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Research

Complications and Mortality of Systemic Vasculitis – A Postmortem Clinicopathologic Study of 234 Rheumatoid Arthritis Patients

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Abstract

Systemic vasculitis of autoimmune origin (A-SV) may be regarded as one of the basic manifestations of rheumatoid arthritis (RA). RA may be complicated by lethal septic infection (SI) as well, frequently accompanied by systemic septic vasculitis (S-SV).

Aim

The aim of this study was to determine the prevalence of A-SV and S-SV in RA, and to outline the complications and mortality associated with A-SV or S-SV.

Patients and Methods

Twohundred thirty four (234) non- selected autopsy patients with RA were studied. RA was confirmed clinically according to the criteria of the American College of Rheumatology (ARA).

The presence of A-SV and S-SV was determined at autopsy and confirmed by a detailed review of extensive histological material. The basic disease, its complication(s), and the lethal outcome associated with A-SV or S-SV were determined and analyzed retrospectively, reviewing the clinical and pathological reports.

Results and Conclusion

Systemic vasculitis (SV) was found histologically in 50 (21.37%) of 234 patients.

A-SV complicated RA in 43 (86.0%) of the 50 patients. A-SV led to death in 26 (60.47%) of 43 patients: in 4 (9.30%) cases due to coronary arteritis with a large anteroseptal myocardial infarct (MI), in 13 (30.23%) cases A-SV caused multifocal microinfarcts of the myocardium (myocardiocytolysis -My). In 3 (6.98%) cases vasculitis of the pulmonary and bronchial arterioles and small arteries led to vasculogenic rheumatoid pneumonia with disseminated (multifocal) lobular-sublobular pneumonia (RhPn). In 4 (9.30%) cases vasculitis of cerebral arteries and arterioles caused multiple microcystic brain necroses (BrN), and led to death. In one (2.33%) patient A-SV caused necrosis of the intestines (IN), and in another case (2.33%) thrombosis of the main renal artery led to incipient renal necrosis (RN) and renal insufficiency. A-SV was not lethal in 17 (39.53%) of 43 patients.

The silent myocardial infarction (multifocal My), the antibiotic resistant multifocal lobular-sublobular migratory pneumonia (RhPn), and the multifocal brain necrosis may be regarded as new clinicopathologic entities caused by A-SV in RA.

S-SV existed in 7 (14.0%) of 50 patients as an accompanying phenomenon only, a vascular manifestation of the generalized lethal septic infection, without direct role in mortality.

A-SV proved to be a much more insidious complication of RA in contrast to S-SV.

Keywords

Rheumatoid Arthritis; Systemic Vasculitis of Autoimmune and Septic Origin; Myocardiocytolysis; Rheumatoid Pneumonia; Multifocal Brain Necrosis

Abbreviations

RA: Rheumatoid Arthritis; SV: Systemic Vasculitis; A-SV: Systemic Vasculitis of Autoimmune origin; S-SV: Systemic Vasculitis of Septic origin; SI: Septic Infection; ARA: American College of Rheumatology; MI: Large Myocardial Infarction; My: Myocardiocytolysis – multifocal microinfarcts of the myocardium; RhPn: Rheumatoid Pneumonia; BrN:

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Brain necrosis; IN: Necrosis of the Intestines; RN: Renal Necrosis; Cl+: Clinically diagnosed; Cl-: Clinically not diagnosed; Ath: Atherosclerosis of coronary arteries; Hy: Hypertension; Tb: post-primary; Fc: fibrocaseous; F: fibrous; mTb: active miliary dissemination of Tb; DM: adult type II Diabetes Mellitus; CAA: Cerebral Amyloid Angiopathy; Ca: Carcinoma; ND: No Data

Introduction

Systemic vasculitis of autoimmune origin (A-SV) may be regarded as one of the basic manifestations of rheumatoid arthritis (RA) [1]. RA may be complicated by lethal septic infection (SI) as well, frequently accompanied by systemic septic vasculitis (S-SV).

The aim of this study was to determine the prevalence of A-SV and S-SV in RA, and to outline the complications and mortality of A-SV or S-SV.

Patients and Methods

Twohundred thirty four (234) non- selected autopsy patients with RA were studied. RA was confirmed clinically according to the criteria of the American College of Rheumatology (ARA) [2].

The presence of A-SV and S-SV was determined at autopsy and confirmed by a detailed review of extensive histological material in agreement with the recommendations of the Consensus Conference (2013) [3], Scott et al (1981) [4], and Schilling and Fassbender (1988) [5]. 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.

The basic disease, its complication(s), and the lethal outcome caused by A-SV or S-SV were determined and analyzed retrospectively and correlated with the clinical and pathological reports.

All patients received steroids and methotrexate, leflunomid or sulphasalazyn as basic therapy. Biological therapy was not available at the National Institute of Rheumatology between 1970 and 1999.

Demographics of different patient cohorts were compared with the Student (Welch) t-probe [6]. The link between A-SV and S-SV, furthermore the relation of A-SV or S-SV to mortality and clinical diagnosis was analyzed by Pearson's chi-squared (χ^2) test [6].

Results

Systemic vasculitis (SV) was found histologically in 50 (21.37%) of 234 patients. SV was associated with generalized lethal septic infection (SI) in 7 (14.0%) of 50 cases, and was regarded as S-SV. The close relationship between S-SV and SI (χ^2=36.9454, p<0.0000), supported the septic origin of SV in these 7 cases.

A-SV complicated RA in 43 (86.0%) of 50 cases, excluding other causes of vasculitis, like hypertension, diabetes mellitus, tumors, etc. The negative associations' coefficient and inverse and not significant relationship between A-SV and S-SV (associations' coefficient= -1, χ^2=0.6070, p<0.43) supported the autoimmune origin of SV in these 43 cases.

Demographics, onset and duration of disease complicated by A-SV or S-SV are summarized in Table 1.

Table 1: Sex, mean age with SD, (range), onset of disease and disease duration (in years) of RA patients with or without systemic vasculitis

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	234	66.25±13.15	16– 88	51.02±16.58	14.76±10.79
Female	170	66.31±12.82	16 – 88	50.46±15.92	15.42±11.12
Male	64	66.08±13.97	19 – 88	52.55±18.18	12.96±9.60
SV	50	67.32±10.68	32 – 88	56.00±14.94	11.83±10.56
Female	30	67.40±12.03	32 – 88	56.29±14.26	12.54±9.83
Male	20	67.15±8.24	53 – 83	55.58±15.88	10.79±11.47
A-SV	43	68.26±10.80	32 – 88	56.85±15.24	12.08±10.82
Female	26	68.96±11.84	32 – 88	58.04±13.68	12.71±9.58
Male	17	67.12±8.84	53 – 83	55.06±17.16	11.13±12.39
S-SV	7	61.57±7.74	51 – 70	51.14±12.03	10.43±8.78
Female	4	57.25±7.36	51 – 69	45.75±13.12	11.50±11.15
Male	3	67.33±3.09	63 – 70	58.33±4.19	9.00±5.00
Without A-SV or S-SV	184	65.96±13.72	16 – 88	49.29±16.77	15.78±10.68
Female	140	66.08±12.96	16 – 88	48.90±15.98	16.19±11.32
Male	44	65.59±15.88	19 – 88	50.63±19.25	14.33±7.89

A-SV (n=43) or S-SV (n=7) – without SV (n=184) of 234 RA patients

RA: Rheumatoid Arthritis

SV: Systemic Vasculitis

A-SV: Systemic Vasculitis of Autoimmune origin

S-SV: Systemic Vasculitis of Septic origin

SD: Standard deviation

Comparing the age, sex, onset of RA, and duration of disease at the time of death there was no significant difference between female (p< 0.270, p< 0.008, p< 0.136) and male (p< 0.643, p< 0.442, p< 0.372) RA patients with A-SV (p< 0.236, p< 0.010, p< 0.064) and without SV (except onset of disese), between female (p< 0.127, p< 0.709, p< 0.522) and male (p< 0.606, p< 0.127, p< 0.125) RA patients with S-SV (p< 0.225, p< 0.728, p< 0.193) and without SV (Tables 2).

There was no significant difference in survival time, onset or duration of RA between patients with A-SV and S-SV (p< 0.092, p< 0.324, p< 0.689), neither between females (p< 0.060, p< 0.205, p< 0.867) nor males (p< 0.947, p< 0.550, p< 0.601).

A-SV and S-SV developed in both sexes, and at any time in the course of the disease (Table 2).

A-SV: Systemic vasculitis of autoimmune origin existed in 43 (86.0%) of 50 patients; complicated with lethal outcome (bold) in 26 (60.47%), and without fatal outcome in 17 (39.53%) of 43 patients

Cl+: Clinically diagnosed A-SV in 7 (16.28%) of 43 patients (clinically recognized 5 of 26 lethal cases, and 2 of 17 not lethal cases)

Cl-: Clinically not diagnosed A-SV in 36 (83.72%) of 43 patients (clinically not recognized 21 of 26 lethal cases, and 15 of 17 not lethal cases)

S-SV: Systemic vasculitis of septic origin existed in 7 (14.0%) of 50 patients, and proved to be an accompanying phenomenon, vascular manifestation of generalized lethal septic infection.

In 2 of these 7 cases S-SV existed in combination with A-SV, based on the coexistence of characteristic granulomatous (nodular) type of A-SV and non specific leucocytic vasculits of septic origin.

S-SV has no direct role in mortality, and contributed to the death only, caused by generalized septic infection

Cl+: Clinically diagnosed S-SV in 3 (42.86%) of 7 patients

Cl-: Clinically not diagnosed S-SV in 4 (57.14%) of 7 patients

Table 2: The statistical correlations ("p" values of significance) between female and male RA patients with A-SV and S-SV in comparison without SV

RA patients	**Age**	**Disease duration**	**Onset of disease**
with A-SV n=43 versus **without SV** n=184	p< 0.24	p< 0.06	p< 0.01
Female n=26 versus n=140	p< 0.27	p< 0.14	p< 0.01
Male n=17 versus n=44	p< 0.64	p< 0.37	p< 0.44
with S-SV n=7 versus **without SV** n=184	p< 0.235	p< 0.19	p< 0.73
Female n=4 versus n=140	p< 0.137	p< 0.52	p< 0.71
Male n=3 versus n=44	p< 0.61	p< 0.13	p< 0.13
with A-SV n=43 versus **with S-SV** n=7	p< 0.09	p< 0.69	p< 0.32
Female n=26 versus n=4	p< 0.06	p< 0.87	p< 0.21
Male n=17 versus n=3	p< 0.95	p< 0.60	p< 0.55

RA: Rheumatoid **A**rthritis
SV: Systemic **V**asculitis
A-SV: Systemic **V**asculitis of **A**utoimmune origin
S-SV: Systemic **V**asculitis of **S**eptic origin

Table 3: Basic disease, complications and cause of death in RA with systemic vasculitis n=50 (21.37 %) of 234 patients

Basic disease		Complication (1-2)		Cause of death	Associated disease(s)	Cl+ Cl-	Pr n /year
1	RA	A-SV	Coronary arteritis-arteriolitis	Myocardiocytolysis, multiple		Cl-	20/70
2	RA	A-SV	Coronary arteriolitis	Myocardiocytolysis, multiple	Ath	Cl-	81/70
3	RA	A-SV	Pulmonary arteritis Bronchial arteritis	Rheumatoid pneumonia		Cl-	V/A
4	RA	A-SV	Coronary arteritis-arteriolitis Myocarditis	Heart failure	Ath-DM	Cl-	114/71
5	RA	A-SV	Vasculitis of pancreatic arteries and arterioles Vasculogenic pancreatitis, multiple Multifocal vasculogenic cortical necrosis of adrenal gland	Circulatory failure	TbF	Cl-	174/72
6	RA	A-SV		Cachexia	Ath	Cl-	288/73
7	RA	A-SV	Coronary arteritis-arteriolitis Nodular coronary arteritis Nodula valvulitis, Nodular endocarditis Myocardial rheumatoid nodules Nodular epicarditis AA amyloidosis	Myocardiocytolysis, multiple	TbFc-mTb	Cl+	395/76
8	RA	A-SV	Coronary arteriolitis Microinfarctions, multiple	Circulatory failure	Ath-Cirrhosis	Cl+	20/80
9	RA	A-SV	Coronary arteritis-arteriolitis Eosinophilic mycarditis Cortical necrosis of adrenals	Myocardiocytolysis, multiple		Cl+	110/80
10	RA	A-SV		Purulent bronchiolitis		Cl-	175/82
11	RA	S-SV	Purulent coxitis (b.s.) Purulent synovitis Multiple myocardial abscessus Relapsing chronic thrombovasculitis Embolic focal glomerulonephritis (Löhlein) Multiple decubital ulcers Septic splenitis Coronary arteritis-arteriolitis Endocarditis Myocarditis Epicarditis	Lethal septic infection Clinically diagnosed SI; clinically identfied E. Coli, Proteus mirabilis		Cl+	332/84

12	RA	A-SV	Pulmonary arteritis Bronchial arteritis	Rheumatoid pneumonia		Cl-	25/85
13	RA	A-SV	AA amyloidosis	Uremia	Hy-DM	Cl-	43/85
14	RA	A-SV	AA amyloidosis	Myocardial necrosis	Ath-DM	Cl-	90/85
15	RA	A-SV	Pulmonary arteritis Bronchial arteritis	Rheumatoid pneumonia	Ath	Cl-	119/85
16	RA	A-SV	Aortitis Coronary arteritis-arteriolitis Pancarditis Nodular valvulitis, Nodular endocarditis Myocarditis Myocardial rheumatoid nodules Epicarditis Vasculogenic pancreatitis, multiple Vasculitis of intestines	Circulatory failure	Ath-TbF	Cl-	36/86
17	RA	A-SV	Cerebral vasculitis, multiple Microcystic brain necrosis, multiple 1 Deep vein thrombosis Pulmonary embolism Glomerulonephritis Interstitial nephritis	Septic infarct of the lung		Cl-	123/86
18	RA	S-SV	Aortitis Coronary arteriolitis Endocarditis Myocarditis Vasculitis of intestines Haemorrhagic necrosis of intestines Renal abscess Decubital ulcer	Lethal septic infection Clinically not recognized SI; Haemorrhagic pancreatitis was clinically identfied Aspergillus (bronchial) Histologically identified	Fatty liver (suspected alcoholic)	Cl-	166/86
19	RA	A-SV	Coronary arteritis-arteriolitis Nodular valvulitis AA amyloidosis (Azotemia)	Circulatory failure		Cl-	243/87
20	RA	A-SV	Coronary arteritis-arteriolitis Valvulitis Endocarditis Myocarditis	Myocardiocytolysis, multiple		Cl+	275/87
21	RA	A-SV	Cerebral vasculitis, multiple Mesaortitis Coronary arteriolitis Secondary Sjögren's disease Thyreoiditis	Microcystic brain necrosis, multiple Bronchopneumonia	DM-TbF-CAA	Cl-	279/87

22	RA	A-SV	Coronary arteritis-arteriolitis Nodular valvulitis Endocarditis Myocarditis Myocardial rheumatoid nodules	Myocardiocytolysis, multiple		Cl-	312/87
23	RA	A-SV	Thrombovasculitis renal artery Coronary arteriolitis	Renal necrosis		Cl+	194/88
24	RA	A-SV	Coronary arteriolitis Epicarditis Vasculitis of intestines AA amyloidosis (incipient)	Myocardiocytolysis, multiple	TbF-mTb	Cl-	240/88
25	RA	A-SV	Coronary arteritis-arteriolitis Pancarditis Nodula valvulitis Nodular endocarditis Myocarditis Myocardial rheumatoid nodules Nodular epicarditis	Myocardiocytolysis, multiple	Ath	Cl-	295/88
26	RA	A-SV	Valvular endocarditis	Heart failure	DM	Cl-	40/89
27	RA	A-SV	Coronary arteriolitis Acute endocarditis Myocardial rheumatoid nodules	Myocardiocytolysis, multipl	TbFc-mTb	Cl-	227/89
28	RA	A-SV	Coronary arteritis-arteriolitis Nodula valvulitis, Myocardial rheumatoid nodules Nodular epicarditis	Myocardiocytolysis, multiple		Cl-	285/89
29		S-SV and A-SV	Nodular coronary arteritis Valvulitis Endocarditis Myocarditis Pericarditis Duodenal ulcus perforation Peritonits Septic splenitis Subphrenic abscess Pulmonary embolism (septic) Hemorrhagic pneumonia Meningitis	Lethal septic infection Clinically diagnosed SI; clinically identfied: Pseudomonas aeruginosa, Proteus mirabilis Aspergillus (bronchial) - histologically identified only		Cl-	318/89
30	RA	A-SV	Aortitis Coronary arteriolitis Pancarditis Nodula valvulitis Nodular endocarditis Myocarditis Myocardial rheumatoid nodules Nodular epicarditis Myocardial microinfarctions	Circulatory failure	Ath-DM-TbFc	Cl-	41/90

31	RA	A-SV	Coronary arteritis-arteriolitis Coronary thrombovasculitis	Myocardial necrosis	Ath-TbFc-Ca	Cl-	65/90
32	RA	A-SV	Coronary arteriolitis Nodular pancarditis Nodular valvulitis, Myocardial rheumatoid nodules Nodular epicarditis Myositis	Circulatory failure	Ath-TbFc-mTb	Cl-	87/90
33	RA	A-SV	Coronary arteriolitis Pancarditis Endocarditis Myocarditis Epicarditis	Circulatory failure		Cl+	146/91
34	RA	A-SV	Coronary arteriolitis	Myocardiocytolysis, multiple		Cl-	221/91
35	RA	A-SV	Coronary arteritis Nodular pancarditis Nodular valvulitis, Myocardial rheumatoid nodules Nodular epicarditis Myositis	Circulatory failure Bronchopneumonia	Ath	Cl-	14/92
36	RA	A-SV	Thrombovasculitis of mesenteric artery	Haemorrhagic intestinal necrosis	DM	Cl-	144/92
37	RA	A-SV	Cerebral vasculitis, multiple Vasculitis of skeletal muscle-Myositis	Microcystic brain necrosis, multiple Purulent bronchitis and bronchiolitis Bronchopneumonia	Hy	Cl-	117/93
38	RA	A-SV	Coronary arteritis-arteriolitis Myocardiocytolysis, multiple Coronary thrombovasculitis Vasculitis of skeletal muscle-Myositis Vasculitis of peripherial nerve	Myocardial necrosis, acute		Cl-	213/93
39	RA	A-SV	Cerebral arteritis-arteriolitis AA amyloidosis Decubital ulcer (sacral)	Microcystic brain necrosis, multiple		Cl-	219/93
40	RA	S-SV	Bursectomia (Status post operationem) Coronary phlebitis Fibrous endocarditis Myocarditis Fibrinous pericarditis Purulent bronchitis and bronchiolitis	Lethal septic infection Clinically diagnosed and healed SI (without identified pathogenic agents) – Cause of deth: Circulatory failure		Cl-	279/93
41	RA	A-SV	Thrombosis of femoral vein	Pulmonary embolism		Cl-	287/93

42	RA	A-SV	Coronary arteritis-arteriolitis Myocardiocytolysis, multiple Coronary thrombovasculitis Myocardial fibrosis Vasculitis renal artery Multiple renal anemic infarcts Incipient anemic renal necrosis Gastric vasculiitis Cerebral vasculitis Microcystic brain necrosis, multiple Interstitial pneumonitis Purulent bronchitis and bronchiolitis Vasculitis of skeletal muscle-Myositis Thrombosis of femoral vein	Myocardial necrosis, acute		Cl-	116/94
43	RA	S-SV	Decubital ulcer (sacral) Coronary arteritis Valvulitis Endocarditis Myocarditis Pericarditis Myocardiocytolysis, multiple Vasculitis of renal arteries and arterioles Vasculitis of skeletal muscle-Myositis Vasculitis of peripherial nerve	Lethal septic infection Clinically diagnosed SI; pathogenic agents not identified (the patient died before)		Cl+	200/94
44	RA	S-SV	Decubital ulcer (sacral) Embolic focal glomerulonephritis (Löhlein) Septic splenitis Myocarditis Vasculitis of skeletal muscle-Myositis	Lethal septic infection Clinically diagnosed SI; clinical identfication of pathogenic agents in our institute not done, the patient was transferred to an other institute:	Operated breast cancer	Cl-	28/95
45	RA	S-SV and A-SV	Coronary arteritis Nodular valvulitis Myocardial fibrosis Purulent myocarditis Pericarditis fibrous-fibrinous Interstitial pneumonitis Obliterative broncholitis Duodenal ulcer (penetrant) Myositis	Lethal septic infection Clinically not diagnosed SI	TbFc-mTb	Cl+	375/95

46	RA	A-SV	Nodular myocarditis Pericarditis Thrombovasculitis of pancreatic artery Glomerulonephritis Myositis AA amyloidosis Duodenal ulcer	Massive internal bleeding		Cl-	36/96
47	RA	A-SV	Coronary arteriolitis, sporadic AA amyloidosis Mesaortitis Nodular valvulitis Myocardial fibrosis Epicarditis	Circulatory failure		Cl-	123/97
48	RA	A-SV	Coronary arteriolitis, sporadic AA amyloidosis Myocardial fibrosis Gastritis with erosions accompanied with vasculitis	Circulatory failure		Cl-	171/97
49	RA	A-SV	Nodular coronary arteritis Coronary arteriolitis Valvulitis nodularis Myocarditis nodularis Endocarditis nodularis Pericarditis rheumatica Thrombovasculitis of pulmonary artery	Myocardiocytolysis, multiple		Cl+	231/97
50	RA	A-SV	Coronary arteritis-arteriolitis Valvulitis nodularis Myocarditis nodularis	Myocardiocytolysis, multiple	Isolated AA amyloidosis of the heart	Cl-	89/98

Pr n /year – the number of autopsy reports / year

Basic disease: underlying disease related to death

Complication: consequence of basic disease leading directly to death

Cause of death (bold): fatal outcome of basic disease

Associated (accompanying) disease: important disorder without direct causal role in death.

Remarks to Table 3

Myocardiocytolysis – Multiple (multifocal) microinfarction of myocardium (My)

Myocardial necrosis (infarct) (MI)

Atherosclerosis (Ath) –was diagnosed in RA patients only when it was present macroscopically as a "*severe" atherosclerotic process (characterized by occlusive thrombosis or sclerotic ulcers*) or, when it was the *basic disease leading to death*. Moderate changes like hyaline or sclerotic plaques – without causal role in death – were not mentioned as "atherosclerosis"; such changes are frequent in elderly RA patients.

Hy = Hypertension

CAA – Cerebral Amyloid Angiopathy – Aβ protein-related isolated amyloidosis localized to the brain in one, and isolated AA amyloidosis localized to the heart was detected (histologically diagnosed) in one of 50 RA patients with SV.

Tb – Post-primary (Fc – fibrocaseous, or F – fibrous) tuberculosis of the lung

mTb – active miliary dissemination of Tb

DM – adult type II diabetes mellitus

V/A – the patient died in another institute and was evaluated by the authors

A-SV existed in 43 (86.0%) of 50 patients with SV, and led to death in in 26 (60.47%) of 43 patients: in 4 (9.30%) cases due to coronary arteritis with a large anteroseptal myocardial infarct (MI) (3 cases caused by coronary thrombovasculitis and in one case caused by coronary arteritis in combination with severe AA amyloidosis), in 13 (30.23%) cases A-SV caused multifocal microinfarcts of the myocardium (myocardiocytolysis - My) (Figures 1-3).

In 3 (6.98%) cases vasculitis of the pulmonary and bronchial arterioles and small arteries led to vasculogenic rheumatoid pneumonia with disseminated (multifocal) lobular-sublobular pneumonia (RhPn) (Figures 4-6).

In 4 (9.30 %) cases vasculitis of cerebral arteries and arterioles caused multiple microcystic brain necroses (BrN) (Figures 7-8), and led to death in two cases due to bronchopneumonia, in a third one due to pulmonary embolism and septic infraction of the lung, and in the forth case led to death directly (cerebral coma).

In one (2.33%) patient A-SV caused necrosis of the intestines (IN), and in another case (2.33%) thrombosis of the main renal artery led to incipient renal necrosis (RN) and renal insufficiency.

A-SV was not lethal in 17 (39.53%) of 43 patients.

There was a significant correlation between A-SV and mortality (χ^2=6.5617, p<0.01).

A-SV was clinically recognized in 7 (16.28%) of 43 patients, and clinically not diagnosed A-SV in 36 (83.72%) of 43 patients. There was no significant correlation between A-SV and clinical diagnosis of A-SV (χ^2=0.3178, p<0.57).

Lethal vasculitis was clinically recognized in 5 of 26 fatal (11.63% of 43), and recognized in 2 of 17 not fatal (4.65% of 43) cases. There was no significant correlation between the clinical diagnosis of A-SV and mortality (χ^2=0.4922, p<0.48).

There was a very strong and positive correlation between A-SV and My (χ^2=55.5547, p<0.000), or A-SV and RhPn (χ^2=8.5489, p<0.003).

The relationship between A-SV and MI (χ^2=0.3547, p<0.55), or A-SV and BrN (χ^2=0.0384, p<0.91) were not sig significant; the overwhelming majority of MI or BrN were caused in by Ath, and only a few by A-SV in our autopsy population.

The characteristic manifestations of A-SV in the heart, lung and brain are demonstrated on Figures 1-8.

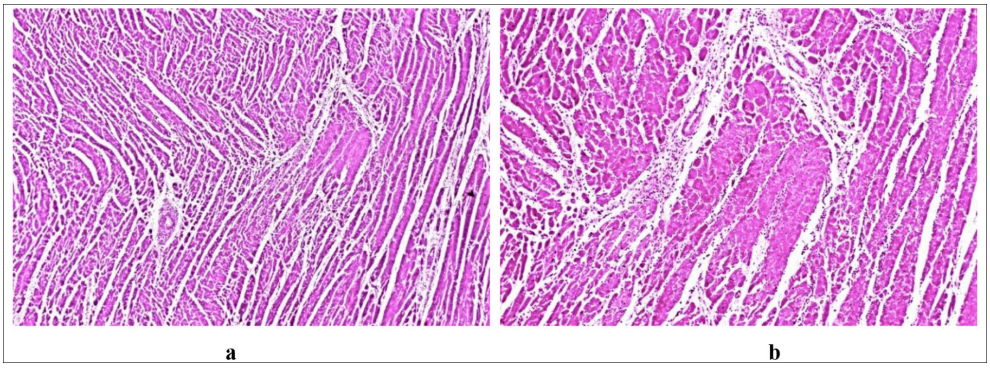

Figure 1: RA, heart, non-specific coronary arteriolitis, early stage of focal myocardial necrosis (homogenization of myocardiocytes)
(a) HE, x50 (b) same as (a) x125 (The original magnification corresponds to the 24x36 mm transparency slide – the correct height: weigth ratio is 2:3).

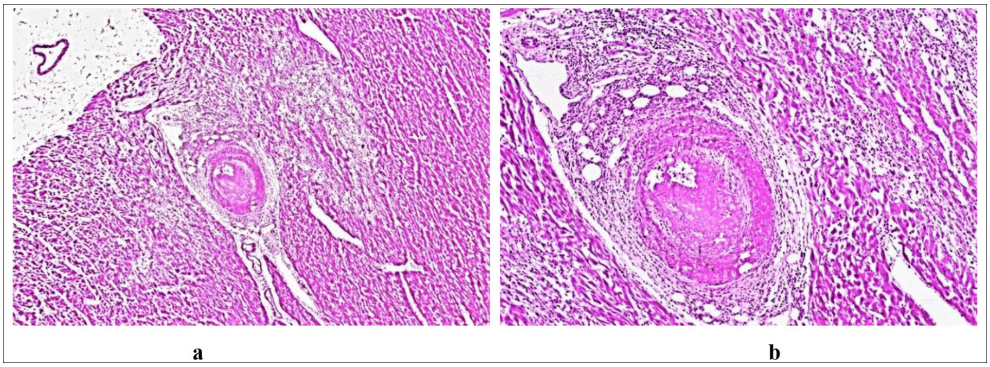

Figure 2: RA, heart, small artery, fibrinoid necrotic thrombovasculitis, focal myocardocytolysis with early fibrosis (a) HE, x20 (b) same as (a) x50

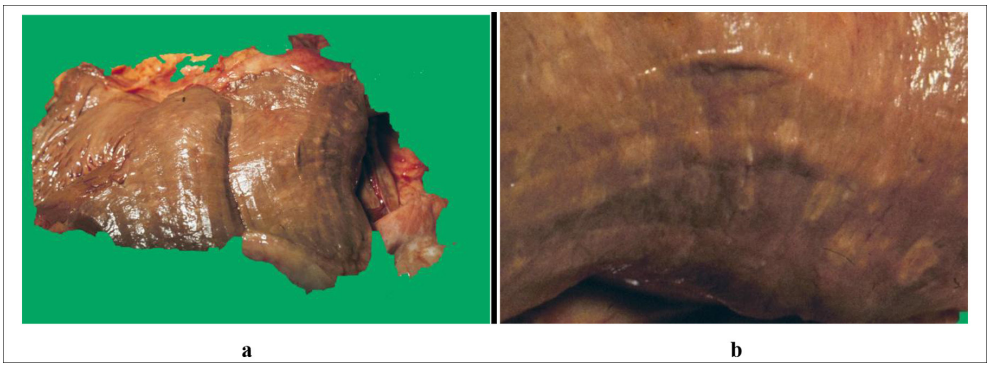

Figure 3: Heart, multiple microinfarts (myocardiocytolysis) of myocardium in different stage of necrosis (a) Macrophoto, x1 (b) same as (a) x5

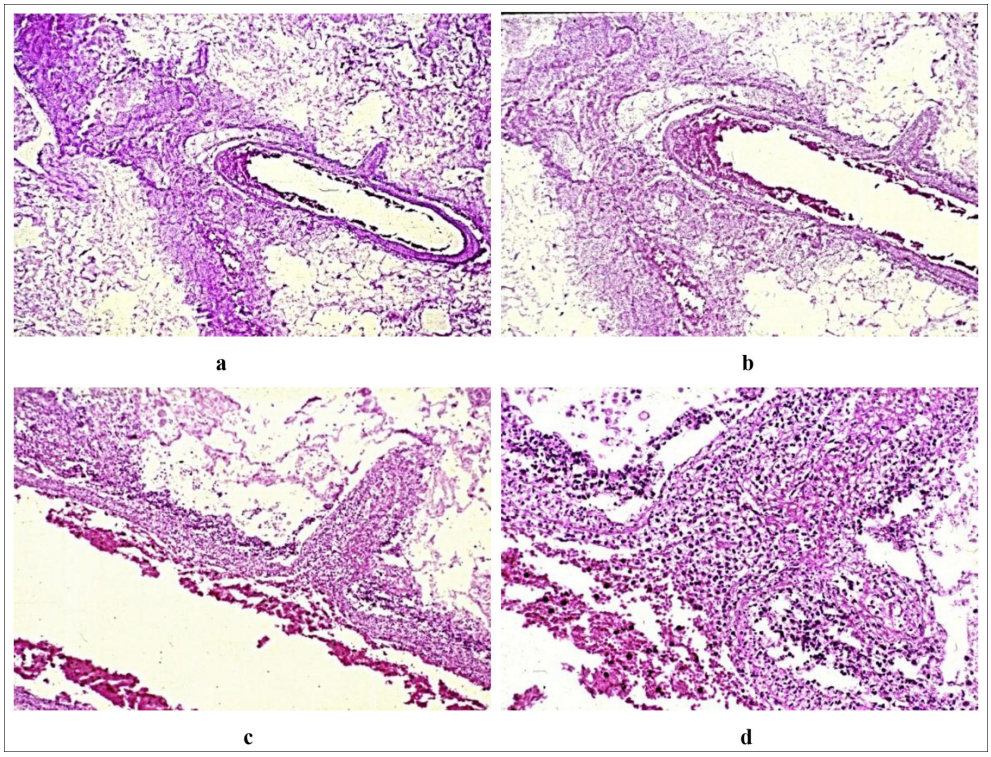

Figure 4: RA, lung, medium size pulmonary artery and arteriole junction, non-specific, acute (necrotizing) vasculitis, early stage of focal (sublobular) vasculogenic pneumonia (a) HE, x20 (b) same as (a) x50) (c) same as (a) x125 (d) same as (a) x200

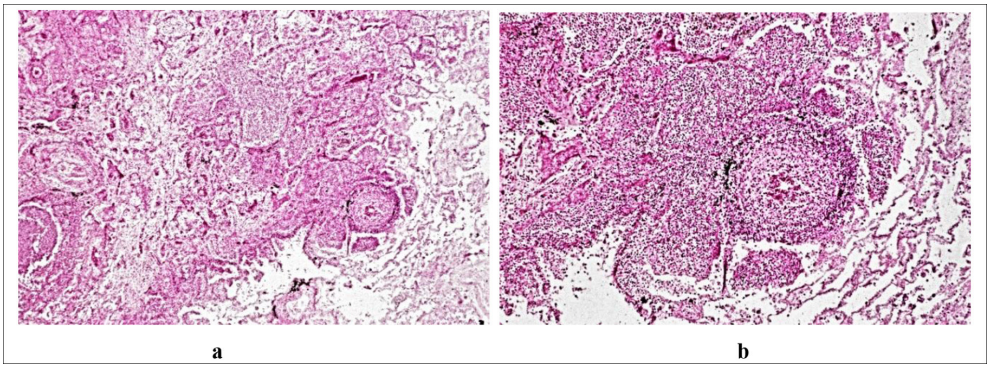

Figure 5: RA, lung, small bronchial artery, non-specific, acute (necrotizing) vasculitis, advanced stage of sublobular vasculogenic pneumonia (a) HE, x20 (b) same area as (a), x50

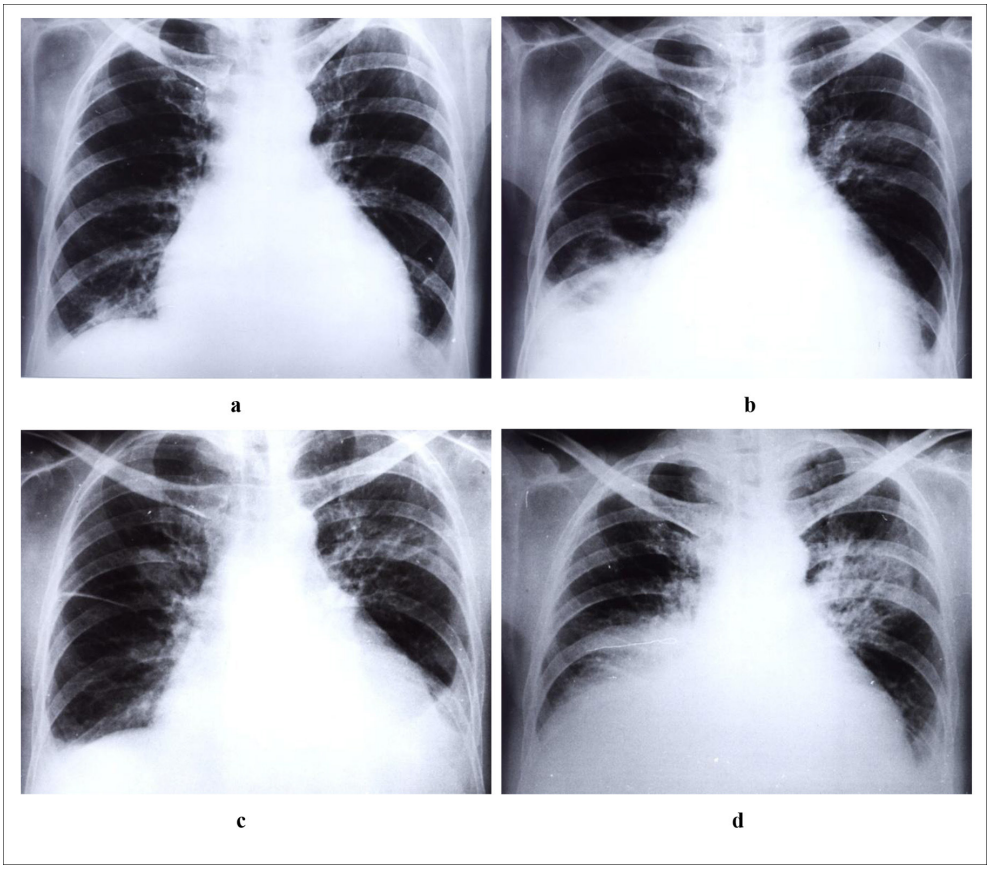

Figure 6: Chest radiograph (a) 25.08.1976, cardiomegaly (b) 28.09.1976, migrating pneumonic infiltrates (c) 15.10.1976, migrating pneumonic infiltrates (d) 29.11.1976, migrating pneumonia, hydrothorax

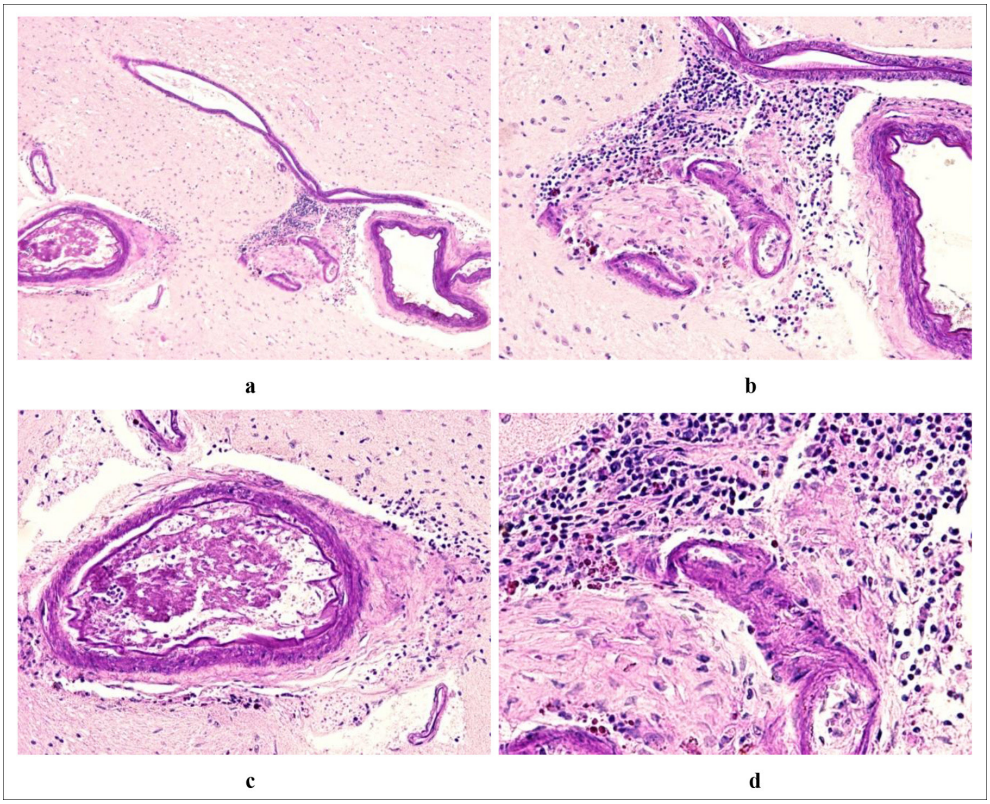

Figure 7: RA, brain, small artery and arterioles with accompanying vein and venule, non-specific vasculitis in dfferent stages of inflammation (a) HE, x40 (b) same as (a) x100 (c) same as (a) x100 (d) same as (a) x200

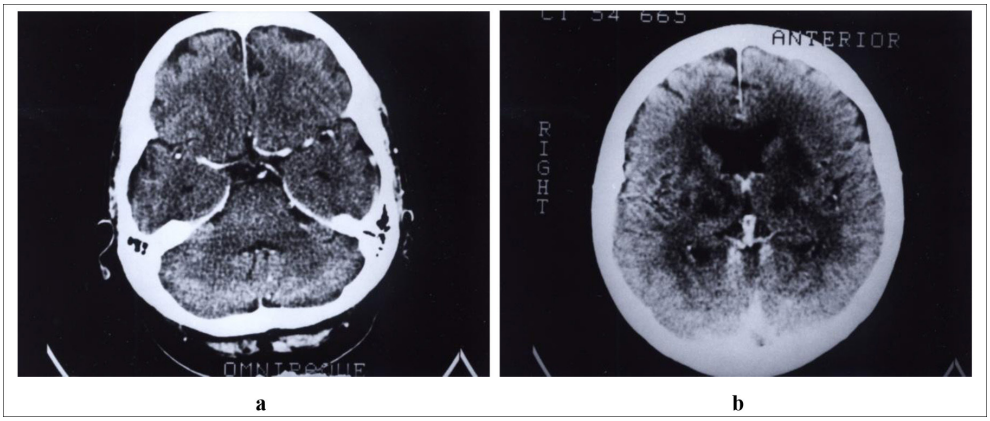

Figure 8: Corresponding to the vascular lesions, multiple microscopic foci of necrosis rise to and exist side by side in different stages of liquefaction as hypodense, patchy changes on CT scan

Systemic vasculitis of septic origin (S-SV) existed in 7 (14.0 %) of 50 patients, and proved to be an accompanying phenomenon, vascular manifestation of generalized lethal septic infection. In 2 of these 7 patients S-SV existed in combination with A-SV, based on the coexistence of characteristic granulomatous (nodular) type of A-SV and non specific leucocytic vasculits of septic origin.

In these seven cases S-SV had no direct role in mortality (χ^2=0.3178, p<0.57), the cause of death was generalized septic infection. S-SV was clinically recognized in 4 (57.14 %), and clinically not diagnosed in 3 (42.86 %) of 7 patients. The correlation between S-SV and clinical diagnosis of S-SV was significant (χ^2=19.5083, p<0.000).

Discussion

In the pertinent literature the prevalence of systemic vasculitis in RA autopsy population is summarized in Table 4.

Most of these earlier studies [7-18] based on the evaluation of some organs, discuss the prevalence of SV in RA patients only, do not mention the origin of it, and do not specify the role of vasculitis as a factor in mortality.

Beside our earlier publications [19-21], according to our best knowledge, a detailed analysis of SV regarding the prevalence and role of vasculitis in mortality 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.

Table 4: Prevalence of systemic vasculitis in autopsy material of rheumatoid arthritis (the origin of SV not mentioned)

Authors	**Year of Publication-[References]**	**Autopsy**	**Prevalence**	**Mortality**
		n=	**of vasculitis**	**of vasculitis**
			n – %	n – %
Cruickshank	1954 [7]	72	18 – 25%	ND
Sinclair and Cruickshank	1956 [8]	16	9 – 56.3%	ND
Cruickshank*	1958 [9]	100	20* – 20%	ND
Lebowitz	1963 [10]	62	6 – 10%	ND
Sokoloff	1964 [11]	19	2 – 10.5%	ND
Karten**	1969 [12]	102	6** – 6%	ND
Gardner	1972 [13]	142	7 – 4.9%	ND
Davis and Engleman	1974 [14]	62	6 – 10%	ND
Eulderink	1976 [15]	111	ND	7 – 6.3%
Albada-Kuipers et al.	1986 [16]	173	17 – 10%	ND
Boers et al.	1987 [17]	132	18 – 13.6%	ND
Suzuki et al.	1994 [18]	81	25 – 30.8%	ND
Bély and Apáthy	1994 [19-20]	161	36 – 22.4%	19 – 11.8%
Bély and Apáthy***	2005 [21]	234	51 – 21.8	23 – 9.8%

ND No Data

* Coronaritis

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

*** One of 51 SV associated with cancer (paraneoplastic vasculitis) have been excluded in the present study.

The pertinent literature [22-26] about the prevalence of systemic vasculitis of hospitalized in- or outpatients with RA are summarized in Table 5. Most of these studies were based on the evaluation of clinical symptoms: mononeuritis multiplex, peripheral neuropathy, classic skin lesions (purpura, petechiae, deep cutaneous ulceration, peripheral gangrene, digital or nailfold infarcts), and only a part of the cases were confirmed by biopy.

According to Vollertsen's data the survival of RA patients with rheumatoid vasculitis decreased compared to the age- and sex-matched Upper Middle Western (normal) population [23].

In our autopsy population there was no significant difference in average age, onset or duration of RA between female and male patients with autoimmune or septic vasculitis, indicating that A-SV or S-SV may develop in both sexes and at any time in the course of the disease.

It is remarkable that the prevalence of vasculitis declined in both

Table 5: Prevalence of systemic vasculitis in biopsy material of rheumatoid arthritis

Authors	**Year of Publication-[References]**	**Patients**	**Prevalence**	**Mortality**
		n=	**of vasculitis**	**of vasculitis**
			n – %	n – %
Schmid et al.*	1961 [22]	31	17 – 54.8 %	ND
Scott et al.**	1981 [4]	-	50 – 100 %	15 – 30 %
Vollertsen et al**	1986 [23]	-	52 – 100 %	ND
Bartels et al. (outpatients)*** in 1997 in 2006	2009 [24]	 37878 43347	 1585 – 4.2 % 1440 – 3.3 %	 ND ND
Bartels et al. (inpatients)*** in 1997 in 2006	2009 [24]	 3397 3369	 140 – 4.1 % 49 – 1.5 %	 ND ND
Ntatsaki et al.** 1988-2000	2014 [25]	-	18 – 100 %	10 – 55.6 %
Ntatsaki et al.** 2001-2010	2014 [25]	-	47 – 100 %	24 – 51 %
Makol et al.**	2014 [26]	172	86 – 50 %	22 – 26 %

ND No Data

* Histologically confirmed arteritis

** RA patients with clinically diagnosed rheumatoid vasculitis (based on clinical symptoms and/or confirmed by biopsy

*** Clinically diagnosed vasculitis, based on clinical symptoms

hospitalized and ambulatory patients at the turn of the millennium probably due to the introduction of new antiinflammatory drugs [24, 25]. Our autopsy data supported this tendency as well in the last third of the last century related the introduction of steroids and immunseppressive drugs [27].

We found a close (significant) relationship between A-SV and mortality (χ^2=6.5617, p<0.01). The mortality due to A-SV depends on the involved organs (on the location of the affected vessels). For example, a mild A-SV of the brain may be lethal, while severe vasculitis of the skin may not be life-threatening.

The clinical diagnosis of A-SV was independent of the lethal or not lethal outcome A-SV; there was no significant connection between them.

All of our patients with clinically diagnosed A-SV had skin lesions at death or in the past (without skin lesions at death or in the patients history the A-SV was not diagnosed).

In our patients S-SV existed as vascular manifestation of the generalized lethal septic infection without direct causal role in mortality. The correlation between the clinical diagnoses and S-SV was significant.

All of the patients with clinically recognized S-SV had suffusions on the skin at the time of death.

A-SV proved to be a much more insidious complication of RA in contrast with the S-SV.

My and RhPn are regarded as direct consequences of A-SV, supported by the significant and very strong positive correlation between them, and may outline them as new vasculogenic entities in RA. MI or BrN may be direct consequence of A-SV as well, but in our autopsy population the overwhelming majority of MI or BrN were caused by Ath; the relationship between MI or BrN and A-SV were not significant.

Summarized formal pathogenesis of multifocal microinfarction of myocardium in RA

Vasculitis distal to the involved vessels can cause local ischemia and regressive (necrobiotic) changes.

This process is more or less widespread and multifocal, depending on the number of involved vessels, i.e. on the severity of vasculitis.

The size of necrobiotic areas depends on the size of involved vessels. Vasculitis of the main coronary arteries with or without thrombosis may result in ischemia and may lead to a large myocardial infarct, macroscopically similar to myocardial necrosis due to coronary atherosclerosis and/or thrombosis. Vasculitis of the small coronary arteries and arterioles causes small necrotic foci, 1-2 mm of diameter (Figures 1-3).

The vasculitis (just like immunological processes) in RA is a recurrent (relapsing) event. Histologically different (acute -subacute-subchronic-chronic) stages of inflammation can be found simultaneously side by side in the same or in different vessels, reflecting the repeated process of vasculitis.

Repeated (recurring) ischemic attacks will be followed by small foci of myocardial necrosis in different stages of necrobiosis. Homogenous necrotic areas alternating with small lytic foci of myocardium (myocardiocytolysis), and scars of a similar size are existing simultaneously side by side (Figures 1-3).

Because of the recurrent nature of autoimmune vasculitis, the regressive changes accumulate in the myocardium with time and may lead to unexpected sudden death [28].

It is difficult to recognize clinically the small accumulating foci of myocardial necrosis (myocardiocytolysis). The history of vasculitis, transient cardiac complaints, low voltage electrocardiogram (ECG) may help in the diagnosis [28].

Summarized formal pathogenesis of rheumatoid pneumonia (vasculogenic disseminated (multifocal) lobular-sublobular pneumonia) in RA

Severe necrotizing vasculitis, with or without thrombosis plays a major role in the pathogenesis of vasculogenic or so-called rheumatoid pneumonia (RhPn). Diminished blood supply due to vasculitis – distal to the involved vessels – may result in ischemia and vulnerable territories (loci minoris resistentiae) for a secondary infection (via bronchogenic or hematogenic route) (Figures 4-6). According to the size of involved vessels lobular or sublobular pneumonia may develop (usually less than 10-20 millimeters in diameter), more or less respecting the anatomic borders of pulmonary units. The inflammation does not have a hemorrhagic character, in contrast to infarct-pneumonia due to thrombembolisation with simultaneous venous congestion. Vasculogenic RhPn differs from bronchopneumonia as well, which is bronchocentric, has no sharply demarcated borders and is independent of the fine anatomic borders of the lung.

Any forms of autoimmune vasculitis are of a relapsing (recurrent) nature, leading to the silent accumulation of inflammatory foci side by side in different stages of inflammation. The number of inflammatory foci (severity RhPn) depends on the number of involved vessels and on the frequency of repeated exacerbation of vasculitis [29].

Clinically it is difficult to recognize the small (silently accumulating) inflammatory foci in the lungs. The history of vasculitis, transient pulmonary complaints with or without fever may help in the diagnosis. In case of multifocal, transient (migratory) pneumonia which is refractory to antibiotics, RhPn should be considered [29].

The anatomic backgroung of RhPn is presented schematically in Figure 9.

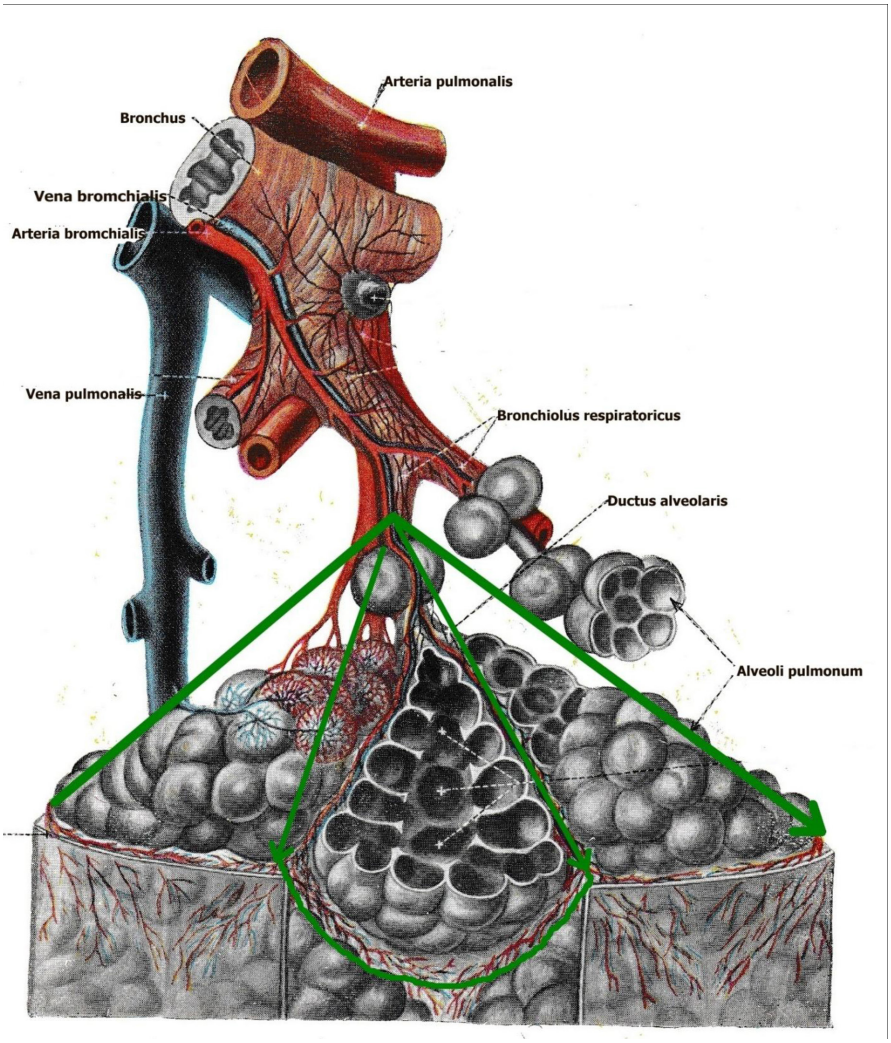

Figure 9: Schematic portrayal of anatomic backgroung or RhPn (the borders of the pulmonary lobules are outlined green)

Summarized formal pathogenesis of recurrent microcystic brain necrosis in RA

Cerebral manifestations of systemic autoimmune vasculitis are relatively uncommon in RA. Cerebral arteritis and/or arteriolitis were rare and mild in our autopsy population as well but, because of its localization, it was often lethal [1]. Cerebral vasculitis may involve the arterioles and small arteries of the brain, and may exist in acute, subacute, and/or subchronic stages of inflammation, combined with chronic structural changes of the vessel wall (the veins and venules seem to be spared) (Figures 7-8). The vasculitis is mostly non-specific (with or without thrombosis or focal hemorrhage), but occasionally massive fibrinoid necrosis may occure. Corresponding to the vascular lesions, multiple microscopic foci of necrosis exist side by side in different stages of liquefaction as hypodense, patchy (microcystic) changes on CT scan. Because of the recurrent nature of autoimmune vasculitis, the regressive changes accumulate within the brain and may lead directly to sudden death of the patient (clinically as cerebral coma), or indirectly (by bronchopneumonia or pulmonary embolisation) [30].

It is very important to look for minor, transient, and recurrent clinical signs of central nervous origin. Cerebral vasculitis should be considered, especially if there is a history of vasculitis [31].

Conclusion

Systemic vasculitis of autoimmune origin (A-SV) is one of the basic manifestations of RA. Cardiac, pulmonary or cerebral complication of A-SV may cause not once clinically difficult diagnostic problems as silent (atypical) myocardial necrosis, antibiotic resistant multifocal migrant pneumonia or progressive microcystic brain necrosis. Accumulation of minor insults in the heart, lung or brain, whith moderate and transient clinical symptoms may hide the deadly danger of A-SV in the background.

The clinical diagnosis of A-SV is based in most of the cases on visible skin lesions. Repeated vasculitis in the patient's history may call attention to invisible organ involvement of A-SV. Knowledge of these clinical pathological entities is important for prevention and effective treatment of these ("we see what we know").

In our autopsy population S-SV existed as vascular manifestation of the generalized lethal septic infection without direct causal role in mortality and was not associated with well defined clinical pathological entities.

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