

Special Issue: Atherosclerosis & CVD Risk

Systemic Vasculitis in Various Organs of 33 Rheumatoid Arthritis and 11 Progressive Systemic Sclerosis Patients – A Comparative Postmortem Study

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Received: February 25, 2015; Accepted: April 25, 2015; Published: May 11, 2015

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Abstract

Objective: The aim of this study was (1) to compare the prevalence and severity of Systemic Vasculitis (SV) in various organs of Rheumatoid Arthritis (RA) and of progressive Systemic Sclerosis (SSc) patients, (2) To determine the complications and lethal outcome caused by vasculitis in RA and SSc.

Patients and Methods: Twelve organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) of 33 RA and of 11 SSc with SV were studied microscopically. RA and SSc were confirmed clinically according to the criteria of the American College of Rheumatology.

The basic disease, the complications, and the lethal outcome caused by vasculitis were determined and analyzed retrospectively, reviewing the clinical and pathological reports, tissue samples, and the histological slides.

The existence (prevalence) of vasculitis in various organs was determined based on the presence of vasculitis in blood vessels of different calibers. The severity of vasculitis in various organs 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).

Results and Conclusions: SV was observed in all of 33 RA and 11 SSc patients with variable prevalence and severity. The average value of prevalence and severity/organ in SSc was appreciably higher than that of RA. In RA patients, not all investigated organs were involved with SV and the existence of blood vessels with vasculitis in each organ was different. In SSc patients SV was present in each of the investigated organs, but with different severity.

In RA the heart, skeletal muscle, pancreas, lung, kidneys and gastrointestinal tract were most markedly involved, while in SSc the kidneys, spleen, lung, pancreas, heart and gastrointestinal tract were.

The high prevalence of SV and the consecutive fibrosis in these organs identify the main targets of autoimmune processes in RA and SSc prior to the more visible skin involvement. The most markedly involved organs denote a favorable site for histological diagnosis of SV, for example skeletal muscle with peripheral nerve (sural nerve) or gastrointestinal tract in RA and the gastrointestinal tract in SSc.

The course of the disease, more precisely mortality due to SV,

depends on the location of the affected vessels (and involved organs), but not on the severity of SV (number of involved vessels). Mild or moderate SV in the heart, lung, kidneys or brain may be lethal even in an early stage of the disease.

Keywords: Rheumatoid Arthritis; Systemic Sclerosis; Systemic Vasculitis; Severity/patients; Severity/Organs

Introduction

In autoimmune diseases the vascular system is the most important target of immunological processes, manifesting as vasculitis or characteristic structural changes of blood vessels.

Systemic vasculitis of autoimmune origin (SV) may be regarded as one of the basic manifestations of rheumatoid arthritis (RA) as well [1]. As Bywaters put it, "Vasculitis is RA itself [2]". The vasculitis and vascular changes are so dominant in progressive systemic sclerosis (SSc) that the disease could be regarded as primary vascular disease. According to Gardner "Evidence of circulatory impairment in systemic sclerosis is so frequent that is natural to ask whether this is fundamentally not a vascular disorder"[3]. This view is also supported by others [4,5].

The aim of this study was [1] to compare the prevalence and severity of SV in various organs of RA and SSc patients, [2] to determine the complications and lethal outcome caused by vasculitis in RA and SSc.

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.

SV of autoimmune origin complicated RA in 33 (20.49%) of 161 cases.

RA: Females 20, average age of 66.95 years, range 82-32, onset of RA: 58.5, disease duration: 10.89 years; males 13, average age of 67.46 years, range 83-53, onset of RA: 54.69, disease duration: 12.77 years at death.

This non-selected autopsy population of 33 RA patients with SV was studied and compared with 11 autopsy patients suffering in SSc.

SSc: Females 10, average age: 53.6 years, range 62-37, onset of SSc: 43.3, disease duration: 10.0 years; male 1, age of 65 years, onset of SSc and duration of disease not known.

Twelve organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) of 33 RA and of 11 SSc with SV were studied microscopically.

RA and SSc were confirmed clinically according to the criteria of the American College of Rheumatology (ACR) [6,7].

The basic disease, the complications, and the lethal outcome caused by vasculitis were determined and analyzed retrospectively, reviewing the clinical and pathological reports, tissue samples, and the histological slides.

The existence (prevalence) and severity of vasculitis in various organs was determined histologically.

Glossary of Definitions

“Prevalence” means the presence of vasculitis in different organs.

“Prevalence” of vasculitis indicates the presence of vasculitis in blood vessels of different calibers in various organs.

“Severity” indicates different degrees of inflammation (density of inflamed sections) of blood vessels in various organs.

“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 by Olympus BX51).

Semi-Objective Score System of “Severity”

“0” – no vasculitis

“1” – occasional blood vessels with vasculitis

“2” – less than 5 involved blood vessels per microscopic field with an x20 objective. (In case of medium size arteries or veins it corresponds to the absolute number of involved medium size vessels of a tissue sample, e.g. less than five medium size vessels/tissue sample)

“3” – Five or more involved blood vessels/microscopic field with a x20 objective

(In case of medium size arteries or veins this corresponds to the absolute number of involved medium size vessels of tissue sample, e.g. 5 or more than five medium size vessels/tissue sample)

The average value of vasculitis / patients was calculated by visually evaluating the histologic specimens (on a 0 to 3 plus scale) and the sum divided by the number of available specimens. The results have been tabulated in the horizontal lines. This technique was used to evaluate each organ and the results are represented in the vertical columns.

Vasculitis was defined as non-specific, fibrinoid necrotic and/or granulomatous types of vasculitis in RA, and as non-specific or fibrinoid necrotic vasculitis with or without fibromuscular and/or intimal proliferation and successive adventitial fibrosis (FIP) in SSc [8].

The correlations were calculated by Student (Welch) t-probe, comparing the severity of vasculitis in RA and SSc patients.

The links between severity, mortality, and clinical diagnosis of vasculitis were determined by χ^2 -test.

Results

Existence (prevalence) and severity of SV in various organs of 33 RA patients

The existence (prevalence) and severity of vasculitis in 12 organs (heart, lung, liver, spleen, kidney, pancreas, gastrointestinal tract, adrenal gland, skeletal muscle, peripheral nerve, skin and brain) of 33 RA patients with SV of autoimmune origin is summarized in table 1 and illustrated in figure 1a and Figure 1b.

The SV revealed significantly lower values of severity in RA patients ($p < 0.00003$), than in SSc patients. These values were also significantly lower in each organ of RA patients compared with SSc patients.

SV led to death in 19 (57.57%) of 33 RA patients: in one case due to coronary arteritis with a large antero septal Myocardial Infarct (MI); in 11 cases SV caused multifocal micro infarcts of the myocardium (myocardio cytolysis - My); in 3 cases vasculitis of the pulmonary and bronchial arterioles and small arteries led to vasculogenic rheumatoid pneumonia with disseminated (multifocal) lobular-sublobular pneumonia (RhPn). In 2 cases SV caused Brain Infarcts (BrN), in one patient it caused Necrosis of the Intestines (IN); in another case thrombosis of the main renal artery led to renal insufficiency and incipient Renal Necrosis (RN) and was the cause of death.

SV was clinically recognized in 6 (18.18%) of 33 patients.

Vasculitis was not present in every organ of 33 RA patients with SV.

Eight patients (24.24%) of 33 had severe (with average cumulative value of severity/RA patient with SV >0.333), and 25 (75.76%) of 33 had a mild degree of SV (with average cumulative value of severity/RA patient with SV <0.333).

Five patients (15.15%) of 33 had extreme severe SV (with average cumulative value of severity/RA patient with SV >0.630), and 28 (84.85%) of 33 had a mild or moderate degree of SV (with average cumulative value of severity/RA patient with SV <0.455).

Severe SV had a direct causal role in the death in 4 of 8, and mild SV in 15 of 25 cases. There was no significant correlation between the severity of SV and mortality ($\chi^2=0.2481$, $p<0.61$).

Severe vasculitis was clinically recognized in 2 of 8, and mild in 4 of 25 cases. There was no significant correlation between the clinical diagnosis of SV and severity ($\chi^2=0.33$, $p<0.56$).

Table 1: Existence (prevalence) and severity of SV in various organs of 33 RA patients (according to increasing average values of severity of vasculitis/ patient).

	Heart	Lung	Liver	Pancreas	Kidney	AG	G-I	Spleen	Muscle	Nerve	Skin	Brain	Avg/Pts	Total		CI+
N ^o	Avg	Avg	Avg	Avg	Avg	Avg	Avg	Avg	Avg	Avg	Avg	Avg			CoD	CI-
1	0.000	0.500	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.042	0.500	BrN	CI-
2	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.500	0.000	0.000	0.000	0.042	0.500		CI-
3	0.333	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	*	0.167	0.000	0.045	0.500		CI+
4	0.333	0.000	0.000	*	0.000	0.000	0.000	*	0.000	*	0.167	0.000	0.056	0.500		CI-
5	0.000	0.000	0.000	0.000	0.500	0.000	0.000	0.000	0.333	0.000	0.000	0.000	0.069	0.833		CI-
6	0.667	0.167	0.167	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.083	1.000		CI-
7	0.000	0.000	0.333	0.000	0.000	0.000	0.333	0.000	0.333	0.000	0.000	0.000	0.083	1.000	IN	CI-
8	0.333	*	0.000	*	0.000	*	0.167	*	*	*	*	0.000	0.100	0.500		CI+
9	0.000	0.000	0.000	0.333	0.500	0.000	0.000	0.000	0.333	0.167	0.000	0.000	0.111	1.333		CI-
10	0.000	1.333	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.111	1.333	PhPn	CI-
11	0.333	0.000	0.000	0.000	0.167	0.167	0.167	0.000	0.000	0.167	0.333	0.000	0.111	1.333	MI	CI-
12	0.000	1.833	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.153	1.833	PhPn	CI-
13	0.667	0.333	0.333	0.000	0.000	0.000	0.000	0.500	0.000	0.000	0.000	0.000	0.153	1.833	My	CI-
14	1.167	0.000	0.000	0.000	0.000	0.000	0.000	0.667	0.000	0.000	0.000	0.000	0.153	1.833	My	CI-
15	0.167	0.000	0.000	0.000	0.500	*	0.000	0.000	0.000	1.167	0.000	0.000	0.167	1.833	My	CI-
16	0.167	0.167	0.000	*	0.167	0.333	0.000	0.000	0.333	0.667	*	0.000	0.183	1.833	BrN	CI-
17	1.667	0.333	0.000	0.167	0.000	0.000	0.000	0.000	0.000	*	*	0.000	0.217	2.167	My	CI+
18	0.500	0.000	0.000	0.000	0.333	0.000	0.167	0.500	0.667	*	0.333	0.000	0.227	2.500	My	CI-
19	0.167	0.000	0.167	*	0.667	0.500	*	0.167	*	*	*	0.000	0.238	1.667	My	CI-
20	1.000	0.333	0.000	0.000	0.333	0.000	0.000	1.000	0.000	0.167	*	0.000	0.258	2.833	My	CI-
21	0.000	0.000	0.000	*	0.833	0.500	*	*	0.333	*	0.500	0.000	0.271	2.167		CI-
22	1.500	0.000	0.000	0.000	0.000	0.333	0.167	0.000	0.667	0.333	*	0.000	0.273	3.000	My	CI+
23	1.000	0.000	0.167	0.167	0.000	0.833	0.000	0.333	0.833	0.167	0.000	0.000	0.292	3.500		CI-
24	0.000	1.500	*	0.167	0.167	*	*	*	0.000	0.000	*	*	0.306	1.833	PhPn	CI-
25	0.000	0.000	0.333	*	0.167	0.167	1.333	0.333	*	*	*	0.167	0.313	2.500		CI-
26	1.167	0.500	0.500	0.000	0.333	0.000	0.000	0.333	0.833	0.333	0.000	0.000	0.333	4.000	My	CI-
27	1.500	*	0.000	*	0.000	*	*	*	*	*	*	0.000	0.375	1.500		CI-
28	0.333	0.667	0.667	*	0.667	0.667	0.000	0.000	0.833	0.000	0.167	1.000	0.455	5.000	RN	CI+
29	0.000	0.333	0.000	1.333	1.500	1.500	1.000	0.000	*	*	*	0.000	0.630	5.667		CI-
30	2.500	0.500	0.500	0.833	0.000	*	0.833	0.833	0.667	0.500	0.000	0.000	0.652	7.167	My	CI-
31	0.500	0.000	0.833	1.000	1.500	0.333	0.833	1.000	1.000	0.833	0.167	0.000	0.667	8.000		CI-
32	0.167	2.000	0.167	1.000	1.333	0.333	0.833	1.667	0.833	0.167	0.333	0.167	0.750	9.000		CI-
33	2.500	0.333	2.667	3.000	0.667	2.167	2.667	0.833	2.000	1.167	0.000	0.000	1.500	18.000	My	CI+
Count	33	31	32	25	33	28	29	28	28	23	23	32	36	36	19	
Total	18.67	10.83	6.83	8.00	10.33	7.83	8.50	8.17	10.50	5.83	2.17	1.33				
Avg	0.566	0.349	0.214	0.320	0.313	0.280	0.293	0.292	0.375	0.254	0.094	0.042				
*Missed	0	2	1	8	0	5	4	5	5	10	10	1				
Without	11	16	20	16	16	16	18	16	13	11	15	29				
With SV	22	15	12	9	17	12	11	12	15	12	8	3				
% / Org	66.67	48.39	37.50	36.00	51.52	42.86	37.93	42.86	53.57	52.17	34.78	9.38				
p <	0.053	0.004	0.076	0.002	0.000	0.036	0.006	0.006	0.017	0.004	0.000	0.019	0.00003			

p <: Levels of significances comparing the severity of vasculitis in various organs of RA and SSc patients

AG: Adrenal gland; G-I: Gastrointestinal Tract; CoD – Cause of Death due to systemic vasculitis; CI+: Clinically diagnosed “vasculitis”; CI-: Clinically not recognized “vasculitis”

Red – Severe SV / Pts (SV >0.333/ Pts) – 9 of 36

Yellow – Extremely severe SV / Pts (SV >0.630/ Pts) – 5 of 36

Yellow – Severe vasculitis / Organ: Heart. Muscle. Lung. Pancreas. Kidney (SV >0.3 /Organ)

*Some tissue samples of the 12 organs were not available for evaluation (consequently the “total value” of “prevalence” in these patients with SV is lower; the average values of severity of SV have been corrected according to the number of evaluated organs).

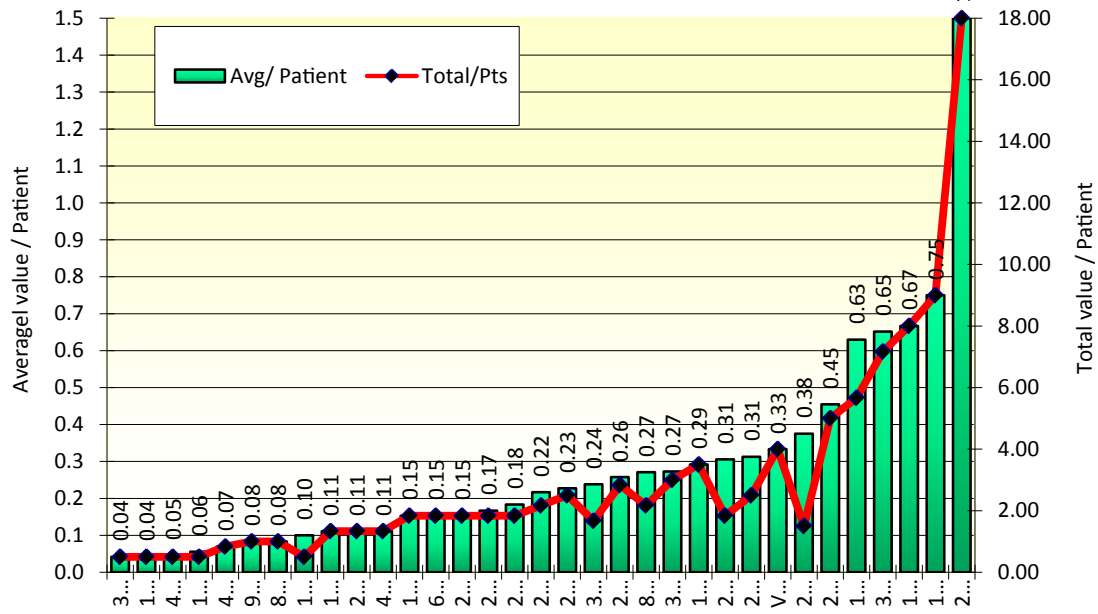


Figure 1a: Severity of vasculitis in 33 RA patients with autoimmune SV.

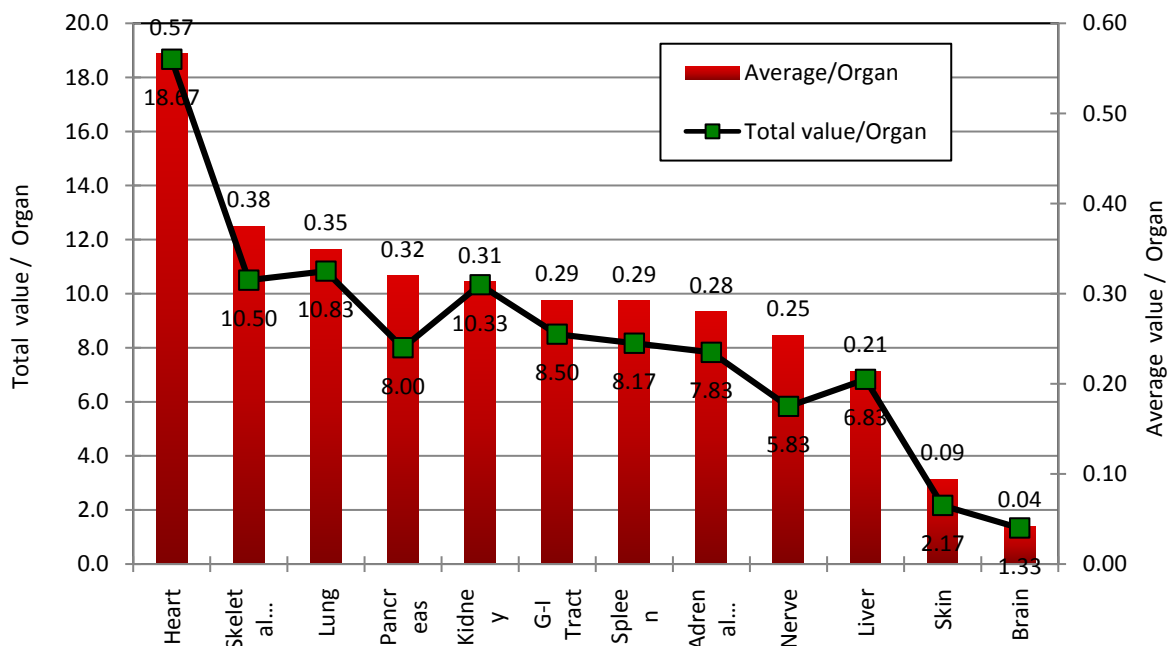


Figure 1b: Severity of autoimmune vasculitis in various organs of 33 RA patients.

Vasculitis was lethal in 19 (57.57%), and not lethal in 14 (44.42 %) of 33 cases.

Lethal vasculitis was clinically recognized in 4 of 19 fatal (21.05% of 19), and recognized in 2 of 14 not fatal (14.29% of 14) cases.

There was no significant correlation between the clinical diagnosis of SV and mortality ($\chi^2=0.2481, p<0.96$).

The severity of vasculitis in RA patients showed a step-wise ascending curve according to increasing average values of vasculitis / patient. There was no gradual transition between the

“extremely severe” and “mild or moderate degree” of SV (Figure 1.1 and Figure 2).

In RA the heart, skeletal muscle, lung, pancreas, kidneys and gastrointestinal tract were the most markedly involved organs by SV (Figure 1b).

Existence (prevalence) and severity of SV in various organs of 11 SSc patients

The existence (prevalence) and severity of vasculitis in 12 organs (heart, lung, liver, spleen, kidney, pancreas, gastrointestinal tract, adrenal gland, skeletal muscle, peripheral nerve, skin and brain) of 11 SSc patients with SV is summarized in table 2 and illustrated in figure 3a

SV revealed significantly higher values of severity in SSc patients ($p < 0.00003$), than in RA patients. The values of severity were also significantly higher in all organs of SSc patients than in RA patients.

SV with or without fibro muscular and/or intimal proliferation and consecutive interstitial fibrosis led to death in all (100%) 11 SSc patients. Six patients died of uremia (due to complex nephropathy) and 5 patients died of circulatory failure (due to endo-myocardial fibrosis or myocardiocytolysis - with or without honeycomb lung).

The cause of death was clinically recognized in all (100%) cases, but vasculitis expressis verbis was mentioned only in 2 of 11 SSc patients.

Vasculitis was present in all organs (100%) 11 SSc patients.

Seven patients (63.63%) had severe (with an average cumulative value of severity/SSc patient with SV >1.0), and 4 (36.36%) had mild SV (with an average cumulative value of severity/SSc patient with SV <1.0)

Two patients (18.18%) of 11 had extremely severe SV (with an average cumulative value of severity/SSc patient with SV >1.75), and 9 (81.82%) of 11 had a mild or moderate degree of SV (with an average cumulative value of severity/SSc patient with SV <1.0).

The severity of SV did not influence the lethal outcome due to uremia (association’s coefficient =-0.6, $\chi^2=0.1604$, $p<0.68$) or heart failure (association’s coefficient =0.6, $\chi^2=0.1604$, $p<0.61$).

Vasculitis (“expressis verbis”) was mentioned only in 2 of 11 SSc patients. In both cases the SV was severe. There was no significant correlation between the clinical diagnosis of SV and severity ($\chi^2=0.1364$, $p<0.71$).

The severity of vasculitis in SSc patients showed a step-wise ascending growth according to increasing average values of vasculitis/patient. There was no gradual transition between the “extremely severe” and “mild or moderate degree” of SV (Figure 2 and Figure 3a).

In SSc the kidneys, spleen, lung, pancreas, heart and gastrointestinal tract were the most markedly involved organs by SV (Figure 3b).

The average value of severity/patients in SSc was appreciably higher than that of RA. The severity of vasculitis in both groups of patients showed a step-wise ascending curve according to the

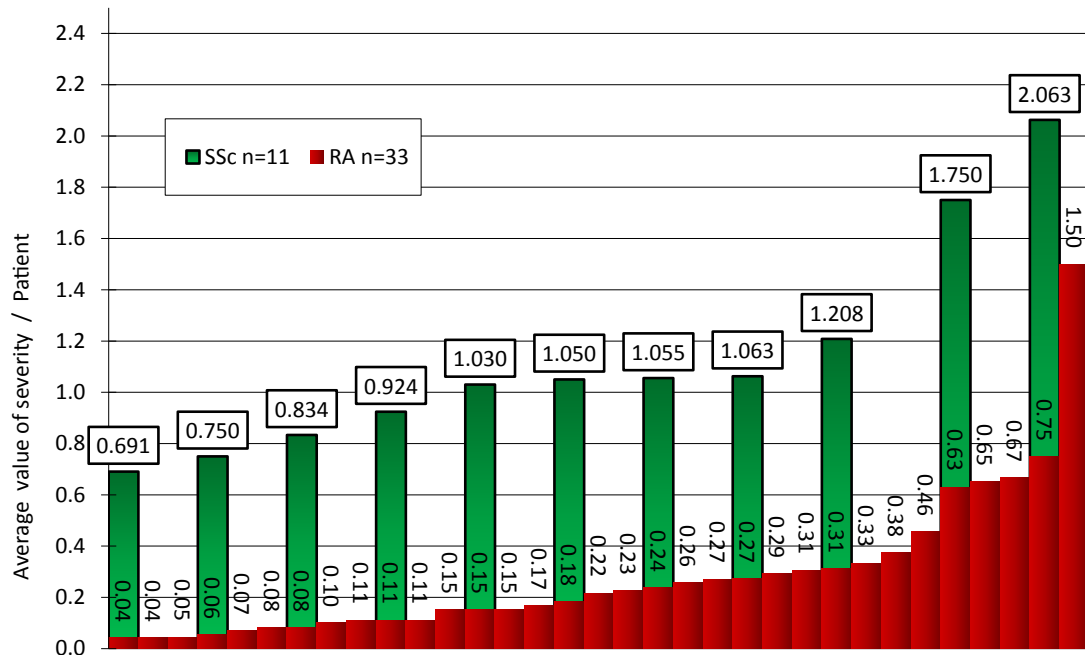


Figure 2: Severity of vasculitis in 11 SSc and 33 RA patients.

Table 2: Existence (prevalence) and severity of SV in various organs of 11 SSc patients (according to increasing average values of severity of vasculitis/patient).

	Heart	Lung	Liver	Pancreas	Kidney	AG	G-I	Spleen	Muscle	Nerve	Skin	Brain		Total		Cl+
N ^o	Avg	Avg	Avg	Avg	Avg	Avg	Avg	Avg	Avg	Avg	Avg	Avg	Avg/Pts		CoD	Cl-
1	0.333	1.000	0.167	1.167	1.500	0.167	*	*	*	*	0.500	*	0.690	4.83	U	Cl+
2	0.333	1.000	*	1.833	1.500	0.167	0.500	*	0.333	1.000	0.500	0.333	0.750	7.50	U	Cl+
3	0.500	1.500	0.667	0.667	2.000	0.667	1.000	0.667	0.833	0.667	0.667	0.167	0.833	10.00	U	Cl+
4	2.167	0.833	3.167	0.833	0.667	0.333	0.333	*	1.000	0.333	0.333	0.167	0.924	10.17	H-L	Cl+
5	2.000	1.000	*	1.500	0.833	1.333	1.000	0.667	0.833	1.000	0.833	0.333	1.030	11.33	H	Cl+
6	0.500	1.667	0.667	*	1.000	0.333	2.000	1.333	1.667	0.667	0.667	*	1.050	10.50	H	Cl+
7	0.333	2.000	0.833	1.833	2.500	1.000	0.667	1.833	0.333	0.333	0.333	0.667	1.056	12.67	U	Cl+
8	0.667	1.500	0.333	*	2.167	*	1.000	1.333	0.833	*	0.667	*	1.063	8.50	U	Cl+
9	3.000	1.333	*	0.500	1.000	1.333	*	2.000	0.333	*	0.167	*	1.208	9.67	H	Cl+
10	1.500	2.667	1.500	2.333	3.500	1.667	2.000	3.000	1.500	0.500	0.667	0.167	1.750	21.00	U	Cl+
11	3.000	2.500	*	*	2.500	3.167	2.500	*	0.667	0.667	1.500	*	2.063	16.50	H	Cl+
Count	11	11	7	8	11	10	9	7	10	8	11	6		11		
Total	14.33	17.00	7.33	10.67	19.17	10.17	11.00	10.83	8.33	5.17	6.83	1.83	11			
Avg	1.303	1.545	1.048	1.333	1.742	1.017	1.222	1.548	0.833	0.646	0.621	0.306				
*Missed	0	0	0	0	4	3	0	1	2	4	1	3				
Without	0	0	0	0	0	0	0	0	0	0	0	0				
With SV	11	11	11	11	7	8	11	10	9	7	10	8				
% / Org	100	100	100	100	100	100	100	100	100	100	100	100				
p < 0.05	0.053	0.004	0.076	0.002	0.000	0.036	0.006	0.006	0.017	0.004	0.000	0.019	0.00003			

p <: Levels of significances comparing the severity of vasculitis in various organs of SSc and RA patients

AG: Adrenal gland; G-I: Gastrointestinal Tract; CoD – Cause of Death (Uremia: U. Heart failure: H. Honeycomb-lung: H-L); Cl+: Clinically recognized “vasculitis” (Ad litteram - “explicit verbis”); Cl-: Clinically recognized cause of death

Red – Severe SV / Pts (SV > 1.0/ Pts) – 7 of 11

Yellow – Extremely Severe SV / Pts (SV > 0.630/ Pts) – 2 of 11

Yellow – Severe vasculitis / Organ: Kidney. Spleen. Lung. Pancreas. Heart (SV > 1.3/Organ)

8/2002 – The SSc patient with systemic primary (B-cell dyscrasia-associated immunoglobulin light chain – AL: λ-chain) amyloidosis. With massive deposits in vessel walls; vascular changes was not included. The patient died of circulatory failure (clinically recognized).

*Some tissue samples of the 12 organs were not available for evaluation (consequently the total value of prevalence in these patients with SV is lower; the average values of severity of SV have been corrected according to the number of evaluated organs).

increasing average values of vasculitis/patient (Figure 2).

Discussion

Prevalence and nature of SV in RA

The pertinent literature [9-23] about the prevalence of systemic vasculitis in RA is summarized in table 3. Most of these earlier studies based on the evaluation of some organs, discuss the prevalence of SV in RA patients only and did not specify the role of vasculitis as a factor in mortality.

Beside our earlier publications [21,22,23], according to our best knowledge, a detailed analysis of SV regarding the prevalence and severity in various organs has not been available in the literature. Because of the diminishing numbers of autopsies such extensive studies are unlikely to be available in the future.

In RA patients not all examined organs were involved by SV, and prevalence and severity of vasculitis in each organ was different (Table 1).

In RA the heart, skeletal muscles, lung, pancreas, kidneys and gastrointestinal tract were most markedly involved, representing the main targets of autoimmune processes in RA (Figure 1a).

In our patients there was no correlation between the severity or mortality and clinical diagnosis of SV. The mortality due to SV depends on the location of the affected vessels (and involved organs), and not by the severity of SV. For example, mild SV involving the brain may be lethal; on the other hand, severe vasculitis of the skin may not be life-threatening. The clinical diagnosis of vasculitis was established mostly by visible skin involvement.

Prevalence and nature of SV in SSc

It is generally accepted, that SV has a basic role in organ involvement of SSc. There are excellent descriptions about the morphology of vasculitis and vascular changes in SSc [24-27], but these do not mention the prevalence in percent, neither in various organs, nor in mortality. Most of the autopsy studies

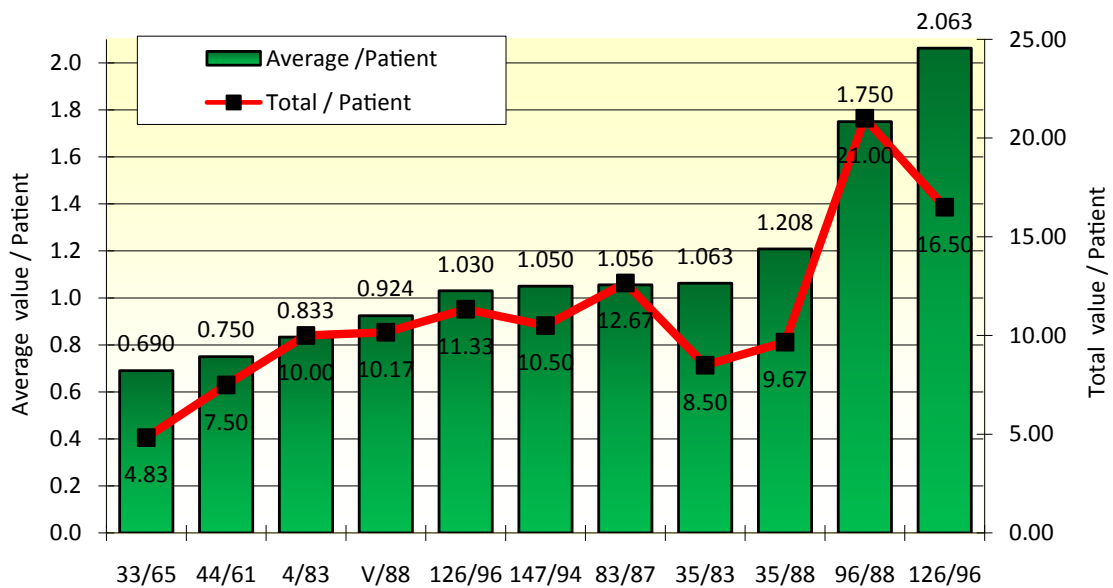


Figure 3a: Severity of vasculitis in SSc patients (n=11 of 11).

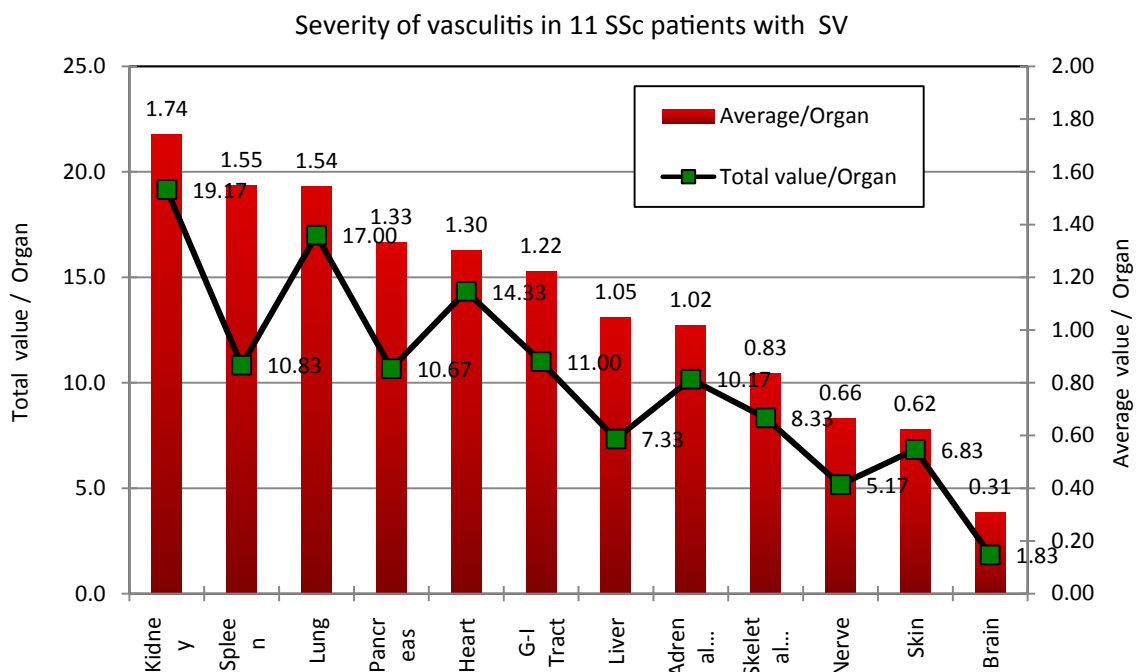


Figure 3b: Severity of vasculitis in 11 SSc patients with SV.

focus on organ involvement only [26,27,28].

In SSc patients SV was present in each of the examined organs, with different degrees of severity (Table 2).

SV was most dominant in the kidneys, spleen, lung, pancreas, heart and gastrointestinal tract of SSc patients in comparison with the involvement of the skin (Figure 3b).

The high prevalence of vasculitis in the kidneys (with complex nephropathy), in the heart (with consecutive endo-myocardial fibrosis or myocardiocytolysis), in the lungs (with interstitial, and “honeycomb” fibrosis), and in the gastrointestinal tract (with consecutive submucosal fibrosis) [26-28] correlate with the characteristic cardiac, pulmonary, renal and gastrointestinal clinical signs of SSc patients, and remind us to carefully evaluate the symptoms of these [29-31].

Table 3: Prevalence of systemic vasculitis in autopsy material of rheumatoid arthritis (not mentioned the origin SV).

Authors	Year of Publication-References	Autopsy n=	Prevalence	Mortality
			of vasculitis n – %	of vasculitis n – %
Cruickshank	1954 [9]	72	18 – 25%	ND
Sinclair and Cruickshank	1956 [10]	16	9 – 56.3%	ND
Cruickshank*	1958 [11]	100	20* – 20%	ND
Lebowitz	1963 [12]	62	6 – 10%	ND
Sokoloff	1964 [13]	19	2 – 10.5%	ND
Karten**	1969 [14]	102	6** – 6%	ND
Gardner	1972 [15]	142	7 – 4.9%	ND
Davis and Engleman	1974 [16]	62	6 – 10%	ND
Eulderink	1976 [17]	111	ND	7 – 6.3%
Albada-Kuipers et al.	1986 [18]	173	17 – 10%	ND
Boers et al.	1987 [19]	132	18 – 13.6%	ND
Suzuki et al.	1994 [20]	81	25 – 30.8%	ND
Bély and Apáthy***	1994 [21-22]	161	36 – 22.4%	19 – 11.8%
Bély and Apáthy	2005 [23]	234	51 – 21.8	23 – 9.8%

ND: No Data

*: Coronaritis

** : 102 patients with RA – partially autopsied (Karten)

***: These studies discuss 33 cases SV of autoimmune origin and 3 of 36 SV of septic origin; these latter 3 SV of septic origin have been excluded in the present study.

The SSc patients died of uremia caused by complex nephropathy, or heart failure due to endo-myocardial fibrosis or myocardio cytolysis with or without honeycomb lung. The severity of SV did not influence the lethal outcome due to uremia or heart failure. Less severe but relapsing vasculitis with consecutive fibrosis may lead to death in these organs by uremia or heart failure. The clinical diagnosis in our patients was based on the Raynaud’s phenomenon or skin involvement not influenced by the severity of SV.

In RA or SSc the most markedly involved organs denote a favorable site for histological diagnosis of SV, for example skeletal muscle with peripheral nerve (sural nerve) or G-I tract in RA and the G-I tract in SSc prior to the more visible skin involvement.

The high prevalence of SV in the pancreas may cause multifocal (microfocal recurrent) acute pancreatitis without lethal outcome in both diseases. The multifocal pancreatitis and multifocal fibrosis due to vasculitis is a newly recognized entity in RA [1,32] and in SSc [33], not mentioned in earlier comprehensive descriptions of pathological changes [26-31].

The “average severity” of vasculitis showed a step-wise profile of intensity in both cohorts of patients. This step-wise change, without gradual transition, may indicate that different genetic, immunologic etc. factors may play a role in determining the severity of vasculitis. Conceivably, the pathogenesis of mild and extremely severe vasculitis may be different.

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