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Complications and Mortality in Systemic Vasculitis – Vasculogenic Clinicopathologic Entities in Rheumatoid Arthritis and Progressive Systemic Sclerosis Autopsy Patients

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Abstract

Objective: The aim of this study was to determine: the complication(s) and mortality of systemic vasculitis or vascular changes of autoimmune origin (A-SV) in rheumatoid arthritis (RA) and progressive systemic sclerosis (SSc) patients, and to outline the consecutive complex pathological changes (clinicopathological entities) due to A-SV in various organs.

Patients and methods: One hundred sixty one (161) non- selected autopsy patients with RA were studied. This non-selected autopsy population of RA patients was compared with 11 autopsy patients suffering of SSc.

RA and SSc were confirmed clinically according to the criteria of the American College of Rheumatology (ARA).

The basic disease, the complication(s), and the lethal outcome caused by vasculitis were determined and analyzed retrospectively after reviewing the clinical and pathological reports, and confirmed by a study of extensive histological material.

The possible role of A-SV in RA or SSc, specifically in relation to complications and cause of death, furthermore to coexistent associated diseases was analyzed by Pearson's chi-squared (χ^2) test.

Results and conclusions: A-SV complicated RA in 33 (20.49%) of 161 cases. A-SV led directly to death in 19 (57.57%) of 33 RA patients, and was present in further 14 (42.42%) of RA patients without a direct role in death. Twenty three of 33 patients died of cardiac, 6 of respiratory insufficiency, and 4 of cachexia, intestinal or renal necrosis. There was a significant and positive correlation between A-SV and multifocal myocardiocytolysis (χ^2=40.7086, p<0.00001), or multifocal rheumatoid pneumonia (χ^2=7.4069, p<0.006), which were outlined as new vaculogenic entities in RA.

SSc was the basic disease leading to death in each of 11 patients, and all of these were complicated by A-SV (with or without fibromuscular intimal proliferation–FIP). Five of 11 SSc patients died of circulatory failure caused by complex cardiomyopathy, with or without honeycomb lung. Complex nephropathy led to uremia in 6 of 11 cases. The significant and positive correlation between FIP and myocardiocytolysis (^{2}=4.4818, p<0.034), or complex nephropathy (χ^2=5.3047, p<0.021) indicate that these complications were directly related to A-SV in SSc patients. The abundant interstitial fibrosis in various organs may have been generated by immunological processes independent of vascular changes.

Keywords: Rheumatoid arthritis; Systemic sclerosis; Systemic Vasculitis; Complications; Cause of death

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 (A-SV) may be regarded as one of the basic manifestations of rheumatoid arthritis (RA) as well. A-SV is one of the main, and the most likely lethal complication to be missed clinically with high probability of RA [1].

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" [2].

The knowledge of complications and associated diseases, furthermore the risk of mortality in various diseases is important in their prevention or earlier and more effective treatment [3]. Studies confirm the increased risk of cardiovascular diseases in RA [4-7]. The cardiovascular complications–beside renal and pulmonary ones – are important in the mortality of SSc patients as well [8-10].

The aim of this study was to determine: the complication(s) and mortality of A-SV in RA and SSc patients, and to outline the consecutive complex pathological changes (clinicopathological entities) due to A-SV in various organs.

Patients (autopsy population)

At the National Institute of Rheumatology 9475 patients died between 1969 and 1992; among them 161 with RA (females 116, average age: 64.95 years, range 87-16, onset of RA: 50.19, average disease duration: 14.79 years; males 45, average age: 66.29 years, range 88-19, onset of RA: 52.57, average disease duration: 13.46 years at death), and all of them were autopsied.

This non-selected autopsy population of RA patients was studied and compared with 11 autopsy patients with SSc (females 10, average age: 53.6 years, range 62-37, onset of SSc: 43.3, disease duration: 10.0

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years; male 1, age of 65 years, onset of SSc and duration of disease not known).

RA and SSc were confirmed clinically according to the criteria of the American College of Rheumatology (ACR) [11,12].

Methods

The basic disease, the complication(s), and the lethal outcome caused by vasculitis were determined and analyzed retrospectively, reviewing the clinical and pathological reports, and confirmed by a detailed review of extensive histological material. From each patient 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 [1].

The possible role of A-SV on RA or SSc, specifically in relation to complications and cause of death, furthermore to coexistent associated diseases was analyzed by Pearson's chi-squared (χ^2) test (the correlations were calculated based on the total number of patients; in case of RA n=161, and SSc n=11) [13].

Results

RA and A-SV

A-SV complicated RA in 33 (20.49%) of 161 cases.

RA with A-SV: 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.

A-SV led directly to death in 19 (57.57%) of 33 RA patients: in one case due to coronary arteritis with a large anteroseptal myocardial infarct (MI); in 11 cases coronary arteritis or arteriolitis caused multifocal microinfarcts of the myocardium (myocardiocytolysis-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 cerebral vasculitis with multifocal brain necrosis led to death (in one case due to bronchopneumonia and in the second one due to femoral vein thrombosis, pulmonary embolism and septic infarction of the lung). In one patient thrombovasculitis of the main mesenteric artery caused hemorrhagic necrosis of the intestines; in another case thrombosis of the main renal artery led to renal insufficiency and incipient renal necrosis and was the cause of death.

A-SV was present in further 14 (42.42%) of 33 RA patients without direct role in death (Table 1).

Twenty three of 33 patients died of cardiac, 6 of respiratoric insufficiency, and 4 of cachexia, intestinal or renal necrosis.

Basic disease		Complication (1-2)		Cause of death	Associated Disease (s)	CI+ CI-	Severity of A-SV*	Pr # /year
1	RA	A-SV	Coronary arteritis-arteriolitis	Myocardiocytolysis, multiple		CI-	0,227	20/70
2	RA	A-SV	Coronary arteriolitis	Myocardiocytolysis, multiple	Ath	CI-	0,238	81/70
3	RA	A-SV	Pulmonary arteritis Bronchial arteritis	Rheumatoid pneumonia		CI-	0,306	V/A
4	RA	A-SV	Coronary arteritis-arteriolitis Myocarditis	Heart failure	Ath -DM	CI-	0,375	114/71
5	RA	A-SV	Vasculogenic pancreatitis, multiple	Circulatory failure	TbF	CI-	0,630	174/72
6	RA	A-SV		Cachexia	Ath	CI-	0,313	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	CI+	0,217	395/76
8	RA	A-SV	Coronary arteriolitis Microinfarction	Circulatory failure	Ath -Cirrhosis	CI+	0,100	20/80
9	RA	A-SV	Coronary arteritis-arteriolitis Eosinophilic mycarditis Cortical necrosis of adrenals	Myocardiocytolysis, multiple		CI+	1,500	110/80
10	RA	A-SV		Purulent bronchiolitis		CI-	0,271	175/82
11	RA	A-SV	Pulmonary arteritis Bronchial arteritis	Rheumatoid pneumonia		CI-	0,153	25/85
12	RA	A-SV	AA amyloidosis	Uremia	DM	CI-	0,111	43/85
13	RA	A-SV	AA amyloidosis	Myocardial necrosis	Ath -DM	CI-	0,069	90/85
14	RA	A-SV	Pulmonary arteritis Bronchial arteritis	Rheumatoid pneumonia	Ath	CI-	0,111	119/85
15	RA	A-SV	Aortitis Coronary arteritis-arteriolitis Pancarditis Nodula valvulitis, Nodular endocarditis Myocarditis Myocardial rheumatoid nodules Epicarditis Vasculogenic pancreatitis, multiple Vasculitis of intestines	Circulatory failure	Ath -TbF	CI-	0,667	36/86

16	RA	A-SV	Cerebral vasculitis, multiple Brain necrosis, multiple Deep vein thrombosis Pulmonary embolism Glomerulonephritis Interstitial nephritis	Inflammed infarct of the lung		Cl-	0,042	123/86
17	RA	A-SV	Coronary arteritis-arteriolitis Nodular valvulitis AA amyloidosis	Circulatory failure		Cl-	0,292	243/87
18	RA	A-SV	Coronary arteritis-arteriolitis Valvulitis Endocarditis Myocarditis	Myocardiocytolysis, multiple		Cl+	0,273	275/87
19	RA	A-SV	Cerebral vasculitis, multiple Secondary Sjögren's disease Thyreoiditis	Brain necrosis, multiple Bronchopneumonia	DM-TbF-CAA	Cl-	0,183	279/87
20	RA	A-SV	Coronary arteritis-arteriolitis Nodular valvulitis Endocarditis Myocarditis Myocardial rheumatoid nodules	Myocardiocytolysis, multiple		Cl-	0,258	312/87
21	RA	A-SV	Thrombovasculitis renal artery Coronary arteriolitis	Renal necrosis		Cl+	0,455	194/88
22	RA	A-SV	Coronary arteriolitis Epicarditis Vasculitis of intestines AA amyloidosis	Myocardiocytolysis, multiple	TbF-mTb	Cl-	0,652	240/88
23	RA	A-SV	Coronary arteritis-arteriolitis Pancarditis Nodula valvulitis Nodular endocarditis Myocarditis Myocardial rheumatoid nodules Nodular epicarditis	Myocardiocytolysis, multiple	Ath	Cl-	0,153	295/88
24	RA	A-SV	Valvular endocarditis	Heart failure	DM	Cl-	0,042	40/89
25	RA	A-SV	Coronary arteriolitis Acute endocarditis Myocardial rheumatoid nodules	Myocardiocytolysis, multiple	TbFc-mTb	Cl-	0,333	227/89
26	RA	A-SV	Coronary arteritis-arteriolitis Nodula valvulitis, Myocardial rheumatoid nodules Nodular epicarditis	Myocardiocytolysis, multiple		Cl-	0,153	285/89
27	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-	0,056	41/90
28	RA	A-SV	Coronary thrombovasculitis Coronary arteriolitis	Myocardial necrosis	Ath-TbFc-Ca	Cl-	0,111	65/90
29	RA	A-SV	Coronary arteriolitis Nodular pancarditis Nodula valvulitis, Myocardial rheumatoid nodules Nodular epicarditis Myositis	Circulatory failure	Ath-TbFc-mTb	Cl-	0,083	87/90
30	RA	A-SV	Coronary arteriolitis Pancarditis Endocarditis Myocarditis Epicarditis	Circulatory failure		Cl+	0,045	146/91
31	RA	A-SV	Coronary arteriolitis	Myocardiocytolysis, multiple		Cl-	0,167	221/91
32	RA	A-SV	Coronary arteritis Nodular pancarditis Nodular pancarditis Nodula valvulitis, Myocardial rheumatoid nodules Nodular epicarditis Myositis	Circulatory failure Bronchopneumonia	Ath	Cl-	0,750	14/92

33	RA	SV	Thrombovasculitis (Mesenteric artery)	Intestinal necrosis	DM	CI-	0,083	144/92

A-SV: – Systemic vasculitis of autoimmune origin (complication with lethal outcome in 19 of 33 patients (bold); complication without fatal outcome in 14 of 33 patients)
CI+: – Clinically diagnosed systemic vasculitis in 6 (18.18%) of 33 patients (clinically recognized 4 of 19 lethal cases, and 2 of 14 not lethal cases).
CI-: – Clinically not diagnosed systemic vasculitis in 27 (81.82%) of 33 patients (clinically not recognized 15 of 19 lethal cases, and 12 of 14 not lethal cases).
Myocardiocytolysis Multiple (multifocal) microinfarction of myocardium (My)
CAA – Cerebral amyloid angiopathy
Tb – Post-primary (Fc – fibrocaseous, or F – fibrous) tuberculosis
mTb – active miliary dissemination of Tb
DM – adult type II diabetes mellitus

Table 1: Mortality due to A-SV in RA – (A-SV n=33 of 161, Mortality of A-SV n=19 of 33).

The basic disease, complication(s) and associated diseases of 33 RA patients with A-SV are summarized in Glossary to Table 1.

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.

Severity of A-SV was determined histologically in one of our previous study [9]:

Atherosclerosis (Ath) –was diagnosed in RA patients only in cases, 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.

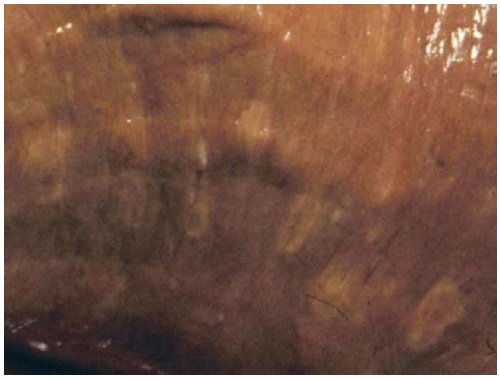

Figure 1: Heart, multiple microinfarts (myocardiocytolysis) of myocardium in different stage of necrosis (Magnification: x4).

The most important complications and causes of death or associated diseases in 161 RA patients with or without A-SV are listed bellow:

My complicated RA in 11 (6.83%) of 161 patients, and all of these were accompanied with A-SV (Figures 1 and 2).

RhPn complicated RA in 3 (1.86%) of 161 patients, and all of these were accompanied with A-SV (Figure 3).

Bronchopneumonia (BrPn) – partly related to RA, and partly related to Ath – was noted in 22 (13.66%) of 161 patients, and was associated with A-SV in 2 of 22 cases.

AA amyloidosis (AAa) was observed in 34 (21.12%) of 161 RA patients, and accompanied with A-SV in 5 of 34 patients.

Atherosclerosis (Ath) accompanied RA in 74 (45.9%) of 161 cases, and was associated with A-SV in 12 of 74 cases.

Cardiac insufficiency (CI – sometimes mentioned as "heart failure", or circulatory failure" – partly related to RA, and partly related to Ath) was registered in 40 (24.84%) of RA 161 patients, and accompanied with A-SV in 9 of 40 patients.

Myocardial infarction (MI – partly related to RA, and partly related to Ath –was found in 11 (6.83%) of RA 161 patients, and accompanied with A-SV in 2 of 11 patients.

Adult type II diabetes mellitus (DM) associated to RA in 30 (18.6%) of 161 patients, and was accompanied with A-SV in 7 of 30 cases.

Post-primary (Fc – fibrocaseous, or F – fibrous) tuberculosis (Tb) was found in 21 (13.4%), complicated by active miliary dissemination

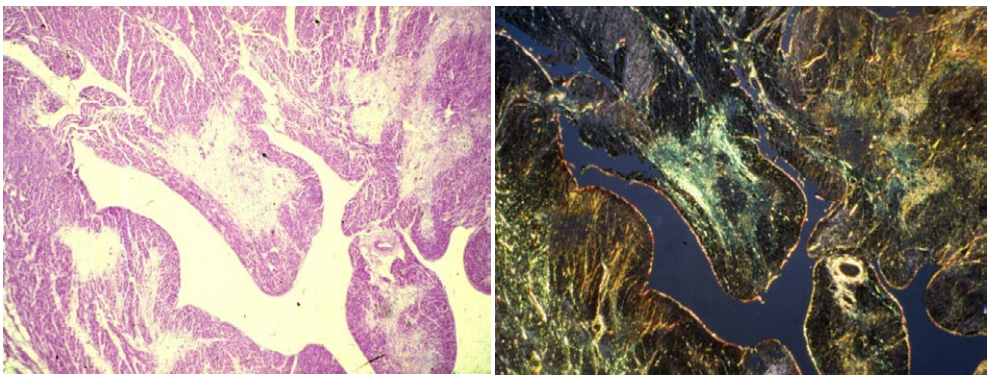

Figure 2: Heart, multiple microinfarcts (myocardiocytolysis) of myocardium in different stages of necrosis
(a) HE, x50 (b) Sirius red F3BA, same as (a) x50.

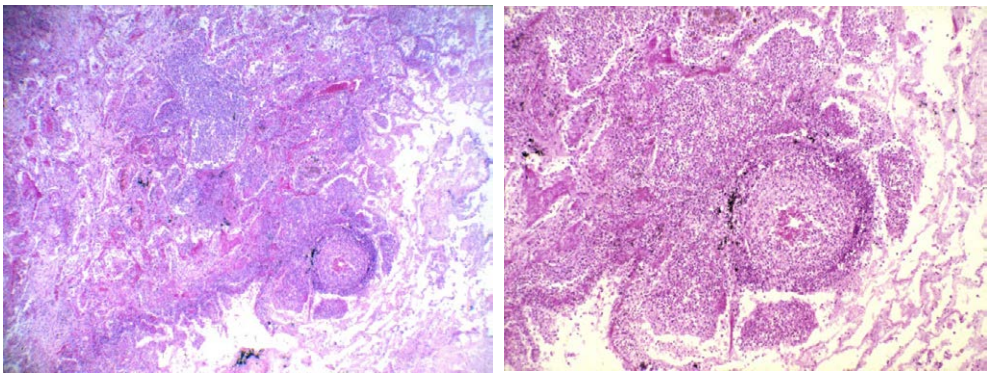

Figure 3: Lung, small bronchial artery, non-specific, acute vasculitis, with sublobular bronchopneumonia (a) HE, x50 (b) same as (a) x125.

(mTb) in 6 (3.73%) of 161 patients. Tb was associated with A-SV in 9, and active mTb in 4 of 21 cases.

The statistical link between A-SV and coexistent complications or associated diseases in 161 RA patients is summarized in Table 2.

There was a significant and positive correlationbetween *A-SV* and *prevalence* of *My* (χ^2=40.7086, p<0.00001) between *A-SV* and *prevalence* of *RhPn* (χ^2=7.4069, p<0.006) between *A-SV* and *prevalence* of *Tb* (χ^2=7.4096, p<0.006), between *A-SV* and *prevalence* of *mTb* (χ^2=5.4751, p<0.019).

The correltion between A-SV and BrPn (χ^2=1.3044, p<0.253), AA amyloidosis (χ^2=0.8870, p<0.346), Ath (χ^2=1.5398, p<0.215), CI (χ^2=0.6622, p<0.415), MI (χ^2=0.036, p<0.849), or DM χ^2=0.1823, p<0.669) was not significant (even in case of BrPn, AAa, Ath, and MI – based on the negative association's coefficients the relationships were inverse).

A-SV and SSc

A-SV and chronic structural changes of blood vessels were present in all of 11 SSc patients.

SSc with A-SV: 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.

SSc was the basic disease leading to death in each of 11 patients (Figure 4), and all were complicated by A-SV. Blood vessels of all calibers (arterioles, small arteries and medium size arteries) were involved (capillaries were not evaluated.

A-SV was characterized by a wide spectrum of vascular changes such as non-specific inflammatory infiltration, fibrinoid necrosis, fibromuscular intimal proliferation (FIP), and/or adventitial fibrosis (with or without thrombosis).

Vasculitis and vascular changes were accompanied by a wide spectrum of histological abnormalities in various organs.

In the heart complex vascular changes – FIP (n=5), multifocal myocardiocytolysis or myocardial necrosis (n=4), and/or endo-myocardial fibrosis (n=10) was present in 10 of 11 SSc patients. Complex vascular changes – FIP was accompanied by myocardiocytolysis or myocardal necrosis in 4 of 5, and endo-myocardial fibrosis in 5 of 10 cases.

The lungs showed complex vascular changes – FIP (n=3), interstitial pneumonitis or fibrosis (n=11), and/or honeycomb-lungs (n=5) (Figure 5) in 11 of SSc 11 patients.

The prevalence of complications or associated diseases	The co-existent complications or associated diseases	The statistical link (with association's coefficient – Ac) between A-SV and complications or associated disease in 161 RA patients
in 161 RA patients	in 33 RA patients with A-SV	
with or without A-SV		
Myocardiocytolysis:	Myocardiocytolysis:	Ac: 1
n=11/161	n=11/33	χ''=40.7088, π<0.00001
Rheumtoid pneumonia:	Rheumtoid pneumonia:	Ac: 1
n =3/161	n =3/33	χ''=7.4069, π<0.006
Bronchopneumonia:	Bronchopneumonia:	Ac*: -0.4832
n=22/161	n=2/33	χ''=1.3044, π<0.253
AA amyloidosis:	AA amyyloidosis:	Ac*: -0.2425
n =34/161	n =5/33	χ''=0.8870, π<0.346
Atherosclerosis:	Atherosclerosis:	Ac*: -0.2435
n=74/161	n=12/33	χ''=1.5398, π<0.215
Cardiac insufficiency:	Cardiaac insufficiency:	Ac: 0.1736
n =40/161	n =9/33	χ''=0.6622, π<0.415
Myocardial necrosis:	Myocardial necrosis:	Ac*: -0.0793
n=11/161	n=2/33	χ''=0.036, π<0.849
Diabetes mellitus:	Diabetes mellitus:	Ac: 0.1027
n=30/161	n=7/33	χ''=0.1823, π<0.669
Tuberculosis:	Tuberculosis:	Ac: 0.5675
n=21/161	n=9/33	χ''=7.4096, π<0.006
mTb:	mTb:	Ac: 0.7935
n=6/161	n=4/33	χ''=5.4751, π<0.019

*Asterisk indicates negative value of association's coefficient (invers relationship between A-SV and complications or associated disease in 161 RA patients). Bold indicates significant value

Table 2: The influence of A-SV on the prevalence of coexistent complications or associated diseases in 161 RA patients.

Complex vascular changes FIP was accompanied by interstitial pneumonitis or fibrosis in 3 of 11, and honeycomb-lungs in 3 of 5 cases.

Complex nephropathy was characterised by complex vascular changes – FIP (n=9) (Figure 6), by interstitial nephritis and/or fibrosis (n=8), by mesangiopetroliferative or membranous glomerulonephritis (n=1), and by multifocal cortical necrosis (n=2) in 9 of SSc 11 patients.

FIP was associated to complex nephropathy in all of these 9 SSc patients.

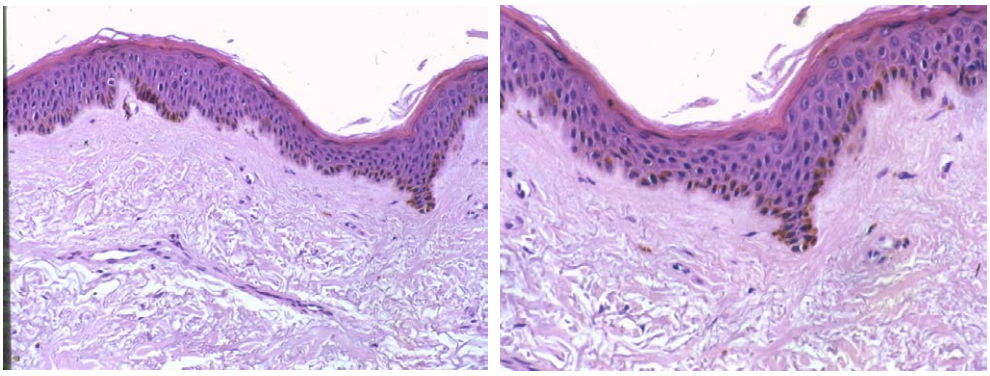

Figure 4: SSc, skin, scleroderma with epidermal atrophy accompanied by slight hyperkeratosisn, and discontinuous hyperpigmentation of the basal layer (a) HE, x50 (b) same as (a) x125.

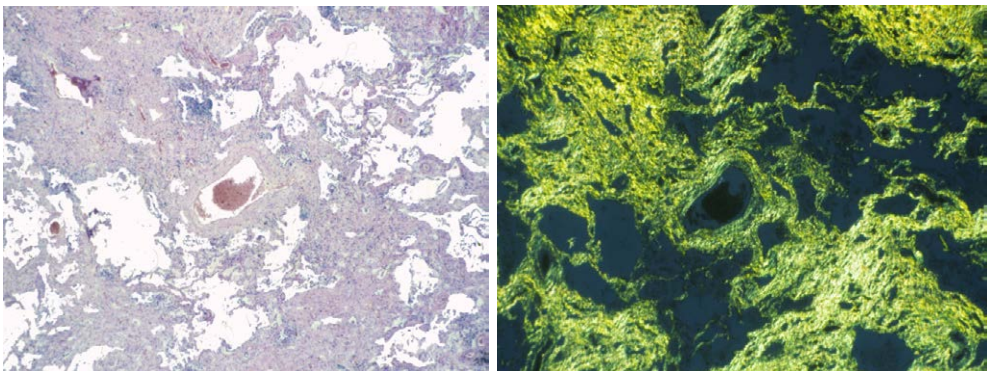

Figure 5: SSc, honeycomb-lung characterized by excessive fibrous tissue, and cystic spaces (a) HE, x50 (b) Sirius red F3BA, same as (a) x50.

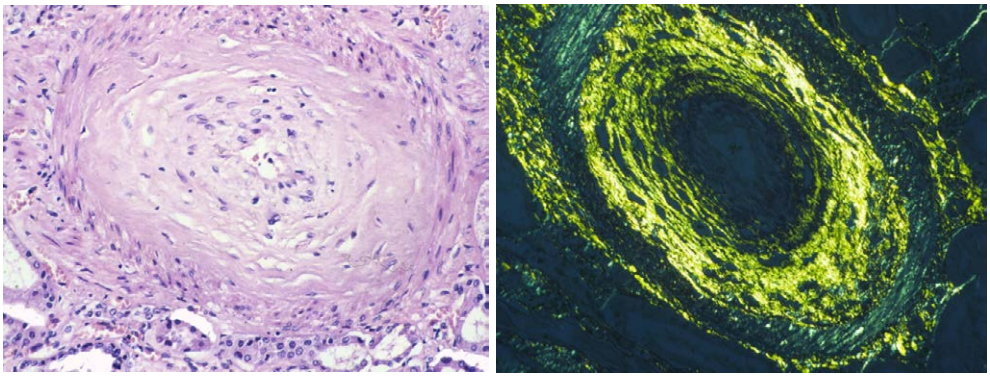

Figure 6: SSc, kidney, small artery, fibromuscular intimal proliferation–FIP and adventitial fibrosis (a) HE, x125 (b) Sirius red F3BA, same as (a) x125.

FIP was accompanied by interstitial nephritis in 8 of 9, by glomerulonephritis in 1 of 1, by tubular necrosis in 2 of 2 cases.

Five of 11 SSc patients died of circulatory failure caused by histological changes of the heart and lungs. The renal changes led to uremia in 6 of 11 cases.

Associated diseases had, no causal role in death of SSc patient.

The basic disease, complication(s) and associated diseases of 11 SSc patients with A-SV and FIP are summarized in Table 3.

A-SV: Systemic vasculitis of autoimmune origin (complication with lethal outcome in 11 of 11 patients; accompanied with fibromuscular intimal proliferation – FIP in 10 of 11 patients)

Severity of A-SV was determined histologically in one of our previous study: [9]

Cl+: Clinically recognized "vasculitis" (Ad litteram – "explicit verbis") in 2 (18.18%) of 11 patients.

Cl-: – Clinically not diagnosed systemic vasculitis in 9 (81.82%) of 11 patients.

Basic disease		Complications		Cause of death	Associated disease(s)	Cl+Cl-	Severity Avg/Pt	Pr # /year
1	SSc	A-SV	Complex nephropathy including FIP Glomerulonephritis and Focal tubural necrosis (multiple) Scleroderma Multifocal pancreatitis Gastrointestinal sclerosis Interstitial pneumonitis Interstitial fibrosis Periductal biliary fibrosis	Uremia		Cl-	0,750	44/61
2	SSc	A-SV	Complex nephropathy including FIP and Interstitialis nephritis Honeycomb lung including Interstitial pneumonitis and FIP Scleroderma Chronic fibrous-fibrinous synovialitis Multifocal pancreatitis Myocardial fibrosis	Uremia		Cl-	0,690	33/65
3	SSc	A-SV	Honeycomb lung including Interstitial fibrosis and Peribronchial fibrinoid necrosis (focal) Fibrous fascitis Myositis Scleroderma Chronic fibrous-fibrinous synovialitis Complex nephropathy including FIP and Interstitialis nephritis Gastrointestinal sclerosis Endo-epicardial fibrosis Periductal biliary fibrosis Periductal fibrosis of pancreas Strumitis-Focal interstitial fibrosis	Bronchopneumonia Circulatory failure		Cl-	0,833	4/83
4	SSc	A-SV	Complex nephropathy including FIP and Interstitialis nephritis Scleroderma Chronic endocardial fibrosis Peri-endoneural fibrosis Gastrointestinal sclerosis Chronic fibrous-fibrinous synovialtis Interstitial fibrosis Peribronchial fibrosis	Uremia		Cl+	1,063	35/83
5	SSc	A-SV	Complex nephropathy including FIP and Interstitialis nephritis Interstitial pneumonitis Scleroderma Gastrointestinal sclerosis Multifocal pancreatitis Chronic fibrous-fibrinous synovialtis Perineural fibrosis Endocardial fibrosis Fibrous fascitis Periductal biliary fibrosis Periductal fibrosis of salivary gland	Uremia	Fibrocaseous tuberculosis	Cl-	1,056	83/87
6	SSc	A-SV	Complex cardiomyopathy including FIP and Endo-myocardial fibrosis-Valvulitis Honeycomb lung including Interstitial fibrosis and FIP Complex nephropathy including FIP and Interstitial nephritis Scleroderma Gastrointestinal sclerosis Peri-endoneural fibrosis Chronic fibrous-fibrinous synovialtis Periductal fibrosis of pancreas Struma-Focal interstitial fibrosis Sclerotising lymphadenopathia	Circulatory failure	Meningeom	Cl+	1,208	35/88

7	SSc	A-SV	Complex nephropathy including Chronic recurrent angiopathy - FIP Interstitial nephritis and Focal (multiple) tubular necrosis Multifocal pancreatitis Periductal fibrosis Perineural fibrosis Complex cardiomyopathy including FIP Microinfarcts (Myocardiocytolysis) and Endo-myocardial fibrosis Chronic fibrous-fibrinous synovialtis Gastrointestinal sclerosis Duodenal ulcer Scleroderma Interstitial pneumonitis Peritracheal and peribronchial fibrosis Peri- and endoneural fibrosis Myositis Sjögren-syndrome Struma-Focal interstitial fibrosis Periductal biliary lymphoid infiltration Periductal biliary fibrosis	Uremia		Cl-	1,750	96/88
8	SSc	A-SV	Interstitialis nephritis Gastrointestinal sclerosis Interstitial pneumonitis Peritracheal-peribronchial fibrosis Chronic fibrous valvulitis (aorta) Scleroderma Fibrous fascitis Chronic fibrous-fibrinous synovialtis Perineural fibrosis Multifocal pancreatitis Periductal fibrosis of pancreas	Uremia	Actinomycosis (Tonsilla)	Cl	0,924	V/89
9	SSc	A-SV	Honeycomb lung including Interstitial fibrosis Complex cardiomyopathy including FIP Myocardiocytolysis, Scarring microinfarcts, Subacute epicarditis Fibrous endocarditis-valvulitis Scleroderma Sjögren-syndrome Gastrointestinal sclerosis Chronic fibrous-fibrinous synovialtis Peri-endoneural fibrosis Complex nephropathy FIP Interstitial nephritis Myositis (Interstitial fibrosis)	Circulatory failure		Cl-	1,050	147/97
10	SSc	A-SV	Complex cardiomyopathy including FIP of coronary artery Myocardiocytolysis, Endo-myocardial fibrosis and Chronic fibrous valvulitis Scleroderma Multifocal pancreatitis Periductal fibrosis of pancreas Myositis Fibrous fascitis Peri-endoneural fibrosis Gastrointestinal sclerosis Interstitial fibrosis (focal) Sclerosing lymphadenitis	Circulatory failure		Cl-	1,030	126/96

11	SSc	A-SV	Complex cardiomyopathy including FIP of coronary artery Myocardial necrosis Circumscript endocardial fibrosis and Interstitial myocardial fibrosis Scleroderma Gastrointestinal sclerosis Honeycomb lung (focal) including Interstitial pneumonitis FIP and Circuscript pleural fibrosis Complex nephropathy including Chronic renal angiopathie -FIP and Interstitial nephritis Peri-endoneural fibrosis Chronic fibrous fascitis Myositis Sclerotising lymphadenitis Systemic AA amyloidosis	Heart failure		Cl-	2,063	196/97

Table 3: Mortality due to A-SV in SSc–(A-SV n=11 of 11, complicated by FIP n=10 of 11).

All of 11 SSc patients were complicated with A-SV; and FIP was present in 10 of 11 A-SV cases.

The statistical link between FIP and coexistent complications in 11 SSc patients is summarized in Table 4.

Ac: association's coefficient

Bold indicates significant value

There was a significant and positive correlationbetween *FIP* and *prevalence* of *My* or myocardial necrosis (χ^2=4.4818, p<0.034) between *FIP* and *prevalence* of *complex nephropathy* (χ^2=5.3047, p<0.021). In our patients the correltion between FIP and interstitial pneumoniitis and/or interstitial fibrosis (^{2}=0.3636, p<0.546), honeycomb-lung (χ^2=2.3871, p<0.122), interstitial nephritis (χ^2=0.0763, p<0.7825), tubular necrosis (χ^2=0.0763, p<0.7825), or glomerulonephritis (χ^2=0.7486, p<0.386) was not significant.

The prevalence of histological changes	Co-existence of FIP	The statistical link (with association's coefficient – Ac) between FIP and histological changes in 11 SSc patients
in various organs	in various organs	
of 11 SSc patients	of 11 SSc patients	
Endomyocardial fibrosis: n=10/11	accompanied by FIP:	Ac: 0.9166
	n=5/10	χ″=0.0091, π<0.9237
Myocardiocytolysis or myocardial necrosis:	accompanied by FIP:	Ac: 1
n=4/11	n=4/4	χ″=4.4818, π<0.034
Interstitial pneumonitis and/or fibrosis:	accompanied by FIP:	Ac: 1
n =11/11	n =3/11	χ″=0.3636, π<0.546
Honeycomb-lung:	accompanied by FIP:	Ac: 1
n=5/11	n=3/5	χ″=2.3871, π<0.122
Complex nephropathy:	accompanied by FIP:	Ac: 1
n=9/11	n =9/9	χ″=5.3047, π<0.021
Interstitial nephritis:	accompanied by FIP:	Ac: 0.7777
n=9/11	n=8/9	χ″=0.0763, π<0.7825
Tubular necrosis:	accompanied by FIP:	Ac: 1
n=2/11	n=2/2	χ″=0.0763, π<0.7825
Glomerulonephritis:	accompanied by FIP:	Ac: 1
n=1/11	n=1/1	χ″=0.7486, π<0.386
Ac: association's coefficient Bold indicates significant value		

Table 4: The influence of FIP on the prevalence of coexistent complications in 11 SSc patients.

Discussion

Vasculitis or vascular changes of autoimmune origin are among the most important complications of RA or SSc, and are considered a direct consequence of the basic diseases.

The explicit extra-articular manifestation of A-SV, and extensive involvement of the cardiovascular, respiratory, urinary, and alimentary system in RA [14-16], or SSc [17-19] support and explain our data of mortality caused by A-SV of autoimmune origin.

Comments to A-SV in RA

In our study RA and A-SV, with or without other complications (AA amyloidosis) or associated diseases (atherosclerosis, etc,), led to death by cardiac insufficiency in 23 (multifocal microinfarction of myocardium – My n=11, large myocardial necrosis n=2, by heart failure or circulatory failure n=10), and due to respiratory insufficiency in 6 (rheumatoid pneumonia – RhPn n=3, bronchopneumonia n=2, infarct pneumonia n=1) of 33 cases. Four of 33 patients died of cachexia, intestinal or renal necrosis).

My or 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.

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 arteries and arterioles causes small necrotic foci, 1-2 mm of diameter (Figure 1).

The immunological processes in RA are recurrent events, and all types of autoimmune vasculitis are of a relapsing nature. 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.

Homogeneous necrotic areas alternating with small lytic foci of myocardium (myocardiocytolysis) and scars of a similar size are existing simultaneously side by side (Figure 2).

Because of the recurrent nature of autoimmune vasculitis the regressive changes accumulate in the myocardium with time and may lead to unexpected sudden death [20].

It is difficult to clinically recognize small accumulating foci of myocardial necrosis (myocardiocytolysis). The history of vasculitis, transient cardiac complaints, low voltage electrocardiogram (ECG) may help in the diagnosis [20].

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) (Figure 3). 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 thrombovasculitis 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 [21].

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 [21].

The lack of significant (even inverse) correlation between A-SV and bronchopneumonia, AA amyloidosis, atherosclerosis, cardiac insufficiency, myocardial necrosis, or adult type II diabetes mellitus show, that these complications or associated diseases are more or less independent of A-SV.

The significant and positive correlation between A-SV and tuberculosis or miliary tuberculosis means a positive influence of A-SV (or its therapy with immunosuppressive drugs, or anti-TNF alpha treatment) on prevalence of tuberculosis with or without active miliary dissemination in RA. The presence of A-SV increases the risk of tuberculosis, and endogenous exacerbation and miliary dissemination of tuberculosis [1].

Comments to A-SV in SSc

In SSc patients A-SV with or without FIP led to death by uremia in 6, by cardiac insufficiency in 4, and by respiratory insufficiency in 1 (honeycomb-lung and bronchopneumonia) of 11 cases.

There was a strong positive (significant) correlation between FIP and complex nephropathy (χ^2=5.3047, p<0.021), or myocardiocytolysis and/or myocardial necrosis (χ^2=4.4818, p<0.034). Our data support the thesis that SSc could be regarded as a primary vascular disease [2,22].

We did not find significant correlation between FIP and interstitial inflammation or fibrosis. The lack of significant correlation between FIP and endo-myocardial fibrosis, pneumonitis-pulmonary fibrosis, interstitial nephritis, glomerulonephritis, tubular necrosis may be explained by the small number of cases.

The pathogenic role of capillaries and capillary changes (could) should not be ruled out in these interstitial histological changes of the heart, lungs or kidneys (capillaries with very characteristic electronmicroscopic changes were not evaluated in this study).

"There is intense interest in the possibility that dermal fibroblasts may synthesize excess and/or abnormal collagen and proteoglycan, partly for genetic reasons, but partly in response to local abnormalities of the circulation" [23].

The progressive sclerosis in various organs of SSc patients may be the result of direct qualitative changes in the interstitial collagen fibres, generated by extravascular immunological processes independent of vascular changes. Previous studies support this possibility as well [24-26].

Conclusion

Interactions of coexisting complications in RA or SSc modify the basic disease as well as the typical clinical manifestations of the complications. These changes may lead to misdiagnosis or late recognition of the complications.

The coexisting associated diseases may mask the characteristic clinical symptoms of RA or SSc and may lead to an incorrect diagnosis or late recognition of basic diseases or on the contrary even the recognition of associated diseases may be delayed.

Knowledge of formal pathogenesis of new clinical pathological entities is important from the viewpoint of prevention and effective treatment of these.

Detailed histological evaluation – based on a large autopsy population of RA and SSc patients in one institution may support or statistically confirm theories (for example Gardner's concept [23]) regarding the determination of excessive interstitial fibrosis in SSc patients.

Our recommendation is to look for minor symptoms of modified complications and associated diseases; knowing of these possibilities ("we see what we know") may help in treatment or prevention.

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