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Research Article

Myocardial Necrosis Caused by Systemic Vasculitis or Atherosclerosis in Rheumatoid Arthritis – A Postmortem Clinicopathologic Study of 161 Patients

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Abstract

Aim: The aim of this study was to determine the complication(s) and mortality caused by coronary arteritis or arteriolitis of autoimmune origin (C-A/a) and atherosclerosis of coronary arteries (Ath) in RA.

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

Tissue samples of heart were available for histologic evaluation in 138 patients. Large myocardial infarction, multifocal microinfarcts of the myocardium (myocardiocytolysis – My), C-A/a and Ath were determined and characterized histologically.
The possible role of C-A/a and Ath in the pathogenesis of cardiac complications and cause of death (MI and My) was analyzed by Pearson's chi-squared (χ^2) test.

Results: Systemic vasculitis of autoimmune origin complicated RA in 33 (23.91%) of 138 patients. C-A/a were involved by non-specific, fibrinoid necrotic or granulomatous type of A-SV in 21 of 138 patients. Vessels of all calibers were involved: subepicardial main coronary arteritis in 2, subepicardial and intramural arteritis/arteriolitis in 10, and intramural arteritis/arteriolitis in 9 of 21 patients. Vasculitis was present in acute, subacute, subchronic and chronic stages of inflammation in blood vessels of different sizes.

C-A/a led directly to death in 12 of 21 patients; in one case caused by a large anteroseptal MI, and in 11 cases by My. In further 9 cases C-A/a contributed only to the lethal outcome. Severe Ath was registered as basic (lethal) disease in 30 (21.74%), and as an associated disease in 32 (23.19%) of 138 patients.

An incipient, recent or healed large MI was found in 14 (10.14%), and My in 20 (14.49%) of 138 patients. There was a significant and positive correlation between C-A/a and My ($\chi^2 = 28.6924$, $p < 0.00001$). The link between C-A/a and MI ($\chi^2=0.2448$, $p < 0.62$) was not significant. Conversely, the relationship between Ath and MI showed a strong and significant positive correlation ($\chi^2 = 8.7213$, $p <0 .003$), while the link between Ath and My ($\chi^2 = 0.9590$, $p < 0.32$) was not significant.

Discussion: Based on the statistically strong and significant association between My and C-A/a, this form of myocardial necrosis may be regarded as a special manifestation of vasculitis or a new vasculogenic entity in RA.

Based on the significant correlation, severe atherosclerosis of the main coronary arteries may be regarded as the leading cause of a large MI, in contrast with the less frequent main coronary arteritis.

Keywords: *Rheumatoid Arthritis; Coronary Arteritis or Arteriolitis of Autoimmune Origin; Atherosclerosis; Myocardial Necrosis*

Abbreviations

C-A/a = Coronary Arteritis or Arteriolitis of Autoimmune Origin; Ath: Atherosclerosis of Coronary Arteries; RA: Rheumatoid Arthritis; ARA: American College of Rheumatology; MI: Large Myocardial Infarction; My: Myocardiocytolysis – Multifocal Microinfarcts of the Myo-

cardium; Ns: Non-Specific Vasculitis; Fn: Fibrinoid Necrotic Vasculitis; Gr: Granulomatous Vasculitis; AA – A – a: Medium Size Artery – Small Artery – Arteriole; VV – V – v: Medium Size Vein – Small Vein – Venule; A-SV: Systemic Vasculitis of Autoimmune Origin; Cl+: Clinically Diagnosed; Cl-: clinically not diagnosed; Tb: Post-Primary (Fc – Fibrocaseous, or F – Fibrous) Tuberculosis; mTb: Active Miliary Dissemination of Tb; DM: Adult Type II Diabetes Mellitus; Ca: Carcinoma; ND: No Data

Introduction

Heart diseases of a distinct etiology play an important role in the mortality of rheumatoid arthritis (RA) [1]. "The pericardium/epicardium, myocardium, endocardium and valves, and the coronary blood vessels are all at risk [2]". The involvement of the heart in RA may be primary – caused by circulating immunocomplexes and antibodies directly, or secondary – as indirect consequence of amyloidosis, infections, co-existent atherosclerosis, etc.

Objective

The aim of this study was to determine the complication(s) and mortality caused by coronary arteritis or arteriolitis of autoimmune origin (C-A/a) and atherosclerosis of coronary arteries (Ath) in rheumatoid arthritis (RA). The discussion outlines the consecutive complex pathological changes (clinicopathological entities) due to C-A/a in the heart.

Patients and Methods

One hundred sixty-one (161) non- selected autopsy patients with RA were studied (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) [1].

RA was confirmed clinically according to the criteria of the American College of Rheumatology (ARA) [3].

Tissue samples of heart were available for histologic evaluation in 138 patients. Large myocardial infarction (MI) [4], multifocal microinfarcts of the myocardium (myocardiocytolysis – My) [4], C-A/a and Ath were determined and characterized histologically.

Glossary of definitions

"Prevalence" concerns the presence of vasculitis in blood vessels. Prevalence of vasculitis was determined based on the presence of vasculitis in blood vessels of different calibers.

"**Severity**" means different degrees of inflammatory infiltrates in segments or sectors of blood vessels. 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 of Olympus BX51). Semi-objective score system of "severity": "0" – no vasculitis, "1" – occasional blood vessels with vasculitis, "2" – less than 5 involved blood vessels, "3" – five or more involved blood vessels/microscopic field. (In case of AA or VV this corresponds to the absolute number of involved medium size vessels of a tissue sample, e.g. 5 or more than five medium size vessels/tissue sample with a x20 objective).

Types of vasculitis

Non-specific vasculitis (Ns) – is characterized by non-specific leukocytic, lymphocytic, plasmacytic infiltration. Fibrinoid necrosis is minimal or absent

Fibrinoid necrotic vasculitis (Fn) – is dominated by fibrinoid necrosis (fresh or old fibrinoid changes in the vessel wall)

Granulomatous vasculitis (Gr) – the original structure of the vessel wall is replaced by a granulomatous, more or less cellular infiltrate. In the early stages the infiltrate is dominated by histiocytes, with or without multinucleated giant cells, and later by fibroblasts. In the end stage of granulomatous vasculitis the vessel wall becomes less cellular and more fibrotic.

Size of blood vessels

Arteriole (a) – no internal or external elastic membrane, < 500 micrometers in diameter

Small artery (A) – only internal elastic membrane present, vessels 500 - 1000 micrometers in diameter

Medium size artery (AA) – internal and external elastic membrane are present – vessel > 1000 micrometers in diameter

Venule (v), small vein (V), medium size vein (VV) –accompanying (a), (A) or (AA)

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

The possible role of C-A/a and Ath in the pathogenesis of cardiac complications and cause of death (MI and My) was analyzed by Pearson's chi-squared (χ^2) test [5].

Results

Systemic vasculitis of autoimmune origin complicated RA in 33 (23.91%) of 138 patients.

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

Sex	Number of autopsies	Average age in years at death	Range (in years)	Age at onset of disease	Disease duration (in years)
RA patients	138	65.10	88 – 16	51.18	14.25
Female	100	64.58	84 – 16	50.64	14.44
Male	38	65.95	88 – 19	52.74	13.71
With A-SV	33	67.15	83 – 32	56.90	11.68
Female	20	66.95	82 – 32	58.50	10.89
Male	13	67.46	83 – 53	54.69	12.77
Without A-SV	105	64.45	88 – 16	49.38	15.05
Female	80	63.99	84 – 16	48.45	15.38
Male	25	65.12	88 – 19	52.04	13.91

Table 1: *Sex, average age (range), onset and duration of 138 RA in patients with or without A-SV.*

Autoimmune vasculitis without ystemic vasculitis of septic oriigin S-SV.

C-A/a were involved by non-specific (Figure 1a-d), fibrinoid necrotic (Figure 2a-d) or granulomatous type (Figure 3a-d) of A-SV in 21 (63.63% of 33; 15.21% of 138) patients. Different types of vasculitis existed simultaneously in different vessels or combined in the same vessel, and in the same patient.

Vessels of all calibers were involved: subepicardial main coronary arteritis (Figures 4-6a-b) in 2 (9.5%), subepicardial (Figures 7-8a-b) and intramural arteritis/arteriolitis in 10 (47.6%), and intramural arteritis/arteriolitis in 9 (42.9%) of 21 patients (Table 2).

Vessels of all sizes (arteriole, small artery, medium size artery, venule, small vein, and medium size vein) were involved, with varying frequency and severity of vasculitis.

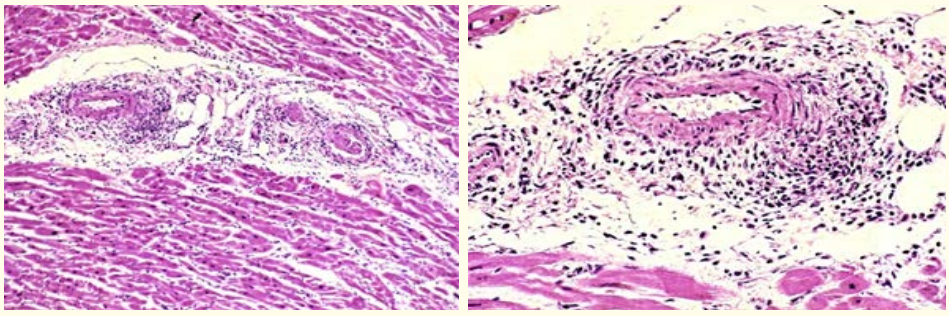

Figure 1a-b: *Heart, intramural small artery and arterioles, non-specific, acute-subacute coronary arteriolitis and (thrombo-) vasculitis.*

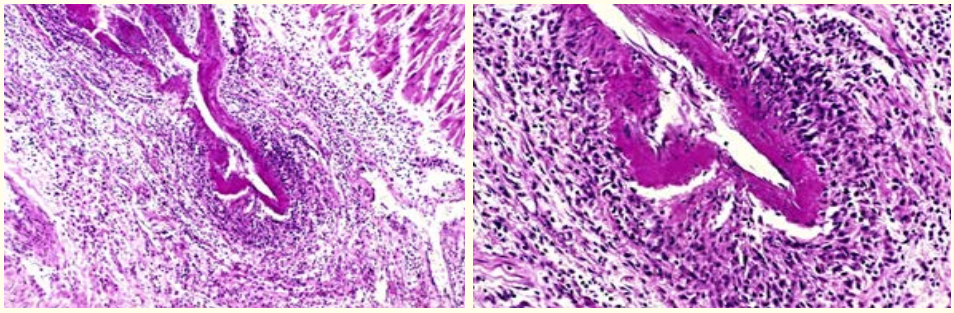

Figure 2a-b: *Heart, intramural small artery, subacute-subchronic, mixed (fibrinoid necrotic and granulomatous) vasculitis.*

(a) HE, x50, (b) same as (a) x125

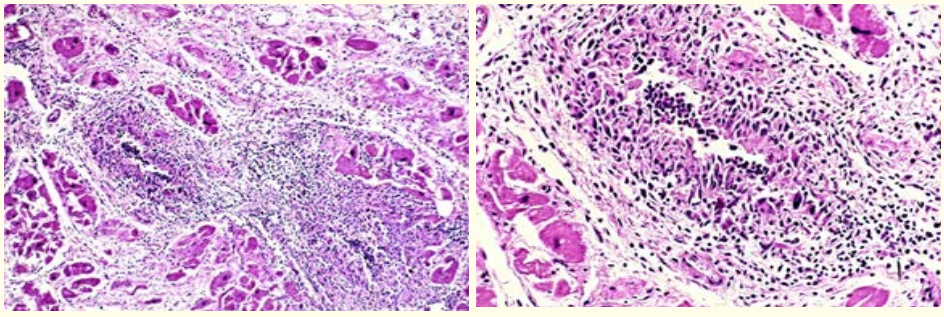

Figure 3a-b: *Heart, intramural small artery and arterioles, granulomatous, subacute-subchronic coronary arteriolitis.*

(a) HE, x50, (b) same as (a) x125

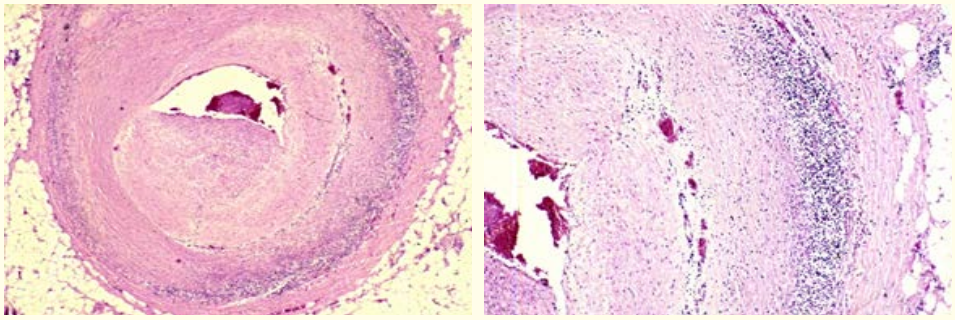

Figure 4a-b: *Heart, main (medium size) coronary artery. Sectorial non-specific subchronic infiltration and chronic fibromuscular intimal proliferation.*

(a) HE, x50 (b) same as (a) x125

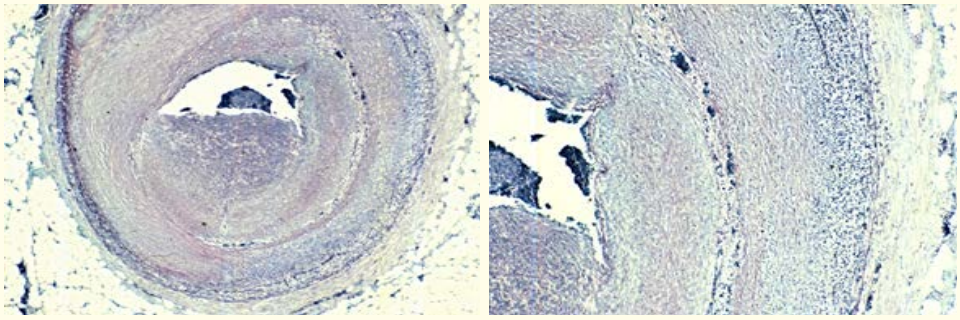

Figure 5a-b: *Heart, main (medium size) coronary artery. Sectorial non-specific subchronic infiltration and chronic fibromuscular intimal proliferation. Multiple, fragmented internal and external elastic membranes are demonstrated by orcein staining.*

(a) Light green-Orcein, x50 (b) same as (a) x125

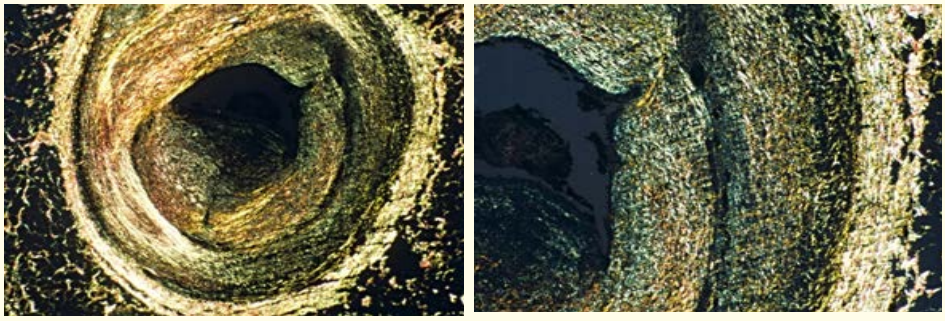

Figure 6a-b: *Heart, subepicardial medium size artery, non-specific chronic vasculitis. The collagen fibers are sprouted and demonstrated by Sirius red F3BA staining.*

(a) Sirius red F3BA, x50 (b) same as (a) x125

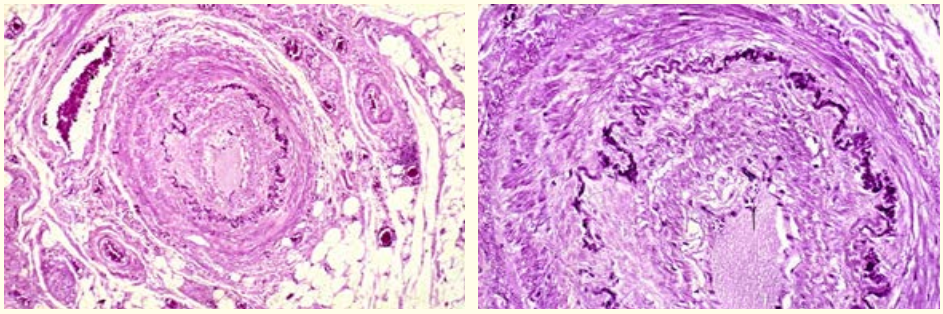

Figure 7a-b: *Heart, subepicardial medium size artery, non-specific chronic vasculitis.*

(a) HE, x 50, (b) same as (a) x125

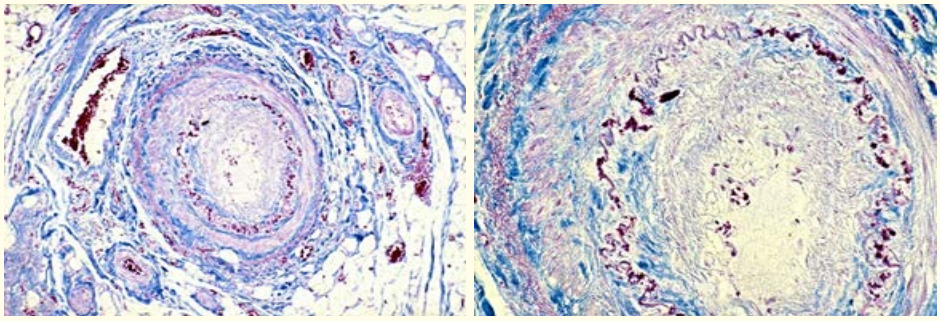

Figure 8a-b: *Heart, subepicardial medium size artery, non-specific chronic vasculitis. The multiple internal and external elastic membranes are fragmented and demonstrated by Masson's trichrome staining.*

(a) Masson's trichrome, x 50, (b) same as (a) x125

Systemic vasculitis of autoimmune origin (A-SV)	33 (23.91%) of 138
Coronary arteritis and or arteriolitis (C-A/a)	21 (63.63%) of 33
Subepicardial (main) coronary arteritis	2 (9.52%) of 21
Subepicardial and intramural arteritis/arteriolitis	10 (47.61%) of 21
Intramural arteritis/arteriolitis	9 (42,87%) of 21

Table 2: *A-SV and coronary arteritis and or arteriolitis in RA patients.*

The prevalence (Table 3 and Diagram 3) and severity (Table 4 and Diagram 4) of vasculitis in different blood vessels of the heart (according to the types of vasculitis) are summarized in Tables 3-4 and Diagrams 3-4.

Vasculitis was present in acute, subacute (Figure 1a-b), subchronic (Figures 2-3a-b) and chronic (Figures 4-8a-b) stages of inflammation in blood vessels of different sizes (Table 5 and Diagram 5).

C-A/a led directly to death in 12 (57.14%) of 21 patients; in one (4.76%) case caused by a large anteroseptal MI, and in 11 (52.38%) cases by My.

Size of involved vessels	Ns	in%	Fn	in%	Gr	in %	Total	Total
Arteriole (a)	15	23,08	4	6,15	8	12,31	27	7,78
Small artery (A)	12	18,46	4	6,15	3	4,62	19	5,48
Medium size artery (AA)	12	18,46	0	0,00	2	3,08	14	4,03
Venule (v)	2	3,08	0	0,00	0	0,00	2	0,58
Small vein (V)	0	0,00	1	1,54	1	1,54	2	0,58
Medium size vein (VV)	0	0,00	0	6,15	1	1,54	1	0,29
Total in absolute value and in %	41	63,08	9	13,85	15	23,09	65	100

Table 3: *Prevalence of coronary arteritis and arteriolitis of autoimmune origin in 21 RA patients.*

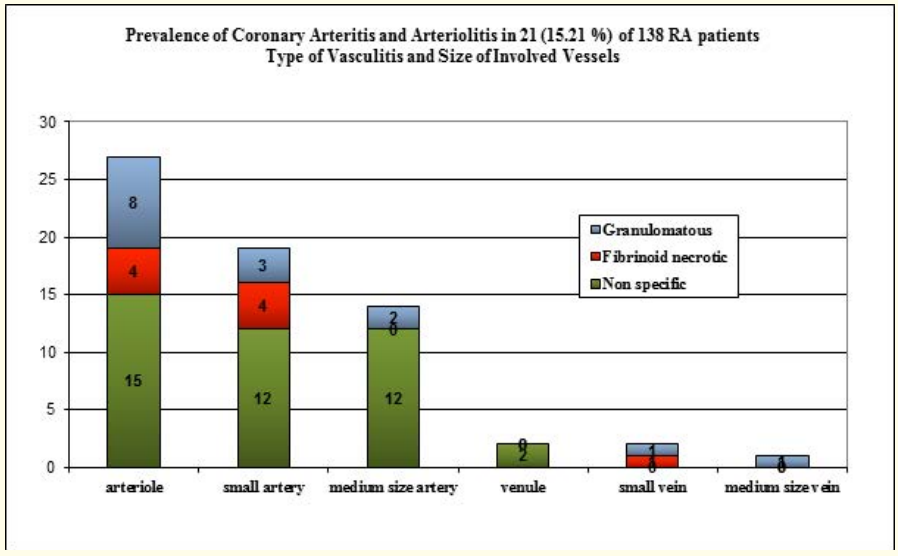

Diagram 3: *C-A/a in RA was characterized by dominant involvement of arterioles and small arteries; the veins were affected less frequently.*

Size of involved vessels	Ns	in%	Fn	in%	Gr	in %	Total	Total
Arteriole (A)	28	23,53	9	7,56	16	13,45	53	44,54
Small Artery (A)	24	20,17	6	5,04	7	5,88	37	31,09
Medium Size Artery (AA)	21	17,65	0	0,00	2	1,68	23	19,33
Venule (V)	3	2,52	0	0,00	0	0,00	3	2,52
Small Vein (V)	0	0,00	1	0,84	1	0,84	2	1,68
Medium Size Vein (VV)	0	0,00	0	0,00	1	0,84	1	0,84
Total in absolute value and in %	76	63,87	16	13,45	27	22,69	119	100

Table 4: *Severity of coronary arteritis and arteriolitis of autoimmune origin in 21 RA patients.*

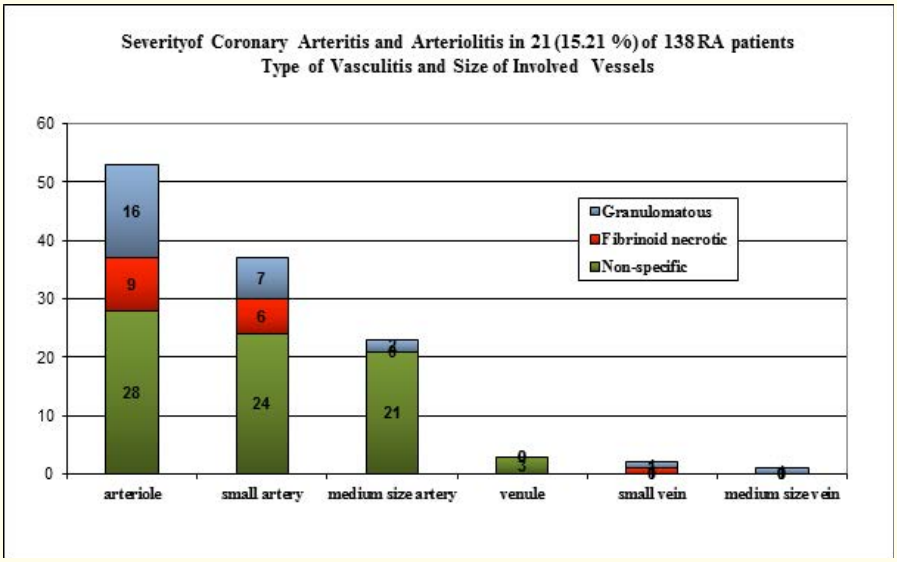

Diagram 4: *Vasculitis was usually severe in frequently involved blood vessels.*

Stages of vasculitis	Ns	in%	Fn	in%	Gr	in %	Total	Total
Acute	5	4,24	2	1,69	2	1,69	9	7,63
Subacute	18	15,25	7	5,93	10	8,47	35	29,66
Subchronic	29	24,58	7	5,93	12	10,17	48	40,68
Chronic	24	20,34	2	1,69	0	0,00	26	22,03
Total in absolute value and in %	76	64,41%	18	15,25%	24	20,34%	118	100%

Table 5: *Stages of coronary arteritis and arteriolitis of autoimmune origin in 21 RA patients.*

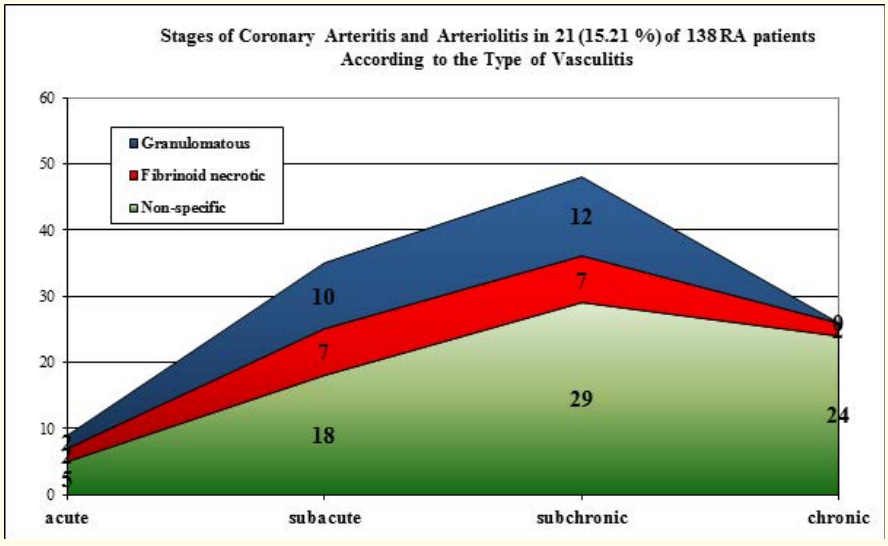

Diagram 5: *Vasculitis and vascular changes were present mostly in advanced (subchronic-chronic) stages at death.*

In further 9 (42.86%) cases C-A/a contributed only to the lethal outcome (Table 6).

Basic disease		Complication (1-2)		Complication (3)	Cause of death	Associated disease(s)	Severity Avg/Pt	Cl+ Cl-	Pr # / year
1	RA	A-SV	Coronary arteritis-arteriolitis		Myocardiocytolysis, multiple1		0,500	Cl-	20/70
2	RA	A-SV	Coronary arteriolitis		Myocardiocytolysis, multiple2	Ath1	0,167	Cl-	81/70
3	RA	A-SV	Coronary arteritis-arteriolitis	Myocarditis	Heart failure1	Ath2-DM	1,500	Cl-	114/71
4	RA	A-SV	Coronary arteritis-arteriolitis	AA amyloidosis	Myocardiocytolysis, multiple3	TbFc-mTb	1,667	Cl+	395/76
5	RA	A-SV	Coronary arteriolitis	Microinfarction	Circulatory failure3	Ath3-Cirrhosis	0,333	Cl+	20/80
6	RA	A-SV	Coronary arteritis-arteriolitis	Cortical necrosis of A-G	Myocardiocytolysis, multiple4		2,500	Cl+	110/80
7	RA	A-SV	Coronary arteritis-arteriolitis	Myocarditis, Pancreatitis	Circulatory failure4	Ath4-TbF	0,500	Cl-	36/86
8	RA	A-SV	Coronary arteritis-arteriolitis	AA amyloidosis	Circulatory failure5		1,000	Cl-	243/87
9	RA	A-SV	Coronary arteritis-arteriolitis	Myocarditis	Myocardiocytolysis, multiple5		1,500	Cl+	275/87
10	RA	A-SV	Coronary arteritis-arteriolitis	Endo-myocarditis	Myocardiocytolysis, multiple6		1,000	Cl-	312/87
11	RA	A-SV	Thrombovasculitis renal artery	Coronary arteriolitis	Renal necrosis		0,333	Cl+	194/88
12	RA	A-SV	Coronary arteriolitis	AA amyloidosis	Myocardiocytolysis, multiple7	TbF-mTb	2,500	Cl-	240/88
13	RA	A-SV	Coronary arteritis-arteriolitis	Pancarditis	Myocardiocytolysis, multiple8	Ath5	0,667	Cl-	295/88
14	RA	A-SV	Coronary arteriolitis	Myocarditis	Myocardiocytolysis, multiple9	TbFc-mTb	1,167	Cl-	227/89
15	RA	A-SV	Coronary arteritis-arteriolitis	Myocardial Rh nodules	Myocardiocytolysis, multiple10		1,167	Cl-	285/89
16	RA	A-SV	Coronary arteriolitis	Pancarditis	Circulatory failure7	Ath6-DM-TbFc	0,333	Cl-	41/90
17	RA	A-SV	Coronary thrombovasculitis	Coronary arteriolitis	Myocardial necrosis1	Ath7-TbFc-Ca	0,333	Cl-	65/90
18	RA	A-SV	Coronary arteriolitis	Nodular pancarditis	Circulatory failure8	Ath8-Tb-Fc-mTb	0,667	Cl-	87/90
19	RA	A-SV	Coronary arteriolitis	Pancarditis	Circulatory failure9		0,333	Cl+	146/91

20	RA	A-SV	Coronary arteriolitis		Myocardiocytolysis, multiple11		0,167	Cl-	221/91
21	RA	A-SV	Coronary arteritis, Pancarditis	Bronchopneumonia	Circulatory failure10	Ath9	0,167	Cl-	14/92

Table 6: *Mortality due to C-A/a (n=12; 57.14 %) in 21 of 138 RA patients.*

Glossary to Table 6

Pr # /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
A-SV: – Systemic vasculitis of autoimmune origin
C-A/a: – Coronary arteritis and arteriolitis
Severity of **C-A/a**: n=**11** (**≤** 0.500) of 33
Cl+: – Clinically diagnosed **A-SV** in **6** (28.57 %) of 21 patients (clinically recognized **3** of 12 lethal cases due to **C-A/a**, and not recognized **3** of 9 not lethal cases).
Cl-: – Clinically not diagnosed **A-SV** in **15** (71.43 %) of 21 patients (clinically not recognized **9** of 12 lethal cases, and **6** of 9 not lethal cases)

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

Atherosclerosis (**Ath**) –was diagnosed in **RA** patients only when 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.

Tb – Post-primary (**Fc** – fibrocaseous, or **F** – fibrous) tuberculosis

mTb – active miliary dissemination of **Tb**

DM – adult type II diabetes mellitus

C-A/a with fatal outcome (C-A/a as basic disease leading to death) was associated with systemic (AA) amyloidosis in 3, Ath in 9, diabetes mellitus in 2, post-primary tuberculosis in 7, or active miliary tuberculosis in 4 and malignant tumors in 1, of 21 patients.

Severe Ath was registered as basic (lethal) disease in 30 (21.74%), and as an associated disease in 32 (23.19%) of 138 patients (Table 7).

Basic disease	Complication (1-2)	Complication (3)	Cause of death	Associated disease(s)	Cl+ Cl-	Protocol n/year
Ath1	Coronary artery sclerosis		Myocardial infarction, acute 1	RA-Bralveolar Ca	Cl-	68/72
Ath2	Myocardial fibrosis		Circulatory failure	RA		193/72
Ath3	Thrombosis of mesenteric artery		Hemorrhagic intestinal necrosis	RA		280/73
Ath4-Hy	Myocardial infarction, healed	Hashimoto Thyreoiditis	Circulatory failure	RA		341/75
Ath5	Myocardial fibrosis		Bronchopneumonia	RA		115/76
Ath6	Myocardial fibrosis	Duodenal ulcer!!!!	Purulent bronchitis and bronchiolitis	RA-TbF-Meningeom	Cl-	318/76

Ath7	Erosive gastritis	Brain necrosis	Hemorrhagic pneumonia, multiple	RA-DM1		352/76
Ath8	Myocardial fibrosis	Gastric ulcer!!!!	Circulatory failure	RA		386/76
Ath9-Hy	Thrombosis of mesenteric artery		Hemorrhagic intestinal necrosis	RA-DM8		4/77
Ath10	Thrombosis of femoral vein		Pulmonary embolism	RA		92/77
Ath11	Myocardial infarction, healed		Circulatory failure	RA-TbF-Op. CaUter	Cl-	208/77
Ath12	Myocardial infarction, healed	Myocardial fibrosis	Circulatory failure	RA		192/79
Ath13	Brain necrosis	Myocardial fibrosis	Bronchopneumonia	RA		193/79
Ath14	Brain necrosis	Myocardial fibrosis	Bronchopneumonia	RA		194/79
Ath15	Coronary artery thrombosis		Myocardial infarction, acute 2	RA		218/79
Ath16	Coronary artery sclerosis	Myocardial fibrosis	Myocardial infarction, acute 3	RA-TbF	Cl-	257/80
Ath17	Coronary artery thrombosis	Myocardial infarction, healed	Myocardial infarction, acute 4	RA-DM2-Gout-TbF		283/80
Ath18	Cerebral artery sclerosis	Strumitis	Brain necrosis, multiple	RA-DM13-G-TbF	Cl-	62/83
Ath19-Hy	Cerebral artery sclerosis	Brain necrosis	Bronchopneumonia	RA		234/83
Ath20-Hy	Coronary artery thrombosis	Myyocardial fibrosis	Myocardial infarction, acute 5	RA		197/84
Ath21	Gangrene of leg	Pulmonary embolism	Circulatory failure	RA		360/84
Ath22	Coronary artery sclerosis	Myocardial infarction, healed	Myocardial infarction, acute 6	RA-DM14		220/86
Ath23	Coronary artery thrombosis	Myocardial infarction, healed	Myocardial infarction, acute 7	RA-Tb-DM5		121/87
Ath24	Myocardial fibrosis		Pulmonary embolism	RA		33/88
Ath25	Coronary artery thrombosis	Glomerulonephritis	Myocardial infarction, acute 8	RA		75/88
Ath26-Hy	Brain necrosis	Thrombosis of femoral vein	Pulmonary embolism	RA-DM6		246/88
Ath27	Brain necrosis	Thrombosis of femoral vein	Pulmonary embolism	RA-Psoriasis		17/90
Ath28	Acute gangrenous appendicitis	Perforation	Peritonitis	RA		193/90
Ath29	Myocardial infarction, healed	Chronic adhesive pericarditis	Circulatory failure	RA		239/90
Ath30-Hy	Hypertension23	Myocardial fibrosis	Bronchopneumonia	RA	Cl-	52/92

Table 7: *Mortality due to atherosclerosis in 30 (21.74 %) of 138 RA patients.*

(Only ***Ath*** *as basic diseases in RA with the most important complications and concomitant diseases).*

Glossary to Table 7

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
Atherosclerosis accompanied RA in 62 (44.92 %) of 138 cases, and led to death as basic disease in 30 (21.73% of 138 and 48.39 % of 62) patients.
Atherosclerosis accompanied RA as associated diseases without direct role of death in 32 (23.19% of 138 and 51.61 % of 62) patients.
Atherosclerosis with fatal outcome (atherosclerosis as basic disease leading to death) was associated with diabetes mellitus in 6, hypertension in 6, post-primary tuberculosis in 6, or active miliary tuberculosis in none and malignant tumors in 1, of 30 patients.

An incipient, recent or healed large MI was found in 14 (10.14%), and My in 20 (14.49%) of 138 patients.

C-A/a accompanied MI in 1 (7.14%) of 14, and My in 11 (55.0%) of 20 patients.

Ath was associated with a large MI in 12 (85.71%) of 14, and with My in 11 (55.0%) of 20 cases.

There was a significant and positive correlation between C-A/a and My ($\chi^2 = 28.6924$, $p < 0.00001$). The link between C-A/a and MI ($\chi^2 = 0.2448$, $p < 0.62$) was not significant (even the negative value of the association's coefficient, 0.4286, indicated an inverse relationship between C-A/a and MI in 138 RA patients.

Conversely, the relationship between Ath and MI showed a strong and significant positive correlation ($\chi^2=8.7213$, $p < 0.003$), while the link between Ath and My ($\chi^2 = 0.9590$, $p < 0.32$) was not significant.

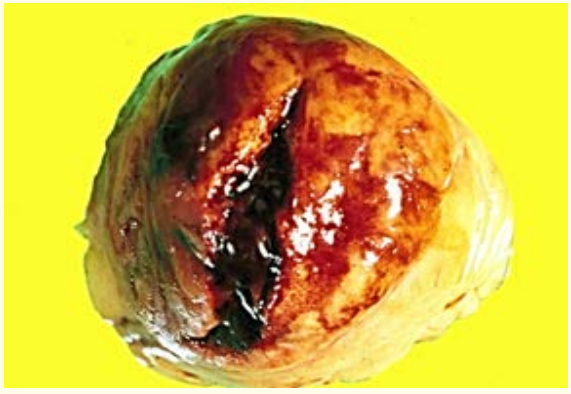

Figure 9

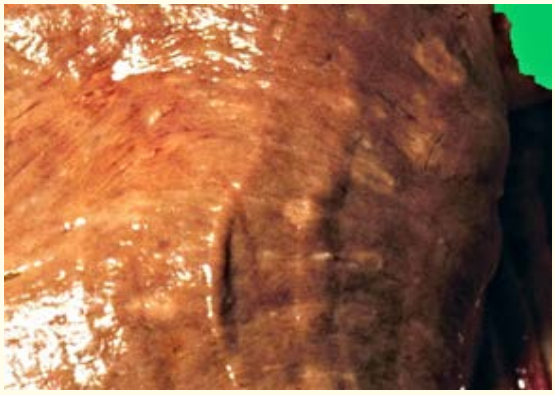

Figure 10

Heart, acute myocardial anteroseptal transmural myocardial necrosis and rupture with correspondent pericarditis.

Vasculitis of the main coronary arteries with or without thrombosis may result in ischemia and may lead to a large myocardial infarct similar to myocardial necrosis due to coronary atherosclerosis and/or thrombosis.

Heart, multiple microinfarcts of myocardium (myocardiocytolysis) in different stages of necrosis (x4).

The stages of myocardial necrosis (My with disseminated microfocal cicatrisation side by side) caused by C-A/a is more variegated histologically in contrast to the more uniform microinfarcts due to Ath.

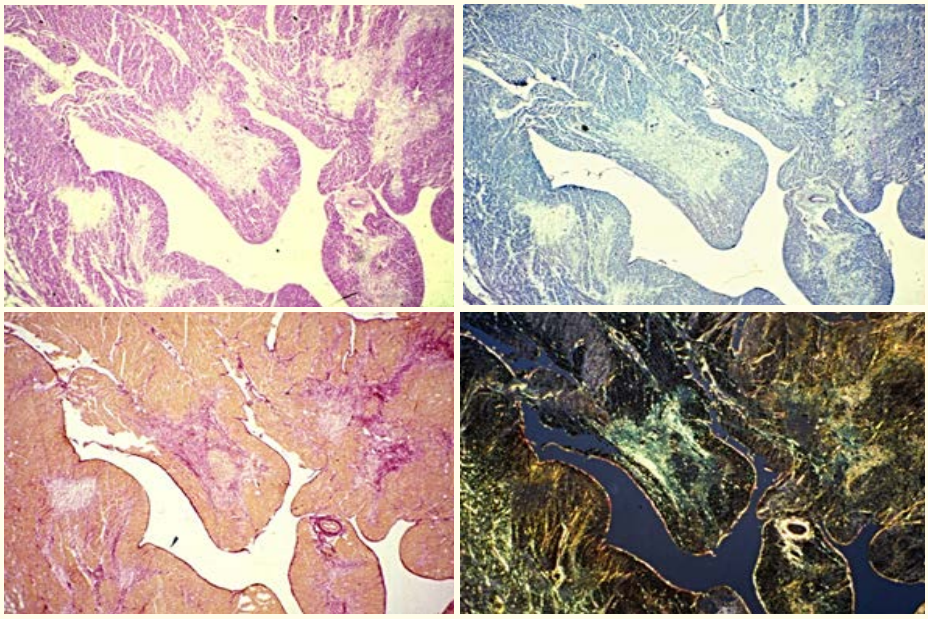

Figure 11a-d: *Heart, multiple microinfarcts of myocardium (myocardiocytolysis) in different stages of necrosis. (a) HE, x50 (b) Microinfarcts in myocardiocytolytic and fibrous end stage of necrosis, Light green-Orcein, same as (a) x50 (c) Sirius red F3BA, same as (a) x125 (d) Sirius red F3BA viewed under polarized light, same as (a), x50*

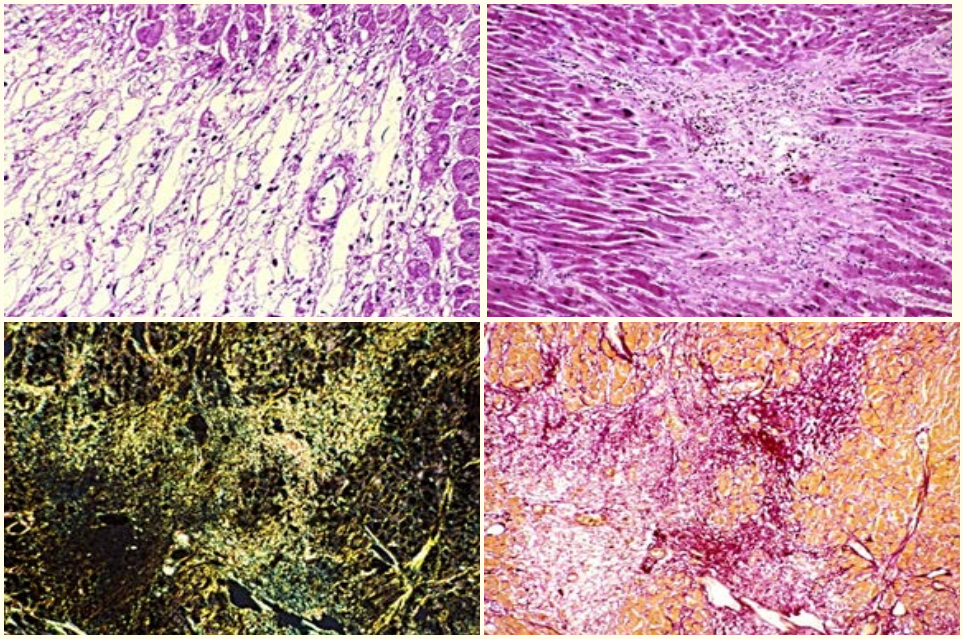

Figure 12a-d: *Heart, multiple microinfarcts of myocardium (myocardiocytolysis) in different stages of necrosis. (a) Microinfarcts in myocardiocytolytic stage of necrosis, HE, x125 (b) Microinfarcts in fibrous end stage, HE, x125 (c) Sirius red F3BA, same as (b) x125 (d) Sirius red F3BA viewed under polarized light, same as (c), m x125*

Discussion

The role of systemic vasculitis in mortality of RA is generally accepted. Most of the earlier studies based on the evaluation of some organs discussed the prevalence of vasculitis only and did not specify the role of vasculitis as a factor in mortality [6-20] (Table 8).

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

Table 8: *Prevalence of systemic vasculitis (SV) at autopsy of RA patients (no mention of the origin of SV)*

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; the latter 3 SV of septic origin have been excluded in the present study.*

From the early times a large number of publications discuss the prevalence of heart diseases in RA with or without its role in mortality [21-30] (Table 9).

Authors	Year of Publication, References	Autopsy n=	Prevalence of vasculitis n – %	Mortality of vasculitis n – %
Baggenstoss and Rosenberg	1943 [21]	30	16 – 53%	7 – 23%
Rosenberg and Baggenstoss	1943 [22]	30	16 – 53%	7 – 23%
Young and Schwedel	1944 [23]	38	33 – 86.8%	9 – 23.7%
Graef	1949 [24]	66	26 – 39.4%	ND
Bywaters	1950 [25]	27	7 – 25.9%	2 – 7.4%
Sokoloff	1953 [26]	101	10 – 9.9%	8 – 50.0%
Sinclair and Cruickshank	1956 [7]	16	13 – 81.3%	ND
Cruickshank	1958 [8]	100	33 – 33.0%	ND
Goehrs., *et al.*	1960 [27]	36	27 – 75.0%	8 – 29.6%

Lebowitz	1963 [9]	62	51 – 9.9%	20 – 32.3%
Bély	1991 [28]	100	19 – 19.0%	ND
Bély., *et al.*	1993 [29]	169	26 – 15.4%	ND
Bély and Apáthy	1993 [30]	169	26 – 15.4%	ND

Table 9: *Prevalence of heart diseases at autopsy of RA patients.*

(No mention of the origin of SV)

According to our best knowledge a detailed analysis of A-SV regarding the prevalence and severity in the heart, and its role in mortality (even in comparison with Ath) has not been available in the literature.

Severe necrotizing vasculitis with or without thrombosis plays a major role in the pathogenesis of multifocal microscopic myocardial necrosis (My) caused by C-A/a.

Vasculitis because of diminished blood supply distal to the involved vessels can cause local ischemia and necrobiotic changes.

The size of necrobiotic areas depends on the size of involved vessels. This process may be more or less widespread and multifocal, depending on the number of involved vessels.

Vasculitis of the small arteries and arterioles causes small necrotic foci, 1 - 2 mm in diameter (Figures 1-3a-b).

Vasculitis of the main coronary arteries (Figures 4-6a-b) with or without thrombosis may result in ischemia and may lead to a large myocardial infarct similar to myocardial necrosis due to coronary atherosclerosis and/or thrombosis.

The immunological processes in RA are repeated events, and all types of autoimmune vasculitis are of a recurrent 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 histologically the repetitious process of vasculitis.

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 may exist simultaneously side by side.

Because of the recurrent nature of autoimmune vasculitis, the regressive changes accumulate in the myocardium with time and may lead to unexpected sudden death [1].

Based on the significant correlation ($\chi^2 = 8.7213$, $p < 0.003$), severe atherosclerosis of the main coronary arteries may be regarded as the leading cause of a large MI, in contrast with the less frequent vasculitis of the main coronary arteries ($\chi^2 = 0.0841$, $p < 0.77$).

Ath of the coronary arterioles may cause microinfarcts of the myocardium as well, similar to the microfocal myocardial necrosis caused by coronary arteriolitis. The stages of myocardial necrosis (My in combination with disseminated microfocal cicatrisation side by side) caused by C-A/a is more variegated histologically in contrast to the more uniform microinfarcts due to Ath.

Based on the statistically strong and significant association between My and C-A/a ($\chi^2 = 16.0807$, $p < 0.00001$), this form of myocardial necrosis may be regarded as a special manifestation of vasculitis or a new vasculogenic entity in RA. Plausibly similar vasculogenic changes of the heart may be expected in other autoimmune diseases (such as systemic sclerosis, panarteritis nodosa, etc.) as well.

Conclusion

Large myocardial necrosis or multifocal microinfarcts of the myocardium (myocardiocytolysis, My) may be caused by C-A/a and Ath as well.

Furthermore C-A/a and Ath may exist in RA in the same patient at the same time. Interactions of coexisting A-SV (with or without C-A/a) and Ath modify the RA and may mask the characteristic clinical symptoms of the coexisting complications and associated diseases. These changes may lead to misdiagnosis or late recognition of the complications or associated diseases.

Exact clinical or pathological identification of cardiac insufficiency is important from the viewpoint of prevention and effective treatment of these.

Detailed histological evaluation based on a large autopsy population of RA supports and statistically confirms that large MI's are of atherosclerotic origin while in case of My, the role of autoimmune vasculitis is plausible.

Clinically it is difficult to recognize small accumulating foci of myocardial necrosis (myocardiocytolysis). Knowledge of formal pathogenesis of C-A/a associated silent myocardial infarction is important to look for minor symptoms ("we see what we know"). The history of vasculitis, transient cardiac complaints, or low voltage electrocardiogram (ECG) may suggest the diagnosis of coronary arteritis or arteriolitis (e.g. My) or may explain the sudden death of patients [1].

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