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Systemic Rheumatoid and Septic Vasculitis: A Comparative Postmortem Study of 161 Rheumatoid Arthritis Patients

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Abstract

Aim: The aim of this study was to characterize the rheumatoid (RV) and Septic Vasculitis (SV) histologically in Rheumatoid Arthritis (RA).

Patients and Methods: RA was confirmed clinically according to the criteria of the American College of Rheumatology (ACR). Postmortem twelve organs of 161 RA patients were studied microscopically. Lethal septic infections were determined at autopsy and analyzed retrospectively, reviewing the clinical and pathological reports. The RV or SV was confirmed histologically. Demographics of different patient cohorts were compared with the Student t-probe. The possible role of SI on the prevalence of RV and SV was analyzed with chi-squared ($\chi 2$) test.

Results and Conclusion: RA was complicated by systemic RV in 33 (20.49%) of 161 patients. Lethal septic infection was observed in 24 (14.91%) of 161 patients accompanied in 3 (12.5% of 24, 1.86% of 161) patients by SV. RV complicated RA in both sexes, and at any time in the course of the disease, elderly (especially female) patients were more likely to be affected by RV than younger or male patients. Septic complications of RA reduced life expectancy and were strongly expressed in female patients with SV. RV and SV are most likely to be distinguished histologically.

Keywords: Rheumatoid; Septic vasculitis; Histological characteristics

Abbreviations: RA: Rheumatoid Arthritis; SI: Lethal Septic Infection; RV: Systemic Rheumatoid Vasculitis; SV: Systemic Septic Vasculitis; ACR: American College Of Rheumatology.

Type of vasculitis: Ns: Non-Specific; Fn: Fibrinoid Necrotic; Gr: Granulomatous.

Size of blood vessels: a: Arteriole; A: Small Artery; AA: Medium Size Artery; v: Venule; V: Small Vein; VV: Medium Size Vein.

Stages of vasculitis: "a": Acute; "b": Subacute; "c": Subschronic; "d": Chronic; Ac: Association Coefficient; f: Female; m: Male; SD: Standard Deviation; ND: No Data; AAa: Systemic Amyloid A amyloidosis; HE: Hematoxylin-Eosin Stain; PAS: Periodic Acid Schiff Reaction.

Introduction

Systemic vasculitis of autoimmune origin plays a pivotal role in the pathogenesis of autoimmune disorders, as well as in rheumatoid arthritis (RA) [1]. Autoimmune diseases may be characterized by the type, prevalence, severity and stages of immune mediated vasculitis involving different size vessels.

Rheumatoid vasculitis (RV) involving of blood vessels in RA may be characterized by non-specific inflammation (Ns) and/or by Fibrinoid necrosis (Fn) or by granulomatous transformation (Gr) of blood vessels in different (acute – "a", subacute – "b", subschronic – "c", chronic – "d) stages of the pathological process [1].

Autoimmune diseases (and RA as well) may be complicated by septic (bacterial, viral, fungal, etc.) infections (SI) accompanied by Systemic Vasculitis of septic origin (SV). The correct clinical and/or patological diagnosis of RV and SV is essential because of fundamental differences in therapy.

Objective

The aim of this study was to characterize RV and SV histologically by the type, prevalence, severity and stages of vasculitis involving blood vessels of different calibre, furthermore to determine the influence of age, sex, onset, and disease duration of RA on prevalence of RV and SV.

Patients and Methods

At the National Institute of Rheumatology 9475 patients died between 1969 and 1992; among them 161 with RA. RA was confirmed clinically according to the criteria of the American College of Rheumatology (ACR) [2]. 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. Lethal SI [1] were determined at autopsy and analyzed retrospectively, reviewing the clinical and pathological reports. The RV or SV was confirmed histologically in agreement with the recommendations of the Consensus Conference (2013) [3]. The prevalence (existence), severity (density), type of systemic vasculitis in blood vessels of different calibers, and the (acute, subacute, subchronic, chronic) stages of vasculitis were determined microscopically [1]. Severity of vasculitis was evaluated by semi-quantitative visual estimation on a 0 to 3 plus scale (based on the number of involved vessels/light microscopic field x40). Demographics of different patient cohorts were compared with the Student t-probe. The possible role of SI on the prevalence of RV and SV was analyzed with chi-squared ($\chi 2$) test.

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Results

Systemic vasculitis was observed in 36 (22.36%), and lethal septic infection in 24 (14.91%) of 161 patients. Systemic vasculitis existed without lethal SI in 33 (91.67%) of 36 patients. Systemic vasculitis without SI was regarded as systemic RV, a direct complication of RA. The negative value of associations coefficient and the lack of (not) significant correlation between systemic vasculitis and lethal SI (ac: -0.3791, ^{2}=0.9826, p<0.3216) supported the direct autoimmune origin of systemic vasculitis in these 33 patients without SI. Systemic vasculitis was associated with SI in 3 (8.33%) of 36 patients, and was regarded as of septic origin. The clinically identified pathogenic agents (E. coli, Proteus mirabilis, Pseudomonas aeruginosa) and the strong, significant and positive correlation between SI and SV (ac: 1, ^{2}=11.2838, p<0.0007) supported the infectious origin of SV. RV and SV did not occur together in our patients, and there was no association between these two entities (ac: -1, ^{2}=0.0078, p<0.9296). Table 1 summarized the demographics, onset and duration of disease of the total population, with and without RV, with and without SI, furthermore with and without SV.

Figure 1 demonstrates the relationships between total population of RA patients and patient cohorts complicated by RV, SI or SV.

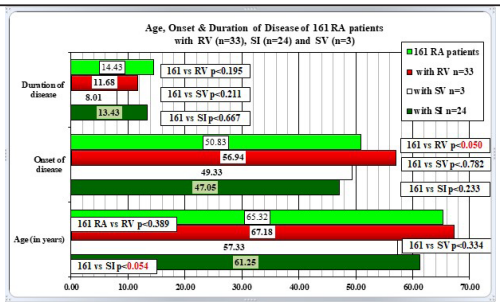

Figure 1: RA started significantly later in patients with RV in comparison to the total population (p<.050). The patients with SI died significantly earlier compared to the total population (p<0.054).

Comparing the age, sex, onset of RA, and duration of disease, RA started significantly later in patients with RV, than without RV (p<0.016); this difference was especially expressed in women (p<0.00048), who

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)	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	66.27 ± 15.50	19 – 88	52.57 ± 19.88	13.46 ± 10.08
with RV	33 of 161	67.18 ± 10.64	32 – 83	56.94 ± 14.63	11.68 ± 10.34
Female	20	66.95 ± 11.11	32 – 82	59.47 ± 10.15	10.63 ± 7.46
Male	13	67.46 ± 9.87	53 – 83	52.92 ± 19.07	13.33 ± 13.55
without RV	125 of 161	65.02 ± 13.48	16 – 88	49.04 ± 17.39	15.45 ± 10.47
Female	94	64.82 ± 11.84	16 – 87	48.08 ± 16.15	16.03 ± 11.03
Male	31	65.65 ± 17.51	19 – 88	52.21 ± 20.65	13.54 ± 8.05
with SI	24 of 161	61.25 ± 8.55	41 – 83	47.05 ± 12.32	13.43 ± 9.49
Female	17	60.41 ± 9.22	41 – 83	47.67 ± 13.72	12.00 ± 9.85
Male	7	63.29 ± 9.84	70 – 52	45.50 ± 7.59	17.00 ± 7.39
without SI	137 of 161	66.04 ± 13.45	16 – 88	51.52 ± 17.58	14.61 ± 10.68
Female	99	65.73 ± 12.01	16 – 87	50.64 ± 15.98	15.28 ± 10.70
Male	38	66.82 ± 16.59	19 – 88	53.94 ± 21.19	12.77 ± 10.38
with SV	3 of 161	57.33 ± 8.96	51 – 70	49.33 ± 6.55	8.007 ± 5.10
Female	2	51.00 ± 0.00	51 – 51	45.50 ± 4.50	5.50 ± 4.50
Male	1	70.00 ± 0.00	70	57.00 ± 0.00	13.00 ± 0.00
without SV of 161 RA	158 of 161	65.47 ± 12.97	16 – 88	50.87 ± 17.12	14.57 ± 10.56
Female	114	65.19 ± 11.75	16 – 87	50.29 ± 15.83	14.98 ± 10.65
Male	44	66.18 ± 15.66	19 – 88	52.44 ± 20.14	13.47±10.22
without SV of 24 SI	21 of 24	61.81 ± 8.34	41 – 83	46.67 ± 13.00	14.33 ± 9.75
Female	15	61.67 ± 9.10	41 – 83	48.00 ± 14.60	13.00 ± 10.07
Male	6	62.17 ± 6.01	52 – 68	43.20 ± 6.11	17.80 ± 7.86

Table 1: There was no significant difference in mean age of RA patients at death with or without RV, with or without SV. Septic complications of RA reduced significantly the lifetime of septic patients compared to the patients without SI (p<0.029) or compared to the total population (p<0.054).

RA patients n=161	Age	Onset of disease	Disease duration
RA pts. n=161 versus pts. with RV n=33 of 161	p<0.389	p<0.050	p<0.195
Female n=116 of 161 versus n=20 of 33	p<0.477	p<0.003	p<0.052
Male n=45 of 161 versus n=13 of 33	p<0.748	p<0.959	p<0.978
RA pts. n=161 versus pts. without RV n=125 of 161	p<0.851	p<0.427	p<0.460
Female n=116 of 161 versus n=94 of 125	p<0.938	p<0.383	p<0.454
Male n=45 of 161 versus n=31 of 125	p<0.876	p<0.948	p<0.973
RA pts. n=161 versus pts. with SI n=24 of 161	p<0.054	p<0.233	p<0.667
Female n=116 of 161 versus n=17 of 24	p<0.171	p<0.805	p<0.333
Male n=45 of 161 versus n=7 of 24	p<0.398	p<0.155	p<0.368
RA pts. n=161 versus pts. without SI n=137 of 161	p<0.644	p<0.755	p<0.893
Female n=116 of 161 versus n=99 of 137	p<0.635	p<0.850	p<0.756
Male n=45 of 161 versus n=38 of 137	p<0.879	p<0.789	p<0.788
RA pts. n=161 versus pts. with SV n=3 of 161	p<0.334	p<0.782	p<0.211
Female n=116 of 161 versus n=2 of 161	p<0. 00000	p<0.477	p<0.273
Male n=45 of 161 versus n=1 of 161	-	-	-
RA pts. n=161 versus pts. without SV n=158 of 161	p<0.917	p<0.987	p<0.911
Female n=116 of 161 versus n=114 of 158	p<0.875	p<0.966	p<0.901
Male n=45 of 161 versus n=44 of 158	p<0.980	p<0.979	p<0.996
RA pts with RV n=33 versus pts. without RV n=125 of 161	p<0.388	p<0.016	p<0.086
Female n=20 of 33 versus n=94 of 125	p<0. 458	p<0.00048	p<0.017
Male n=13 of 33 versus n=31 of 125	p<0.673	p<0.922	p<0.963
RA pts with SI n=24 versus pts. without SI n=137 of 161	p<0.029	p<0.172	p<0.617
Female n=17 of 24 versus n=99 of 137	p<0.052	p<0.473	p<0.268
Male n=7 of 24 versus n=38 of 137	p<0.353	p<0.116	p<0.297
RA pts with SV n=3 versus pts. without SV n=158 of 161	p<0.327	p<0.778	p<0.204
Female n=2 of 3 versus n=114 of 158	p<0.00000	p<0.469	p<0.268
Male n=1 of 3 versus n=44 of 158	-	-	-
RA pts with SV n=3 versus pts. without SV n=21 of 24 SI	p<0.558	p<0.658	p<0.216
Female n=2 of 3 versus n=15 of 21	p<0.001	p<0.710	p<0.298
Male n=1 of 3 versus n=6 of 21	-	-	-
RA pts with RV n=33 of 161 versus pts. with SV n=3 of 24 SI	p<0.256	p<0.237	p<0.428
Female n=20 of 33 versus n=2 of 3	p<0.00001	p<0.138	p<0.444
Male n=13 of 33 versus n=1 of 3	-	-	-

Table 2: The statistical correlations ("p" values of significance) between female and male RA patients with and without RV, SI or SV.

died notably earlier (p<0.017).

The tendency was the same comparing RA patients with RV to the total population (p<0.050). This difference was especially expressed in women (p<0.003), who died significantly earlier than the others (p<0.052).

The risk of fatal outcome was significantly higher in RA patients with SI compared those to the patients without SI, who died significantly earlier (p<0.029), with particular reference to women (p<0.052). The tendency was similar in RA patients complicated by SI in comparison to the total population (p<0.054).

The risk of early death of septic patients increased by onset of SV compared those to the septic patients without SV, but this difference

was not significant (p<0.558–NS). The difference was significant comparing the septic women complicated by SV to septic women without SV (p<0.001). The risk of fatal outcome was extremely high among females with SV as compared to the total population of females without SV (p<0.0000001).

The chance of survival was lower in septic patients complicated by S, than in RA patients complicated by RV (p<0.256–NS); the difference was particularly pronounced and significant comparing septic women with SV to women with RV (p<0.00001). The relationship ("p"values of correlation) of demographics, onset and duration of disease between RA patients with and without RV, SI or SV are summarized in Table 2.

Figure 2 demonstrate the differences and level of significance between female RA patients of total population with and without RV, SI or SV.

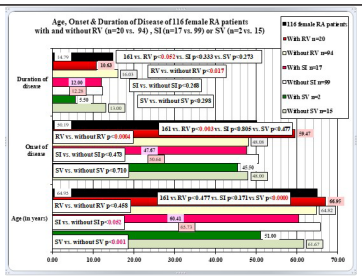

Figure 2: RA started significantly later in women with RV, than in women without RV (p<0.0004). The tendency was similar comparing the women with RV to the total population of women (p<0.003), and these patients died significantly earlier (p<0.017, and p<0.052). The septic complication reduced significantly the lifetime of women with SI compared to women without SI (p<0.052). Septic women complicated by SV died earlier compared to septic women not complicated by SV (p<0.001).

Figure 3 demonstrate the differences and level of significance between male RA patients of total population with and without RV, SI or SV.

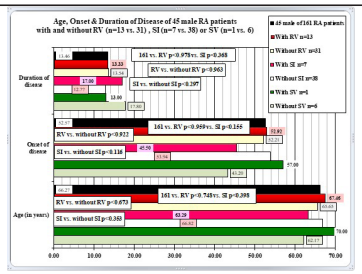

Figure 3: There was no significant difference between male patients with and without RV or SV in mean age, in onset or duration of disease.

Age	f/m	Type	Prevalence of RV						Prevalence of RV						Stages of RV			
		Size	a	A	AA	v	V	VV	a	A	AA	v	V	VV	"a"	"b"	"c"	"d"
1	f	Ns	3	2	2	0	0	0	4	3	3	0	0	0	0	5	6	4
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Gr	1	2	1	0	0	0	1	3	1	0	0	0	0	0	1	4
2	m	Ns	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1
		Fn	3	2	0	0	0	0	5	2	0	0	0	0	0	4	5	0
		Gr	1	1	0	0	0	0	1	1	0	0	0	0	0	2	0	0
3	m	Ns	2	1	2	0	0	0	4	3	4	0	0	0	4	5	1	0
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	f	Ns	1	1	1	0	0	0	2	3	2	0	0	0	0	2	2	2
		Fn	0	1	0	0	0	0	0	2	0	0	0	0	0	1	1	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	m	Ns	4	5	5	0	0	0	9	10	9	0	0	0	0	11	13	9
		Fn	2	1	0	0	0	0	4	2	0	0	0	0	0	3	2	0
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	f	Ns	6	2	1	0	0	0	6	4	2	0	0	0	0	6	8	5
		Fn	2	0	0	0	0	0	3	0	0	0	0	0	0	2	2	0
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

7	f	Ns	1	2	0	0	0	0	2	2	0	0	0	0	0	1	2	1
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Gr	1	2	1	0	1	1	2	4	1	0	1	1	0	3	4	0
8	f	Ns	2	1	0	0	0	0	2	1	0	0	0	0	0	1	3	3
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	f	Ns	9	5	0	0	1	0	25	13	0	0	1	0	9	14	10	4
		Fn	8	6	0	0	1	0	21	13	0	0	1	0	4	14	10	2
		Gr	8	5	2	0	1	1	19	11	2	0	1	1	0	14	14	5
10	m	Ns	4	1	0	0	0	0	8	1	0	0	0	0	1	2	4	4
		Fn	2	1	0	0	0	0	3	1	0	0	0	0	0	1	2	2
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	f	Ns	1	1	1	0	0	0	3	3	3	0	0	0	3	3	3	1
		Fn	1	0	0	0	0	0	2	0	0	0	0	0	1	1	1	0
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	m	Ns	3	2	1	0	0	0	4	3	1	0	0	0	0	4	6	1
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	f	Ns	1	2	1	0	0	0	1	3	1	0	0	0	0	2	4	0
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	f	Ns	1	1	0	0	0	0	2	3	0	0	0	0	2	2	2	2
		Fn	1	0	0	0	0	0	3	0	0	0	0	0	1	1	1	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	m	Ns	7	8	2	0	0	0	18	15	5	0	0	0	0	7	12	15
		Fn	2	1	0	0	1	1	2	3	0	0	3	2	0	4	5	3
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	f	Ns	1	1	0	0	0	0	1	2	0	0	0	0	0	0	2	2
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	f	Ns	7	3	1	0	0	0	12	7	1	0	0	0	0	6	11	10
		Fn	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	m	Ns	4	3	1	0	0	0	10	5	3	0	0	0	1	4	7	8
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
19	f	Ns	5	0	0	3	0	0	7	0	0	4	0	0	0	7	4	1
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	m	Ns	2	1	1	2	0	0	2	1	3	3	0	0	1	4	5	2
		Fn	1	2	0	0	0	0	3	4	0	0	0	0	0	0	3	2
			1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
21	f	Ns	7	5	1	0	1	0	15	10	3	0	2	0	0	4	14	11
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

22	f	Ns	7	1	0	0	0	0	17	2	0	0	0	0	1	7	7	6
		Fn	4	1	0	0	0	0	9	2	0	0	0	0	1	4	5	2
			4	3	0	0	0	0	8	5	0	0	0	0	1	6	7	0
23	m	Ns	2	2	0	0	1	0	5	3	0	0	2	0	1	3	4	4
		Fn	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	m	Ns	1	0	0	0	1	0	2	0	0	0	1	0	0	2	0	0
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	f	Ns	2	3	1	1	0	0	2	3	1	2	0	0	1	5	7	2
		Fn	4	1	0	0	1	0	6	1	0	0	1	0	0	1	4	6
		Gr	3	0	0	0	0	0	8	0	0	0	0	0	1	3	3	0
26	m	Ns	1	1	1	0	0	0	2	2	3	0	0	0	0	1	3	3
		Fn	1	1	0	0	0	0	2	2	0	0	0	0	0	0	0	2
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	f	Ns	1	0	1	0	0	0	1	0	2	0	0	0	0	1	1	1
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	f	Ns	5	2	1	0	0	0	5	2	1	0	0	0	2	6	8	3
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	f	Ns	2	0	0	0	0	0	2	0	0	0	0	0	0	0	2	2
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Gr	1	1	0	0	0	0	2	2	0	0	0	0	0	2	2	0
30	m	Ns	2	0	0	0	0	0	3	0	0	0	0	0	0	2	1	0
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	f	Ns	2	1	0	0	0	0	5	2	0	0	0	0	0	2	3	1
		Fn	0	2	0	0	0	0	0	3	0	0	0	0	0	2	2	0
		Gr	1	0	0	0	0	0	1	0	0	0	0	0	0	1	1	0
32	f	Ns	11	8	4	0	0	0	20	16	4	0	0	0	0	5	23	17
		Fn	4	3	0	0	0	0	8	3	0	0	0	0	0	3	7	6
			1	1	0	0	0	0	2	1	0	0	0	0	0	2	1	0
33	f	Ns	2	3	0	0	0	0	2	3	0	0	0	0	0	4	5	2
		Fn	0	1	0	0	0	0	0	1	0	0	0	0	0	1	1	0
			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
			a	A	AA	v	V	VV	a	A	AA	v	V	VV	“a”	“b”	“c”	“d”
		Σ Ns	110	68	28	6	4	0	204	125	51	9	6	0	26	128	184	127
		Σ Fn	37	23	0	0	3	1	73	39	0	0	5	2	7	43	52	26
		Σ Gr	22	15	4	0	2	2	45	27	4	0	2	2	2	34	35	9
		Σ	169	106	32	6	9	3	322	191	55	9	13	4				
		Total	325						594						673			
	f/m	Type	Prevalence of RV						Severity of RV						Stages of RV			

Table 3: RV was present in blood vessels of different caliber with various prevalence and value of severity in surgical specimens of 12 organs in 33 RA patients. RV existed in different stages of inflammation side by side in different vessels or in the same ones.

Size	f/m	Type	Prevalence of SV						Severity of SV						Stages of SV			
		Size	a	A	AA	v	V	VV	a	A	AA	v	V	VV	"a"	"b"	"c"	"d"
1	f	Ns	5	4	4	0	0	0	11	8	4	0	0	0	0	5	6	4
		Fn	2	1	0	0	0	0	4	2	0	0	0	0	0	0	0	0
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	4
2	f	Ns	3	2	0	0	0	0	4	2	0	0	0	0	0	0	1	1
		Fn	0	1	0	0	0	0	0	1	0	0	0	0	0	4	5	0
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0
3	m	Ns	0	0	1	0	0	0	0	0	1	0	0	0	4	5	1	0
		Fn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Ns	a	A	AA	v	V	VV	a	A	AA	v	V	VV	"a"	"b"	"c"	"d"
		Σ Ns	8	6	5	0	0	0	15	10	5	0	0	0	17	12	11	0
		Σ Fn	2	2	0	0	0	0	4	3	0	0	0	0	7	3	0	0
		Σ Gr	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		Σ	10	8	5	0	0	0	19	13	5	0	0	0	24	15	11	0
		Total	23						37						50			
f/m			Prevalence of SV						Severity of SV						Stages of SV			

Table 4: SV was usually severe in frequently involved blood vessels, with more frequent recurrence of inflammation.

N of RA patients with systemic vasculitis	N of RA patients with Type of vasculitis				Severity Type of vasculitis				Stages				
RV n=33	Ns	Fn	Gr	Σ	Ns	Fn	Gr	Σ	"a"	"b"	"c"	"d"	Σ
arteriole	33,85	11,38	6,77	52,00	34,34	12,29	7,58	54,21	3,27	17,09	20,95	11,89	53,19
small artery	20,92	7,08	4,62	32,62	21,04	6,57	4,55	32,15	1,19	9,36	13,22	8,32	32,10
medium size artery	8,62	0	1,23	9,85	8,59	0	0,67	9,26	0,59	2,08	4,31	3,27	10,25
venule	1,85	0	0	1,85	1,52	0	0	1,52	0,15	0,89	0,59	0,00	1,63
small vein	1,23	0,92	0,62	2,77	1,01	0,84	0,34	2,19	0,15	0,89	0,59	0,45	2,08
medium size vein	0	0,31	0,62	0,92	0	0,34	0,34	0,67	0	0,15	0,45	0,15	0,74
Total	66,46	19,69	13,85	100	66,50	20,03	13,47	100	5,35	30,46	40,12	24,07	100
SV n=3	Ns	Fn	Gr	Σ	Ns	Fn	Gr	Σ	"a"	"b"	"c"	"d"	Σ
arteriole	34,78	8,70	0	43,48	40,54	10,81	0	51,35	4,00	16,00	18,00	10,00	48,00
small artery	26,09	8,70	0	34,78	27,03	8,11	0	35,14	2,00	8,00	12,00	8,00	30,00
medium size artery	21,74	0	0	21,74	13,51	0	0	13,51	0,00	8,00	8,00	6,00	22,00
venule	0	0	0	0	0	0	0	0	0	0	0	0	0
small vein	0	0	0	0	0	0	0	0	0	0	0	0	0
medium size vein	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	82,61	17,39	0	100	81,08	18,92	0	100	6,00	32,00	38,00	24,00	100

Table 5: Prevalence, severity, stages and type of RV and SV (vertical columns) in blood vessels of 12 organs (distribution expressed in% of total sum) arranged according to the size of blood vessels (horizontal lines).

Prevalence, severity, and stages of calibre tion (recurrence of vascular changes) are different aspects of the same pathological process, and run parallel each other. RV was detected in arterioles in 169 (52.0%), small arteries in 106 (32.62%), medium size arteries in 32 (9.85%), venules in 6 (1.85%), small veins 9 (2.77%), and medium size veins 3 (0.92%). In most cases RV was non-specific (n=216; 66.46%), and less frequent fibrinoid necrotic (n=64; 19.69%) or granulomatous (n=45; 13.85%), and showed a more diverse (variegated) appearance. The RV was usually severe in the frequently involved blood vessels. RV existed in various stages of inflammation side by side in different blood vassels, even in the same one (Table 3 and Figure 4).

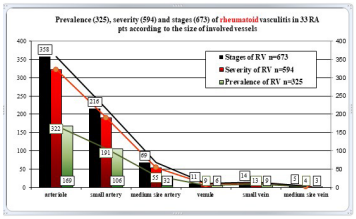

Figure 4: RV was usually severe in frequently involved blood vessels, with more frequent recurrence of inflammation.

Table 3 demonstrates the absolute values of prevalence, severity and stages of RV arranged according to the type of vasculitis/patient (horizontal lines), size of involed vessels, and stages of inflammation (vertical columns)

Figure 4 demonstrates the absolute values of prevalence, severity and stages of RV according to the involved vessels by calibre.

Table 4 demonstrates the absolute values of prevalence, severity and stages of SV arranged according to the type of vasculitis/patient (horizontal lines), size of involed vessels, and stages of inflammation (vertical columns)

SV involved arterioles in 10 (43.48%), small arteries in 8 (34.78%), and relatively frequently the medium size arteries (n=5; 21.74%); venules, small veins, and medium size veins were not involved by SV (n=0; 0.0%). SV was non-specific in 19 (82.61%), fibrinoid necrotic in 4 (17.39%) cases; granulomatous vasculitis was not detected in SV (n=0; 0.0%), and its appearance was histologically more monotonous. The SV was usually severe in the frequently involved blood vessels. SV existed in various stages of inflammation side by side in different blood vassels, even in the same one (Table 4 and Figure 5).

Figure 5 shows the absolute values of prevalence, severity and stages of SV in RA patients with SI according to the involved vessels by caliber

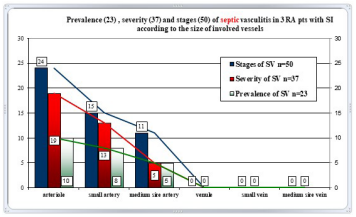

Figure 5: The involvement of medium aizes arteries was more pronounced, than of arterioles or small arteries. Venule, small vein, and medium size vein were never involved in SV.

Comparing distribution of RV and SV expressed in%, the prevalence, severity and stages of RV and SV were similar and nearly the same in blood vessels of different sizes (Table 5 and Figures 6-8). The veins were not involved and granulomatous vasculitis was not detected in RA patients with SV. SV was histologically more monotonous in comparison to RV, and involved relatively more frequently the medium size arteries.

Figure 6 shows the distribution of prevalence, severity and stages of RV (n=33) and SV (n=3) in% (according to the size of blood vessels).

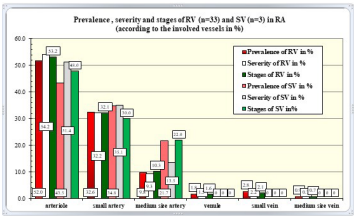

Figure 6: The prevalence, severity and stages of RV and SV expressed in%was nearly the same; the involvement of medium size arteries by SV was relatively pronounced in contrast to the arterioles and small arteries. Venule, small vein, and medium size vein were not involved by SV.

Figure 7 Distribution of prevalence, severity and stages of RV and SV in % (according to the type of vasculitis)

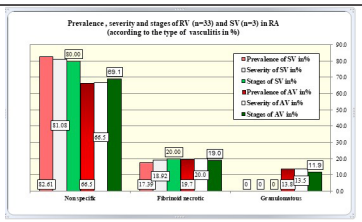

Figure 7: The prevalence, severity and stages of non-specific and fibrinoid necrotic vasculitis (expressed in %) was nearly the same in RA patients with RV and SV. Granulomatous vasculitis was not detected in SV.

RV and SV existed in different stages of the pathological process simultaneously side by side in blood vessels of different calibre even in the same vessel. Subchronic-chronic stages of vasculitis were dominant in RV and SV as well, with minimal shift to acute stage in the case of SV (Table 5 and Figure 8).

Figure 8 shows the stages of RV in RA patients according to the type of vasculitis

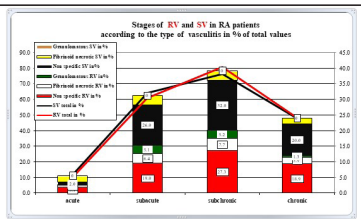

Figure 8: The presence of granulomatous vasculitis was characteristic of SV. Granulomatous type of vasculitis was not detected in RA patients with SV.

(distribution expressed in% of total sum).

Figures 9 and 10 show different types and stages of RV involving blood vessels of different calibre. Original magnifications correspond to the 24 × 36 mm transparency slide; the correct height: width ratio is 2:3. The printed size may be different; therefore the original magnifications are indicated.

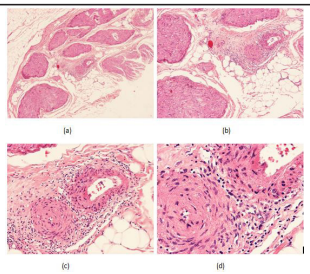

Figure 9: RA, RV, Sural nerve Small artery, non-specific vasculitis, subacute and chronic inflammatory segments side by side in the same vessel (a) HE, x 20, (b) same as (a) x40, (c) same as (a) x100, (d) same as (a) x200.

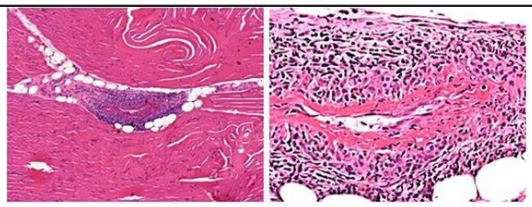

Figure 10: RA, RV, skeletal muscle Arteriole, fibrinoid necrotic subchronic vasculitis with partial granulomatous transformation of the vessel wall(a) HE, x 40, (b) same as (a) x200

Figures 11-13 show different types and stages of SV involving blood vessels of different calibre.

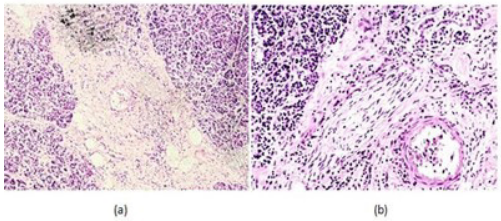

Figure 11: RA, SV, Pancreas Arteriole, non-specific acute vasculitis, accompanied by mild edematous ("serous"), pancreatitis of septic origin (a) HE, x 50, (b) same as (a) x125

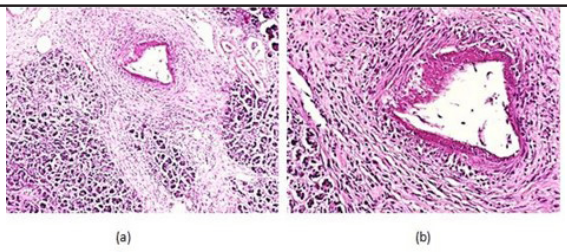

Figure 12: RA, SV, Pancreas Small artery, fibrinoid necrotic subchronic vasculitis, accompanied by mild interstitial pancreatitis of septic origin (a) PAS reaction, x 50, (b) same as (a) x125

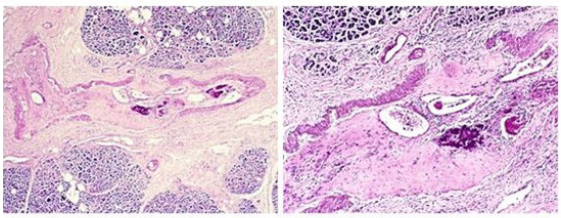

Figure 13: RA, SV, Pancreas Medium size artery, non-specific chronic recurrent vasculitis, with chronic stages of inflammation, focal calcification, and prominent structural changes side by side in the same segment HE, x20 (b) same as (a), HE, x40

Discussion

It is difficult to estimate the true prevalence of RV or SV in RA. In most clinical studies the diagnosis of RV is based on the evaluation of clinical symptoms: weight loss, fever, mononeuritis multiplex, peripheral neuropathy (numbness or weakness), classic skin lesions (purpura, petechiae, deep cutaneous ulceration, peripheral gangrene, digital or nailfold infarcts), and only some cases are confirmed by biopy, and even fewer by autopsy.

Rheumatoid vasculitis usually occurs in patients with severe, longstanding, nodular, destructive RA [4]. The majority of RA patients with RV is seropositive and has elevated inflammatory markers [5]. Unfortunately the classic clinical-laboratory parameters mentioned in the pertinent literature (Latex, BUN, creatinine, albumin, alfa-2 globulin, CRP, Waaler-Rose, RBC, and ESR) are not specific for vasculitis and do not predict vasculitis. They are related to the basic activity of RA, to renal complications of RA or to the actual intensity of inflammatory processes of the disease [6-8]. Moreover sub-clinical RV can occur "without characteristic clinical symptoms ('sub-clinical' vasculitis)" [9].

Present study confirmed the conclusion of our previous study [10] that there is no significant difference in the mean age of female and male patients at death with and without RV; RV complicates RA in both sexes, and at any time in the course of the disease. Elderly (especially female) patients are more likely to be affected by RV than younger or male patients.

Septic complications of RA reduced life expectancy of patients, especially of septic female patients and it was strongly expressed in septic female patients complicated by SV.

To the best of our knowledge a detailed analysis regarding the types, prevalence, severity and stages of RV and SV in RA, furthermore the proportion (distribution) of RV and SV in blood vessels of different asculi has not been available in the literature beside our earlier publications [1,11].

The correct clinical and/or asculitis l diagnosis of RV and SV is essential because of fundamental differences in therapy. Thus it is important to recognize clinically SI (with or without SV), and to diagnose histologically the nature of asculitis.

In RV the non-specific, fibrinoid necrotic and granulomatous type of vasculitis may exist simultaneously in different vessels or combined in the same vessel at the same time. Arteries of all sizes and veins are involved, with varying prevalence and severity of RV. Different stages of vasculitis exist simultaneously in different vessels, characterized by subacute-subchronic stages of inflammation. The stages of inflammation in RV are more frequent and severe than in SV.

In SV non-specific and fibrinoid necrotic type of vasculitis may exist simultaneously in different vessels or combined in the same vessel at the same time. Granulomatous vasculitis was not detected in SV; the presence of granulomatous vasculitis suggests RV. Vasculitis may involve all size of arteries, with relatively higher prevalence and severity of medium sized arteries. The more frequent and more severe involvement of medium size arteries is characteristic of SV versus RV. The venules, small and medium size veins were not attected by SV; inflammation of veins supports RV. Non-specific and fibrinoid necrotic types of SV existed in different stages of a pathological process with subchronic-chronic dominance and with minimal simultaneous acute shift in blood vessels at the same time.

Coexistence of RV and SV may not be excludedin RA although in present study they did not occur together.

Conclusion

RV complicated RA in both sexes, and at any time in the course of the disease, elderly (especially female) patients were more likely to be affected by RV than younger or male patients. Septic complications of RA reduced life expectancy and were strongly expressed in female patients with SV. RV and SV are most likely to be distinguished histologically. The presence of granulomatous vasculitis suggests RV (granulomatous vasculitis was not detected in RA patients with SV). Inflammation of veins supports RV (the venule, small, and medium size vein were not involved by SV). Subacute-subchronic stages of inflammation (with dominant infiltration of T-lymphcytes) are characteristic of RV. RV is more severe, and shows more variegated histologic changes, whereas the changes in SV are more monotonous and indicate a less severe inflammation. Vasculitis in SV is usually (mainly) non-specific, and involves relatively often medium size arteries, and it is characterized mostly by leukocytic, lymphocytic and plasmacytic infiltration (with dominance of B-lymphcytes in its subacute-subchronic stages).

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