.92 µmol/l) suggest also, that primarily it is not vasculitis which is responsible for the reduced renal function.

Laboratory parameters of patients with cAV showed the same tendency. The levels of BUN (8.50 ± 3.36 mmol/l) and creatinin (71.94 ± 30.35 µmol/l) were within the normal range (BUN 2.00 - 8.90 mmol/l and creatinin 62 - 106 µmol/l), furthermore were significantly lower compared to patients without sAV (BUN 12.28 mmol/l and creatinin 144.70 µmol/l) or to the total population (BUN 11.44 mmol/l and creatinin 127.92 µmol/l), which also support the possibility that the restricted renal changes are not caused by vasculitis.

The role of amyloidosis may be more important in impared renal function than sAV or cAV. AA amyloidosis coexisted in 5 of 33 patients with sAV [33], in 3 of 21 with cAV [28,33], in 28 of 105 without sAV, and was present in 33 of 138 patients of the total population [33].

The relationship between patient cohorts with sAV (5 AAa of 33 - 15.15%) and without sAV (28 AAa of 105 - 26.66%) was weaker, and was stronger between patients with cAV (3 AAa of 21- 14.28%) and without sAV (28 AAa of 105 - 26.66%). The "p" values of significance expressed these differences regarding BUN (p < 0.020 versus p < 0.011) and creatinin (p < 0.00017 versus p < 0.00009; the levels of significance increased (the levels of significance is lower between 15.15% and 26.66%, and higher between 14.28% and 26.66%).

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Compared the patients with sAV (5 AAa of 33 - 15.15%) to the total population (33 AAa of 138 - 23.9%), or cAV (3 AAa of 21 - 14.28%) to the total population (33 AAa of 138 - 23.9%), the levels of significance showed consequently the same tendency regarding BUN ($p < 0.036$ versus $p < 0.020$) and creatinin ($p < 0.001$ p versus < 0.00036; the levels of significance increased, supporting the role of AAa in restricted renal function.

All groups of RA patients were anemic, RBC values decreased in patients with sAV (3.958 T/l), with cAV (3.967 T/l), without sAV (3.69 T/l) in the total population (3.76 T/l), below the normal range of laboratory parameters (4.50-5.90 T/l). Respecting the values of standard deviation with and without sAV or cAV the levels of RBC were within the same range, without significant difference. This suggests that the anemia is primarily not due to vasculitis. Renal hypoxia stimulates erythropoiesis in the bone marrow by erythropoietin secreted by the kidneys. Renal hypoxia may be related to renal amyloidosis as well. In massive renal amyloidosis the erythropoietin secretion is expectedly decreased, resulting in anemia.

The low level of serum sodium (with elevated potassium level) or minimal abnormalities in urine specific gravity may also indicate renal involvement [31]. But these values remained in the normal range of laboratory parameters: serum potassium 3.70 - 5.10 mmol/l, serum sodium 135 - 145 mmol/l or urine specific gravity 1005 and 1030 g/ml, which reduce the clinical significance of these parameters, and only their gradual impairment may suggest a trend.

High values of Latex, Waaler-Rose and CRP are indices of basic activity of RA, low levels of serum albumin [34] and high values of alpha2-globulin are related to the basic inflammatory processes of the disease as well, and not to vasculitis [35]. Serum levels of albumin may decrease in any inflammation and should be regarded as a "negative" acute-phase protein [34].

Summarizing our results: the classic clinical-laboratory parameters mentioned in the pertinent literature and analyzed in our study (with or without significant differences) are not sufficient to predict the vasculitis, in agreement with Schmid., *et al.* (1961) [35], and others [5,30,31]. They are connected to the basic activity of RA or to the actual intensity of inflammatory processes of the disease [5]. We found no significant differences in laboratory parameters between patient cohorts with sAV or cAV and without sAV, which were suitable to indicate existing vasculitis. Classic skin lesions (purpura, petechiae, deep cutaneous ulceration, peripheral gangrene, digital or nailfold infarcts), and neurological symptoms (mononeuritis multiplex, peripheral neuropathy) are the main features in suspected vasculitis and remain the leading indicator, prodrome and clinical sign for its detection [2,3,5,6]. Other causes of similar lesions (diabetes, atherosclerosis, drug reactions, infection, neoplasms) should be excluded as well, because of lack the specific clinical signs and symptoms [36]. The low incidence of vasculitis in the skin (34.78%) or the relatively rare involvement of the peripheral nerves (52.17%) makes the biopsy necessary in cases of suspected vasculitis; we suggested the sural nerve biopsy with surrounding muscle as optimal (with 64.29 % prevalence) to confirm and characterize an existing vasculitis (with or without visible involvement of the skin) [22].

Conclusion

The risk of sAV or cAV is higher in elderly female RA patients than in RA patients who did not have vasculitis ($p < 0.002$, resp. $p < 0.010$). The chance of survival of female patients with sAV is lower than for RA patients who do not have vasculitis ($p < 0.052$); the disease duration in patients with cAV was shorter than in patients without sAV, but this difference was not significant ($p < 0.17$ - NS).

Comparing the age, sex, onset of RA, and duration of disease at the time of death we found no significant difference between patients with sAV (n = 33) and cAV (n = 21), neither between females or males; sAV and cAV may complicate RA in both sexes, and at any time in the course of the disease.

The classic clinical-laboratory parameters (mentioned in the pertinent literature and analyzed in our study (Latex, BUN, creatinin, albumin, alfa-2 globulin, CRP, Waaler-Rose, RBC, and ESR) with or without significant differences, are not sufficient to predict vasculitis.

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They are related to the basic activity of RA or to the actual intensity of inflammatory processes of the disease. We found no significant differences in classic laboratory parameters between patient cohorts with sAV or cAV and without sAV, which were suitable for indication of existing vasculitis.

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