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Research Article

Histological Differential Diagnosis of Systemic Autoimmune and Septic Vasculitis - Characteristics of Systemic Vasculitis in Rheumatoid Arthritis, Progressive Systemic Sclerosis, Polymyalgia Rheumatica, and in Acute Bacterial Septic Infection

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Abstract

Background: Systemic autoimmune vasculitis (AV) is one of the most important complications of autoimmune diseases, such as rheumatoid arthritis (RA), progressive systemic sclerosis (PSS), polymyalgia rheumatica (PMR), systemic lupus erythematosus (SLE) etc. Autoimmune diseases can be exacerbated by acute bacterial septic infection (AbSI), which is often accompanied by systemic vasculitis of septic origin (SV). Correct diagnosis of AV and SV and early recognition of this serious complication are crucial, due to the fundamental differences in prognosis and in therapy.

Aim of the Study: The aim of the study was to describe the histological features of systemic autoimmune and septic vasculitis so that they can be distinguished from each other histologically, according to the size of affected blood vessels, based on the type of vasculitis and/or by the stages of inflammation (flare ups).

Patients and Methods: Tissue samples of 161 patients with RA, 12 with PSS, and 24 with AbSI were examined post mortem, furthermore surgical samples of 299 patients with PMR. The characteristics of AV in RA, PSS and PMR were compared with those of SV in AbSI.

Results: RA was complicate by AV (with or without rheumatoid nodules) in 33 (20.49%) of 161 patients. AV affected 325 blood vessels in tissue samples of RA patients. PSS was complicate by AV (with or without fibromuscular intimal proliferation - FIP) in 11 (91.67%) of 12 patients (in one patient AV was not assessable because of the massive AL amyloid infiltration of the vessel walls). AV affected 425 blood vessels in tissue samples of PSS patients. PMR was associated with TA in 71 (23.75%) of 299 patients. TA affected 136 blood vessels in tissue samples of PMR patients. RA was complicate by fatal AbSI in 24 (14.98%) of 161 patients. Fatal AbSI was associated with SV in 3 (12.5%) of 24 patients. SV affected 23 blood vessels in tissue samples of fatal AbSI. AV and SV in RA, PSS, PMR and AbSI affected the entire vascular network. AV and SV affected mainly the arterioles and small arteries in RA, PSS, PMR and AbSI patients comparing to the veins; the veins were spared by SV in AbSI. TA affected mainly the medium-sized arteries compared to the arterioles and small arteries or accompanying veins. In RA three types of AV occurred: non-specific, fibrinoid necrotic, and granulomatous vasculitis; granulomatous type was registered only in RA. In PSS and AbSI the AV or SV were characterized by non-specific and occasionally by fibrinoid necrotic vasculitis. In PMR only non-specific vasculitis was registered.

Conclusion: The granulomatous transformation of blood vessels (with or without fibrinoid necrosis) supported the clinical diagnosis of RA, and the autoimmune origin of systemic vasculitis. Rheumatoid nodule was the most severe form of necrotic and/or granulomatous AV, and represented an absolute diagnostic histological sign of RA. In the early stages of PSS, the vascular changes were already present before the connective tissue sclerosis and the characteristic clinical symptoms appeared. Recognizing these changes helps in the early diagnosis of PSS. The fibromuscular intimal proliferation (FIP), with or without fibrinoid necrosis of the blood vessels walls, was an absolute diagnostic histological sign of PSS. Our study confirmed the systemic nature of TA in PMR patients, involving the entire vascular network. The close statistical correlations between inflamed arteries and veins of temporal branches supported that the vasculitis in these vessels are the manifestation of the same disease. SV in RA was less common and less severe than AV in RA. SV was mostly "non-specific," fibrinoid necrosis occurred, granulomatous transformation of the vessel walls was not detected, and the veins were spared. The absence of granulomatous vasculitis and phlebitis supported the histological diagnosis of SV, i.e. detection of granulomatous vasculitis and phlebitis contradicted the septic origin of systemic vasculitis.

Keywords: *Autoimmune and Septic Vasculitis; Rheumatoid Arthritis; Progressive Systemic Sclerosis; Polymyalgia Rheumatica; Acute Bacterial Septic Infection*

Introduction (Background)

Systemic autoimmune vasculitis (AV) is one of the most important complications of autoimmune diseases, such as rheumatoid arthritis (RA) [1], progressive systemic sclerosis (PSS) [2-4], polymyalgia rheumatica (PMR) [5], systemic lupus erythematosus (SLE) [6] etc.

AV - according to Bywaters (1986) - is the RA itself, as all joint or organ damage, and clinical symptoms can be traced back to AV [7].

PSS is characterized by widespread vascular abnormalities.

Capillaries may be a primary site of injury, followed by diffuse devascularization of multiple tissues as a major consequence. PSS should be classified as a vascular disease, where "the primary site of injury is at the microvascular level" [8].

Gardner likewise came to this conclusion: "evidence of circulatory impairment in systemic sclerosis is so frequent that is natural to ask whether this is fundamentally not a vascular disorder "[9 p.706].

PMR is often associated with or complicated by autoimmune inflammation of the temporal arteries (TA), which may also be a form of giant cell arteritis (GCA).

Due to the risk of vision loss, it is very important to recognize vascular inflammation.

Temporal artery biopsy is the gold standard for establishing the diagnosis of temporal arteritis [10]. Surgical sampling is traditionally performed from the main branch of the temporal artery, although the ophthalmic, ciliary or intracranial arteries are not branches of the temporal artery.

An adequate biopsy requires a length of at least 2-3 cm [10], and should be serially sectioned, as the inflammation is not continuous and only affects sectors or segments of the blood vessels, similarly to other autoimmune vasculitis [2-4].

Autoimmune diseases can be exacerbated by acute bacterial septic infection (AbSI), which is often accompanied by systemic vasculitis of septic origin (SV).

Correct diagnosis of AV and SV and early recognition of this serious complication are crucial due to the fundamental differences in prognosis and in therapy.

Objective of the Study

The aim of the study was to describe the histological features of systemic autoimmune and septic vasculitis so that they can be distinguished from each other histologically, according to the size of affected blood vessels, based on the type of vasculitis and/or by the stages of inflammation (flare ups).

Materials and Methods

Patients

Different patient groups of autoimmune diseases were analyzed, who died or were treated at the National Institute of Rheumatology and Physiotherapy (ORFI).

161 autopsy patients with rheumatoid arthritis (RA) were studied to determine the prevalence, severity and stages of autoimmune vasculitis (AV) in RA.

The patients deceased in the last third of the 20th century, between 1970 and 1990.

Acute bacterial septic infection (AbSI) of fatal outcome was detected only in 24 of 161 RA patients, accompanied with systemic septic vasculitis (SV) in 3 of 24 patients.

12 autopsy patients with progressive systemic sclerosis (PSS) were surveyed, to outline the prevalence, severity and stages of AV, with or without fibromuscular intimal proliferation (FIP). AbSI of fatal outcome was not found between the PSS patients.

The patients died between 1961 and 1997.

299 patients with polymyalgia rheumatica (PMR) were inspected, to identify the prevalence, severity and stages of temporal arteritis (TA). Fatal septic infection (AbSI) was not detected in PMR.

The patients underwent surgical sampling of temporal branches of blood vessels between 1991 and 2012.

The characteristics of AV in RA, PSS and PMR were compared with those of systemic septic vasculitis (SV).

The patients with clinically diagnosed RA, PSS, and PMG fulfilled the criteria of the American College of Rheumatology (ACR) [11-13].

The patient's history and protocols were clinically reviewed by the co-author Ágnes Apáthy rheumatologist, neurologist, the autopsies and histopathologic reports were by Miklós Bély.

Methods

The prevalence (occurrence, presence) and severity (number of affected vessels, density of inflamed vessels) of autoimmune vasculitis (AV), and the stages of inflammation (number of flare-ups, exacerbations) were determined post mortem based on histological examination of tissue samples of twelve organs (heart, lungs, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerves, skin, and brain) in 33 RA patients, and in 12 PSS patients, furthermore in surgical samples from blood vessels of temporal branches of 299 PMR patients.

In the case of AbSI, with or without systemic septic vasculitis (SV), only fatal acute bacterial septic infections were considered, based on examination of tissue samples from the twelve organs mentioned above and surgical samples from the temporal branches.

Fatal outcome of AbSI was determined based on autopsy and clinical protocols.

Fatal AbSI was found only in RA, in PSS or PMR fatal outcome of AbSI was not detected.

AbSI was confirmed by identification of infective and bacterial agents.

The relationship between AbSI and SV was verified using Pearson's chi-square (χ^2) test, excluding the possibility of AV [14].

Statistics

Demographics of different patient cohorts were evaluated with the Student (Welch) T-test comparing the mean age of entire RA population and the mean age of patients with PSS, PMR, or AbSI [14].

The p cutoff for significance was < 0.05.

Comparing two types of data, the most severe criteria of excel calculator were used; two-tailed distribution ("2"), and non-equal variation ("not homoscedastic -3").

The mean age of the patients was variable (between minimal and maximal value of age).

The correlation existing between the AV and SV in RA patients was calculated with Pearson's chi-squared (χ^2) test [14].

Glossary of definitions

"Prevalence of AV" concerns the presence of autoimmune vasculitis in blood vessels of various organs, and conveys information about the involvement of these.

In RA and in PSS the prevalence of AV was specified histologically based on the presence of AV on blood vessels of different calibers of twelve organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) in each patient, and in PMR on blood vessels of temporal branches removed by surgical sampling.

Size of blood vessels [15] in various organs: arteriole (a) no internal or external elastic membrane, less than 500 micrometers in diameter, small artery (A) - internal elastic membrane present, but no external elastic membrane - 500-1000 micrometers in diameter, medium size artery (AA) - more than 1000 micrometers in diameter, internal and external elastic membrane present, venule (v) -, small vein (V) -, medium size vein (VV) - accompanying vessels of (a), (A) or (AA).

"Severity of AV" designates information about the number of affected vessels in various organs.

Severity of AV 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 lens of Olympus BX51 polarizing microscope [1].

Semi-objective score system of "severity":

- "0" - No AV (there is no inflamed blood vessel)
- "1" - Sporadic AV affecting only a few vessels
- "2" - AV affecting less than five blood vessels
- "3" - AV affecting more than five blood vessels

Remarks

The severity score was determined based on the maximum density of blood vessels found in the tissue sample (under a light microscope at 40x magnification).

In case of medium size arteries and veins the "severity" corresponds to the absolute number of involved medium size vessels of a tissue sample, e.g. "0" none, "1" only one, "2" less than five, "3" 5 or more than five medium size vessels per tissue sample with a x20 objective lens.

The severity of TA in PMR was calculated according to number of acute-subacute stages of flare-ups on blood vessels of temporal branches.

Stages of AV

Acute ("a"), subacute ("b"), subchronic ("c") and chronic ("d") stages (repeated flare-ups) were determined according to the inflammatory infiltration and structural changes of blood vessels of different calibers.

"a" - Polymorphonuclear neutrophilic leukocytes are present (with or without eosinophils) - "a" represents acute exacerbation of inflammation (acute stage) in combination with "b" or "c" and occasionally with "d". There is no appropriate class according to Allsop and Gallagher (1981) [16] or McMillen and Lee (2025) [17].

"b" - Characterized by intensive transmural inflammatory infiltration involving complete cross section of the blood vessels, dominated by T-lymphocytes with or without multinucleated giant cells and macrophages (histiocytes), and moderate structural changes (intimal proliferation, homogenization, and/or hyalinization, distortion of internal elastic lamina) of blood vessels corresponding to the "classic" type of TA according to Allsop and Gallagher (1981) [16] or McMillen and Lee (2025) [17].

"c" - More or less pronounced inflammatory infiltration is accentuated towards the outer layers of the blood vessel wall (in the media and adventitia), and dominated by T-lymphocytes (without multinucleated giant cells, with or without macrophages); pronounced structural changes (intimal proliferation, stenotic or occluded lumen, multiple, fragmented, discontinuous, distorted internal elastic lamina) - "c" corresponds to the "atypical" form of TA according to Allsop and Gallagher (1981) [16] or McMillen and Lee (2025) [17].

"d" - Minimal or missing lymphocytic infiltration (without multinucleated giant cells and macrophages); dominant structural changes of the blood vessels (adventitia and media is fibrotic, intima massive, irregularly thickened, with or without fibro-myxoid changes, neovascularization and/or homogenization, hyalinization, internal elastic lamina is multiple, fragmented and discontinuous) - "d" corresponds to the "healed" stage of TA according to Allsop and Gallagher (1981) [16] or McMillen and Lee (2025) [17].

Results

Demographics of different patient groups with autoimmune diseases

RA was complicated with AV in 33 (20.49%), and with fatal AbSI in 24 (14.98%) of 161 patients. Fatal AbSI was associated with SV in 3 (12.5%) of 24 patients (SV did not exist without AbSI).

PSS was associated with AV in 11 (91.67%) of 12 patients. PSS was not complicated by systemic fatal AbSI or SV.

PMR was associated with TA in 71 (23.74%) of 299 patients. PMR was not complicated by systemic fatal AbSI or SV (TA not existed without PMR).

Table 1 summarizes the demographics and mean age of the entire population of RA, PSS and PMR patients, with and without AbSI, AV or SV.

Demographics of patient groups with autoimmune diseases	Number of autopsies	Mean age in years at death ± SD
RA patients (total)	161	65,32 ± 12,99
Female	116	64,95 ± 11,84
Male	45	66,27 ± 15,67
RA patients with AV	33 of 161	67,18 ± 10,80
Female	20	66,95 ± 11,40
Male	13	67,46 ± 10,24
RA patients without AV	128 of 161	64,84 ± 13,49
Female	96	64,53 ± 10,48
Male	32	65,78 ± 11,11
RA patients with AbSI*	24 of 161	61,25 ± 8,73
Female	17	60,41 ± 8,73
Male	7	63,29 ± 6,70
RA patients without AbSI	137 of 161	66,04 ± 13.50
Female	99	65,73 ± 12,07
Male	38	66,82 ± 16,82
AbSI patients with SV**	3 of 24	57,33 ± 10,97
Female	2	51,00 ± 0,0
Male	1	70,00 ± Zero divisor
AbSI patients without SV	21 of 24	61,81 ± 8,55
Female	15	61,67 ± 9,42
Male	6	62,17 ± 6,59
PSS patients (total)	12	55,67 ± 8,23
Female	11	54,82 ± 8,06
Male	1	65,00 ± Zero divisor
PSS patients with AV***	11 of 12	54,64 ± 7,78
Female	10	53,60 ± 7,35
Male	1	65,00 ± Zero divisor

PMR patients (total)	299	71,19 ± 8,44,
Female	250	71,31 ± 8,56
Male	49	70,60 ± 7,75
PMR patients with TA	71	73,24 ± 7,60
Female	61	73,46 ± 7,47
Male	10	71,43 ± 9,07
PMR patients without TA	228	70,53 ± 8,61
Female	189	70,55 ± 8,81
Male	39	70,44 ± 7,70

Table 1: *Demographics and mean age of RA, PSS and PMR patients, with and without AbSI, AV or SV.*

**In the case of AbSI (with or without SV), only the fatal septic infection was considered. AbSI with fatal outcome was detected only in RA.*

***SV did not exist without AbSI.*

****One of 12 patient with PSS suffered from systemic primary (B-cell dyscrasia-associated immunoglobulin light chain) ALλ amyloidosis and died of clinically diagnosed circulatory failure. The vessel walls were saturated with massive ALλ amyloid deposits, so the existence of a possible AV could not be evaluated histologically.*

Abbreviations to table 1: RA: Rheumatoid Arthritis; AV: Systemic Autoimmune Vasculitis; AbSI: Acute Bacterial Septic Infection with Lethal Outcome; SV: Systemic Septic Vasculitis; PSS: Progressive Systemic Sclerosis; PMR: Polymyalgia Rheumatica; TA: Temporal Arteritis; SD: Standard Deviation.

Comparing the mean age of RA patients at the time of death, there was no significant difference in survival time between the total population (n = 161) and patients with AV (n = 33) ($p < 0.389$), neither in women ($p < 0.477$), nor in men ($p < 0.748$) or patients with AbSI (n = 24) ($p < 0.054$), neither in women ($p < 0.088$), nor in men ($p < 0.398$).

AV and AbSI involved both genders and developed at any time in the course of RA (Table 1 and 2).

The patients with AbSI died earlier than the patients without AbSI, the difference was significant (61.25 years versus 66.04 years; $p < 0.029$).

The mean age of RA patients (n = 161) was high comparing to the mean age of PSS patients (n = 12) (65.32 years versus 55.67 years; $p < 0.022$), just like the women (64.95 years versus 54.82 years; $p < 0.022$); the patients with PSS died earlier than the patients with RA.

The difference was not calculated between men, because of the zero divisor.

The life expectancy of RA patients (n = 161) was significantly worse, and the patients died earlier than the PMR patients (65.32 years versus 71.19 years, $p < 0.000001$), just like the women (64.95 years versus 71.31 years, $p < 0.000001$).

The men with RA died also earlier than the men with PMR, but the difference was not significant (66.27 years versus 70.60 years, $p < 0.097$ - NS).

Comparing the mean age of RA patients and the mean age of patients with TA, the difference was significant (65.32 years versus 73.24 years, $p < 0.000000$), just like the women (64.95 years versus 73.46 years, $p < 0.000000$); the RA patients died earlier than the patients with TA.

The men with RA died also earlier than the men with TA, but the difference was not significant (66.27 years versus 71.43 years, $p < 0.236$ - NS).

There was no significant difference between the mean age of the total population with PMR and the mean age of patients with TA (71.19 years vs. 73.24 years, $p < 0.058$ - NS), neither among women (71.31 years vs. 73.46 years, $p < 0.059$ - NS), nor among men (70.60 years vs. 71.43 years, $p < 0.837$ - NS); as well as between the mean age of the total population with PMR and the mean age of patients without TA (71.19 years vs. 70.53 years, $p < 0.404$ - NS), neither among women (71.31 years vs. 70.55 years, $p < 0.395$ - NS) nor among men (70.60 years vs. 70.44 years, $p < 0.902$ - NS).

The life expectancy of patients with TA patients was worse than the life expectancy of patients without TA (73.24 years versus 70.53 years, $p < 0.016$); just like the women (73.46 years versus 70.55 years, $p < 0.016$). Difference was not significant between the men with and without TA (71.43 years versus 70.44 years, $p < 0.795$ - NS).

Table 2 summarizes the mean age of female and male RA patients ("p" correlation values) between female and male RA, PSS, and PMR patients, with AV, AbSI, SV or TA.

RA patients n = 161 (total)	**Age**
RA patients n = 161 versus pts. with AV n = 33	0,389
Female n = 116 of 161 versus n = 20 of 33	0,477
Male n = 45 of 161 versus n = 13 of 33	0,748
RA patients n = 161 versus pts. without AV n = 128	0,761
Female n = 116 of 161 versus n = 96 of 128	0,800
Male n = 45 of 161 versus n = 32 of 128	0,901
RA patients with AV n = 33 versus without AV n = 128	0,298
Female n = 20 of 33 versus n = 96 of 128	0,399
Male n = 13 of 33 versus n = 32 of 128	0,692
RA patients n = 161 versus pts. with AbSI n = 24	0,054
Female n = 116 of 161 versus n = 17 of 24	0,088
Male n = 45 of 161 versus n = 7 of 24	0,398
RA patients n = 161 versus pts. without AbSI n = 137	0,644
Female n = 116 of 161 versus n = 99 of 137	0,635
Male n = 45 of 161 versus n = 38 of 137	0,879
Pts. with AbSI n = 24 versus pts. without AbSI n = 137	0,029
Female n = 17 of 24 versus n = 99 of 137	0,052
Male n = 7 of 24 versus n = 38 of 137	0,353
AbSI pts. with SV n = 3 versus pts. without SV n = 21	0,558
Female n = 116 of 161 versus n = 15 of 21	0,846
Male n = 45 of 161 versus n = 6 of 21	#####

RA patients n = 161 versus pts. with PSS n = 12	0,002
Female n = 116 of 161 versus n = 11 of 12	0,002
Male n = 45 of 161 versus n = 1 of 12	#####
Patients with PSS n = 12 versus pts. with PSS-AV n = 11	0,761
Female n = 11 of 12 versus n = 10 of 11	0,721
Male n = 1 of 12 versus n = 1 of 11	#####
RA patients n = 161 versus pts. with PMR n = 299	0,000001
Female n = 116 of 161 versus n = 250 of 299	0,000001
Male n = 45 of 161 versus n = 49 of 299	0,097
RA patients n = 161 versus pts. with TA n = 71	0,000000
Female n = 116 of 161 versus n = 61 of 71	0,000000
Male n = 45 of 161 versus n = 10 of 71	0,236
PMR pts. n = 299 versus pts. with TA n = 71	0,058
Female n = 250 of 299 versus n = 61 of 71	0,059
Male n = 49 of 299 versus n = 10 of 71	0,837
PMR pts. n = 299 versus pts. without TA n = 228	0,404
Female n = 250 of 299 versus n = 189 of 228	0,395
Male n = 49 of 299 versus n = 39 of 228	0,902
TA pts. n = 71 versus pts. without TA n = 228	0,016
Female n = 61 of 161 versus n = 189 of 228	0,016
Male n = 10 of 161 versus n = 39 of 228	0,795

Table 2: *Statistical correlations ("p" values of significance) between female and male RA, PSS, and PMR patients, with AV, AbSI, SV or TA.*

There was no significant difference in the mean age of RA patients comparing the total autopsy population (n = 161) and the patient cohorts with AV or AbSI; "p" values were higher than 0.05.

The survival of RA patients complicated with AbSI was worse than the life expectancy of RA population without AbSI.

The life expectancy of RA patients was worse than the life expectancy of PMR patients with or without TA, and was better than the life expectancy of PSS. patients.

Abbreviations to table 2: RA: Rheumatoid Arthritis; AV: Systemic Autoimmune Vasculitis; AbSI: Acute Bacterial Septic Infection with Lethal Outcome; SV: Systemic Septic Vasculitis; PSS: Progressive Systemic Sclerosis; PMR: Polymyalgia Rheumatica; TA: Temporal Arteritis.

Characteristics of autoimmune vasculitis (AV) in rheumatoid arthritis

In rheumatoid arthritis AV was present in 33 (20.496%) of 161 patients, and was detected in all (100%) of 12 surveyed organs.

The negative value of association coefficient and the lack of significant correlation between AV and fatal AbSI (association coefficient: -0.3249 c2 = 0.6052, p < 0.4355) supported the direct autoimmune origin of AV.

The prevalence, severity of AV, and the stages of inflammation (flare-ups) was different among patients or in various organs (differed from each other's).

The prevalence, severity of AV, and stages of inflammation changed in parallel in patients and in various organs.

Three types of autoimmune vasculitis occurred in RA: vasculitis characterized by "non-specific" inflammatory infiltration of the vessel walls (Figure 1), vasculitis characterized by "fibrinoid necrosis" of the vessel walls (Figure 2), and vasculitis characterized by "granulomatous" transformation of the vessel walls (Figure 3).

Different types of AV existed side by slide in the same tissue slides simultaneously or combined in the same blood vessels at the same time.

All forms of AV may have been accompanied by the so-called "rheumatic nodules", which were presented (considered) as the most severe necrotic form of AV (Figure 4).

Rheumatoid nodule - in accordance with the clinical diagnosis, and consistent with the clinical symptomatic - was an absolute diagnostic histological sign of RA.

Figure 1-4 illustrate the non-specific, fibrinoid necrotic, and granulomatous vasculitis, furthermore the most severe form of autoimmune vasculitis, the so-called rheumatoid nodule in RA.

Histological images (note to the editor): Original magnifications of all Figures correspond to the 24x36 mm transparency slide; the correct height: width ratio is 2:3. The printed size may be different; therefore, the original magnifications are indicated.

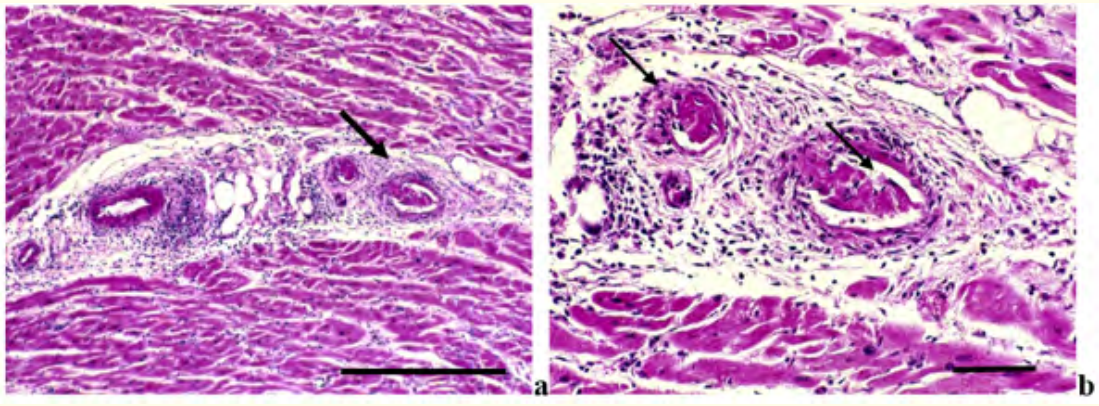

Figure 1a and 1b: *RA, heart, arteriole, with non-specific, sectorial accentuated leuko-lymphocytic infiltration, and a small adjacent arteriola with non-specific vasculitis, and intraluminal thrombus (arrows). (a) Arteriole with moderate non-specific sectorial AV, HE-PAS staining, scale bar: 1250 [µm], magnification: x50. (b) Same as (a), scale bar: 125 [µm], magnification: x125.*

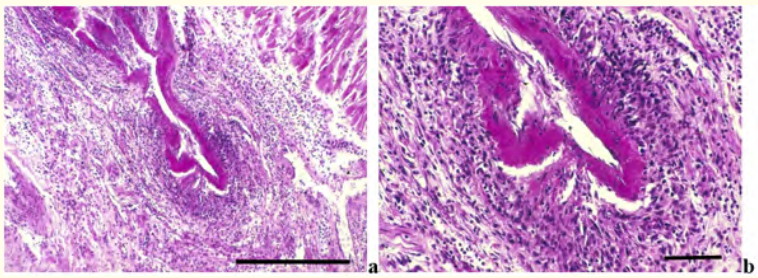

Figure 2a and 2b: *RA, heart, intramural arteriole, fibrinoid necrotic AV. Fibrinoid necrosis of the blood vessel walls is accompanied with non-specific leuco-lymphocytic infiltration. (a) Small artery, HE-PAS staining, scale bar: 1250 [μm], magnification: x50. (b) Same as (a), scale bar: 125 [μm], magnification: x125.*

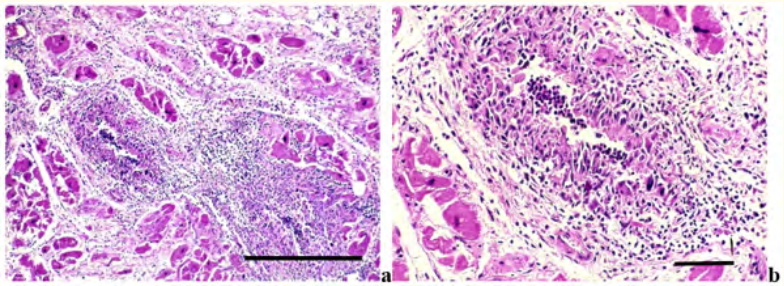

Figure 3a and 3b: *RA, heart, intramural arterioles, "granulomatous" AV. The vessel wall is transformed into granulomatous tissue. AV is characterized by non-specific leuco-, lympho-, histiocytic cellular infiltration. (a) Small artery, HE-PAS staining, scale bar: 1250 [μm], magnification: x50. (b) Same as (a), scale bar: 125 [μm], magnification: x125.*

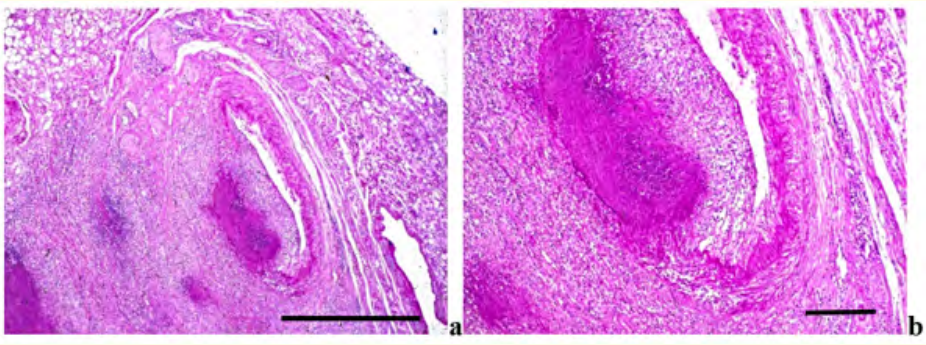

Figure 4a and 4b: *RA, heart, epicardium, small artery, and arterioles of different size with "rheumatoid nodules". One sector of the vessel wall is lacerated (destructed) by a rheumatoid nodule. Granulomatous vasculitis and additional rheumatoid nodules are existing in the environment of the small artery. (a) Subepicardial small artery with rheumatoid nodules of different size, HE-PAS staining, scale bar: 1250 [μm], magnification: x50. (b) Same as (a), scale bar: 125 [μm], magnification: x125.*

AV affected the entire vascular network and occurred on all sizes of vessels (capillaries, arterioles, small arteries, medium size arteries with the accompanying veins).

The average prevalence (presence) and severity (number of affected vessels, density of inflamed blood vessels), furthermore the acute, subacute, subchronic, chronic stages of inflammation (flare-ups) changed parallel on affected blood vessels (Table 3a and 3b and figure 5a and 5b).

Table 3a and 3b and figure 5a and 5b demonstrate (show) the prevalence, severity, and flare-ups of autoimmune vasculitis in RA according to the affected blood vessels (in absolute number and in percentage).

Size of involved vessels	Prevalence	Severity	Stages
Arteriole (a)	169	322	358
Small artery (A)	106	191	216
Medium size artery (AA)	32	55	69
Venule (v)	6	9	11
Small vein (V)	9	13	14
Medium size vein (VV)	3	4	5
Total in absolute value	325	594	673

Table 3a: *Prevalence, severity and stages of AV in 33 RA patients according to the involved blood vessels by size (in absolute value of the total sum of prevalence n = 325, severity n = 594 and stages n = 673).*

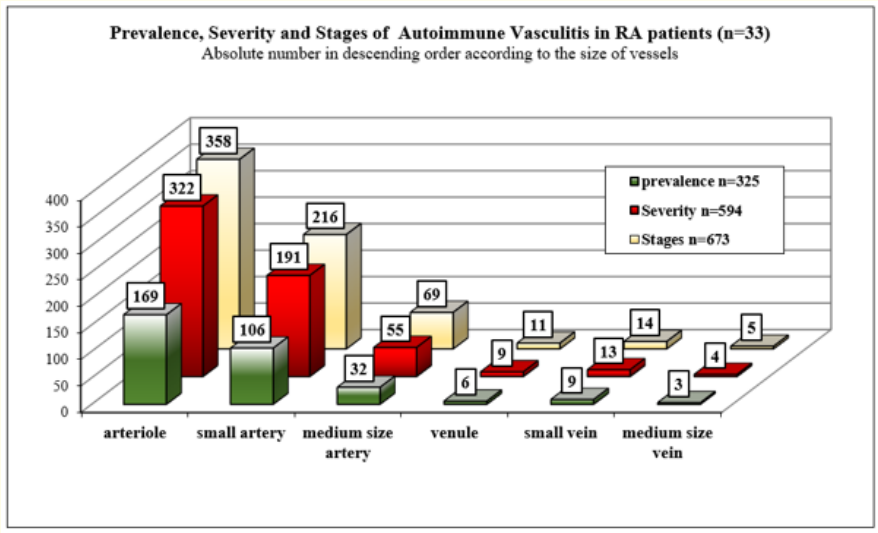

Figure 5a: *Absolute number of affected blood vessels according to the prevalence, severity, and stages of inflammation of autoimmune vasculitis. The affected vessels are arranged in descending order according to the size of arteries and veins. The average prevalence of AV was 9.85/patients, the number of inflamed vessels (severity of AV) 18.0/patient, and the detected exacerbation (stages of AV) 20.39/patient in affected blood vessels of RA.*

Involved vessels	Prevalence in %	Severity in %	Stages in %
Arteriole (a)	52,00	54,21	53,19
Small artery (A)	32,62	32,15	32,10
Medium size artery (AA)	9,85	9,26	10,25
Venule (v)	1,85	1,52	1,63
Small vein (V)	2,77	2,19	2,08
Medium size vein (VV)	0,92	0,67	0,74
Total in %	100%	100%	100%

Table 3b: *Prevalence, severity and stages of AV in 33 RA patients according to the involved blood vessels by size (in percentage of the total sum of prevalence n = 325, severity n = 594 and stages n = 673).*

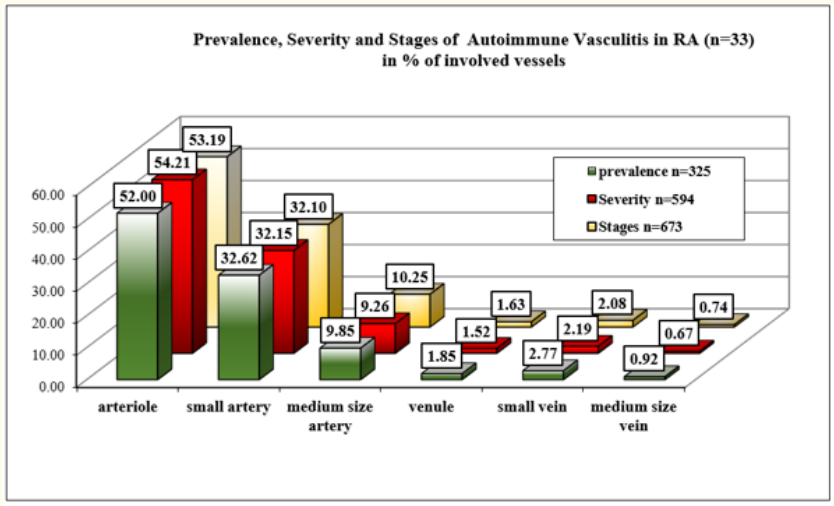

Figure 5b: *Distribution of prevalence, severity and flare-ups of AV according to the size of affected vessels in percentage. Prevalence, severity and flare-ups of AV changed parallel on arteries and veins. Veins were relatively less frequently affected than arteries. Multiple (early, advanced, late) phases of inflammation and structural vascular changes existed simultaneously in the same tissue sections.*

Changes of capillaries are of electron microscopic dimension, and are not discussed in this light microscopic study.

Different (acute, subacute, subchronic and chronic) stages of inflammation (repeated flare-ups) were present simultaneously in the same tissue slide or on different blood vessels existing side by side at the same time.

AV was dominated by subacute-subchronic stages of inflammation and structural changes of blood vessels in RA (Table 4a and 4b and figure 6a and 6b).

Table 4a and 4b and figure 6a and 6b demonstrate (show) different (acute, subacute, subchronic and chronic) stages of inflammation according to the type of vasculitis. Phases of inflammation and structural changes in blood vessels tend to be more subacute-subchronic in stage.

Type and stages of AV	Non-specific	Fibrinoid necrotic	Granulomatous	Total
Acute	26	7	2	35
Subacute	128	43	34	205
Subchronic	184	52	35	271
Chronic	127	26	9	162
Total in absolute value	465	128	80	673

Table 4a: *Acute, subacute, subchronic and chronic stages of inflammation according to the type of vasculitis (in absolute value of the total sum of stages n = 673).*

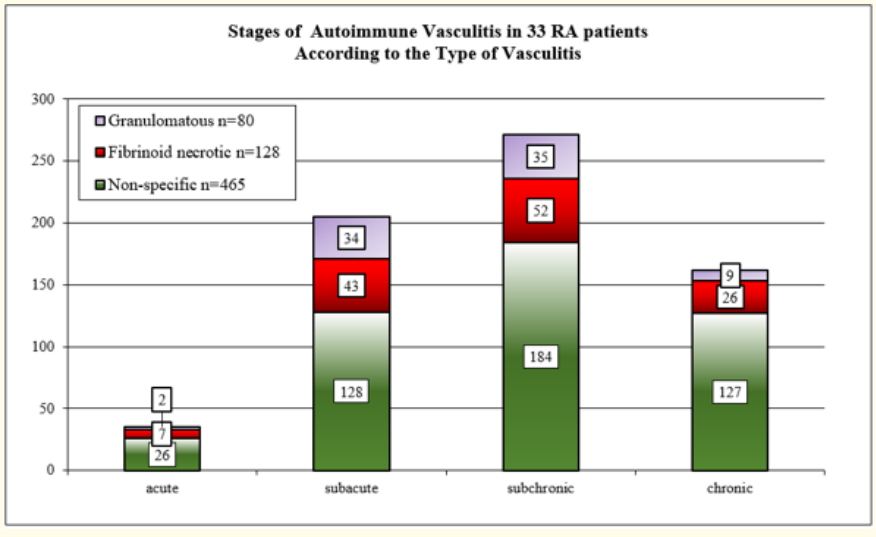

Figure 6a: *Stages of inflammation in absolute number of affected vessels according to the types of AV. Subacute-subchronic stages of inflammation dominated the AV in RA.*

Type and stages of AV	Non-specific	Fibrinoid necrotic	Granulo-matous	Total
Acute	3,86	1,04	0,30	5,20
Subacute	19,02	6,39	5,05	30,46
Subchronic	27,34	7,73	5,20	40,27
Chronic	18,87	3,86	1,34	24,07
Total in absolute value	69,09	19,02	11,89	100,00

Table 4b: *Acute, subacute, subchronic and chronic stages of inflammation according to the type of vasculitis (in percentage of the total sum of stages n = 673).*

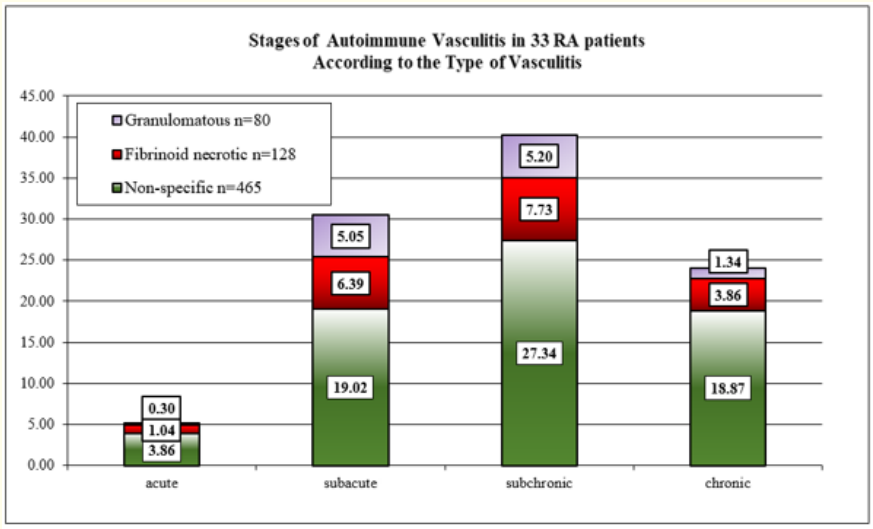

Figure 6b: *Stages of inflammation in % of the total number of involved vessels according to the types of AV. Subacute-subchronic stages of inflammation dominated the AV in RA.*

Prevalence and severity of AV changed in parallel in various organs of 33 RA patients (See trend lines in figure 7).

Occasional differences were done to random sampling and the semi-objectivity of the method.

Figure 7 shows the prevalence and severity of AV in various organs of RA patients (in descending order of prevalence).

The heart, muscles, nerves, kidneys, and lungs were the most commonly affected organs.

The optimal site for histological sampling was found to be the sural nerve with the surrounding muscle tissue, where AV occurred in two-thirds of cases (Figure 7).

In terms of mortality, cardiac involvement was the most dangerous.

Mortality was determined by the location of the AV rather than its severity; moderate cerebral AV may be fatal, in contrast to the frequently involved of muscle and nerve.

Figure 7 shows prevalence and severity of AV in various organs of RA patients.

Characteristics of autoimmune vasculitis (AV) in progressive systemic sclerosis (PSS)

In progressive systemic sclerosis AV was common and severe.

Vascular inflammation existed in all (100%) of 11 patients, and in all (100%) of 12 examined organs.

*AV was assessed only in 11 of 12 PSS patients. One patient had myeloma and because of the massive AL amyloid infiltration of the vessel walls; AV was not assessable.

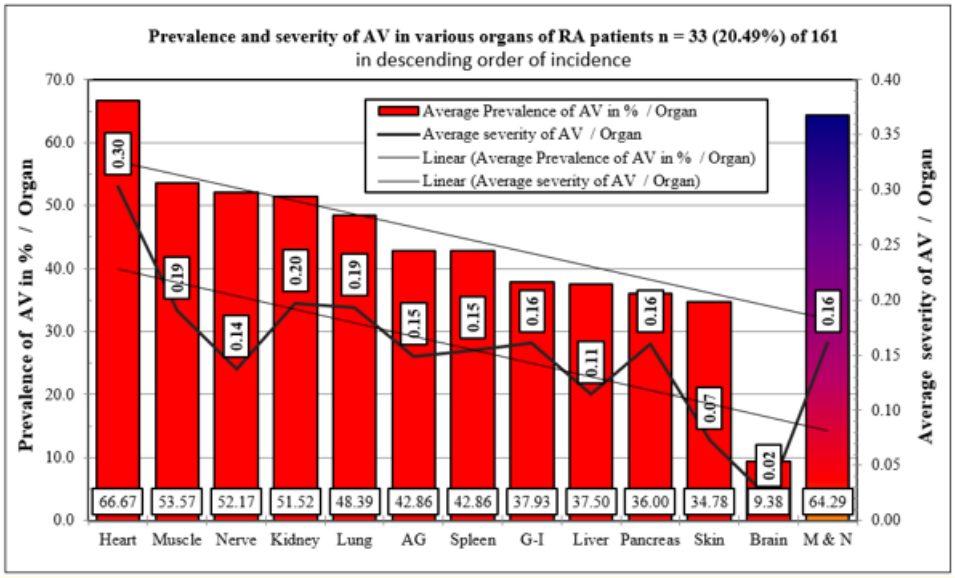

Figure 7: *The prevalence and severity of AV in various organs varied in parallel (see trend lines). Occasional differences were due to the random sampling and the semi-objectivity of the method. The prevalence of AV in the peripheral nerves and surrounding muscle tissue approximated that found in the myocardium; the optimal site for surgical sampling was the sural nerve with surrounding muscle tissue.*

Abbreviations: AG: Adrenal Gland; G-I: Gastrointestinal Tract; M & N: Muscle and Sural Nerve.

The average prevalence and severity of AV, furthermore the stages of inflammation (flare-ups) were different among patients and in various organs (differed from each other's).

The prevalence, severity of AV, and stages of inflammation changed in parallel in individual patients and in various organs

In PSS, vasculitis was mostly "non-specific" (Figure 8), "fibrinoid" necrosis occurred (Figure 9), but "granulomatous transformation" of the vessels was not observed (not found).

Non-specific and fibrinoid necrotic forms of AV existed side by slide in the same slides simultaneously or combined in the same blood vessels at the same time.

Both types of AV might be accompanied by a specific vascular lesion characterized by fibromuscular intimal proliferation (FIP) (Figure 10-12).

The presence of FIP - in accordance with the clinical diagnosis, and consistent with the clinical symptomatic - was an absolute diagnostic histological sign of PSS. The absence of granulomatous vasculitis confirmed the histological diagnosis of PSS.

Figure 8-12 illustrate the non-specific and fibrinoid necrotic vasculitis, furthermore the so-called fibromuscular intimal proliferation of AV, which is histologically a pathognomonic, diagnostic vascular changes of PSS.

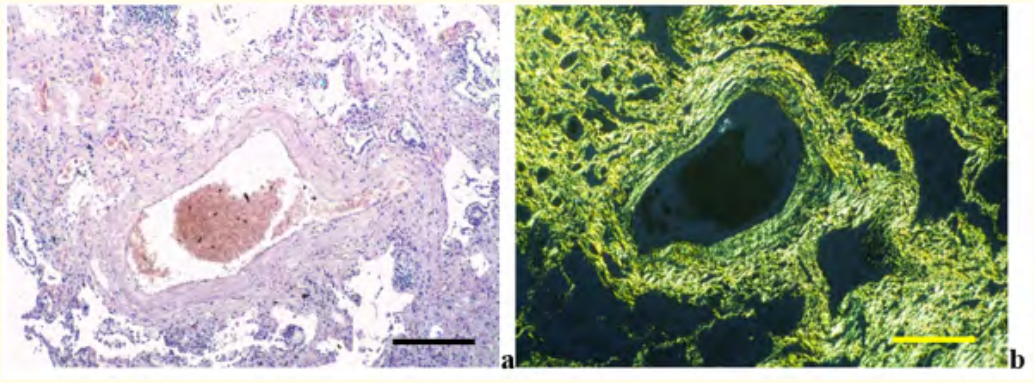

Figure 8a and 8b: *PSS, lung, small artery, non-specific subchronic AV (with interstitial fibrosis of the lung - "honeycomb lung"). (a) Small artery, HE, scale bar: 125 [μm], magnification: x125. (b) Same as (a), Picrosirius red F3BA staining [18, 19] viewed under polarized light, scale bar: 125 [μm], magnification: x125.*

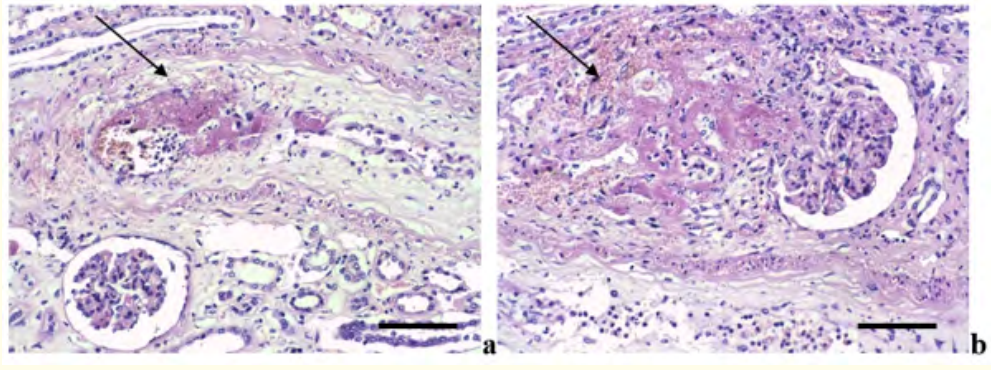

Figure 9a and 9b: *PSS, kidney, arteriole and fibrinoid necrotic preglomerular arterioles. (a) Arteriole, fibrinoid necrotic AV combined with FIP (arrow), HE, scale bar: 125 [μm], magnification: x125. (b) Arteriole, fibrinoid necrotic preglomerular arterioles (arrow), with adjacent arteriole of (a), HE, scale bar: 125 [μm], magnification: x125.*

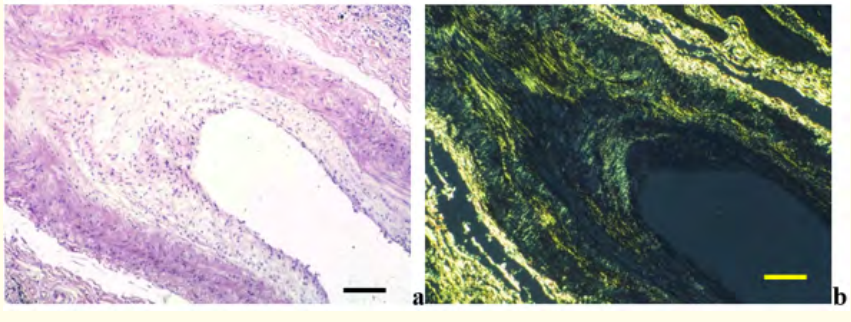

Figure 10a and 10b: *PSS, lung, small artery, FIP (early acute-subacute stage) characterized by mucoid degeneration of the swollen endothelia. (a) Small artery, HE, scale bar: 100 [μm], magnification: x200. (b) Same as (a), Picrosirius red F3BA staining [18,19] viewed under polarized light, scale bar: 100 [μm], magnification: x200.*

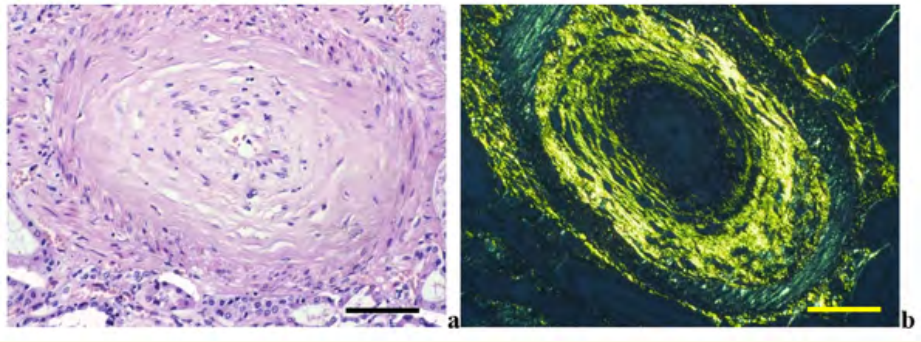

Figure 11a and 11b: *PSS, kidney, small artery, FIP (chronic advanced stage). The vascular endothelium (intima) is thickened, fibrous-homogeneous in structure, the vessel lumen is narrowed (barely recognizable). (a) Small artery, HE, scale bar: 125 [µm], magnification: x125. (b) Same as (a), Picrosirius red F3BA staining [18,19] viewed under polarized light, scale bar: 125 [µm], magnification: x125.*

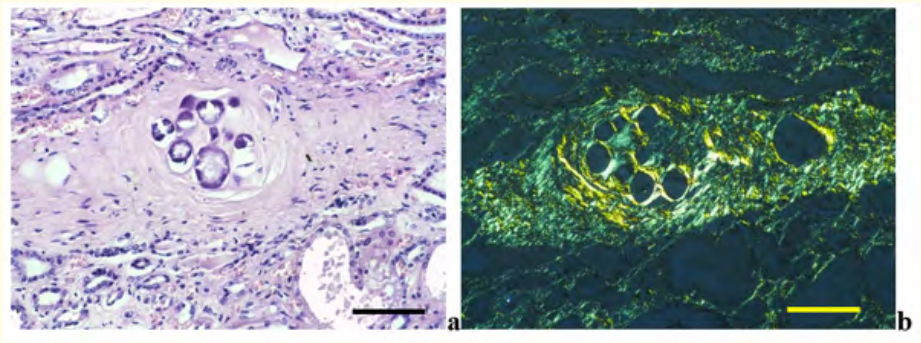

Figure 12a and 12b: *PSS, kidney, arteriole, FIP (chronic end stage). The arteriole is occluded by fibrous tissue with globular calcification. (a) Arteriole, HE, scale bar: 125 [µm], magnification: x125. (b) Same as (a), Picrosirius red F3BA staining [18, 19] viewed under polarized light, scale bar: 125 [µm], magnification: x125.*

The vascular inflammation affected the entire vascular network (capillaries, arterioles, small arteries, medium size arteries with the accompanying veins).

The average prevalence (presence) and severity (number of affected vessels) density of inflamed blood vessels, furthermore the (acute, subacute, subchronic, chronic) stages of flare-ups changed parallel on involved blood vessels (Table 5a and 5b and figure 13a and 13b).

Table 5a and 5b and figure 13a and 13b demonstrate (show) the prevalence, severity, and flare-ups of autoimmune vasculitis in PSS according to the affected blood vessels (in absolute numbers and in percentages).

Size of involved vessels	Prevalence	Severity	Stages
Arteriole (a)	151	263	364
Small artery (A)	116	206	288
Medium size artery (AA)	51	94	129
Venule (v)	32	53	62
Small vein (V)	41	67	87
Medium size vein (VV)	34	53	68
Total in absolute value	425	736	998

Table 5a: *Prevalence, severity and stages of AV in 11 PSS patients according to the involved blood vessels by size (in absolute value of the total sum of prevalence n = 425, severity n = 736 and stages n = 998).*

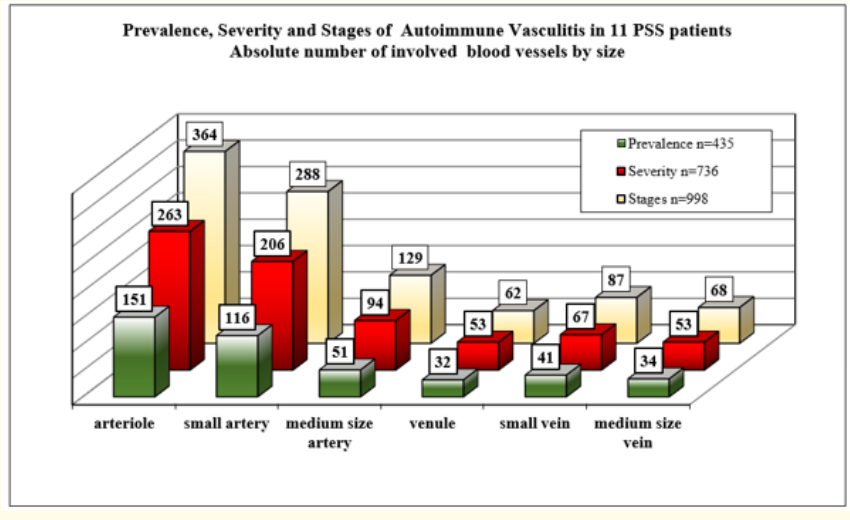

Figure 13a: *Absolute number of affected blood vessels according to the prevalence, severity, and stages of inflammation in autoimmune vasculitis. The affected vessels are arranged in descending order according to the size of blood vessels. The average prevalence of AV was 38.63/patients, the number of inflamed vessels (severity of AV) 66.91/patient, and the detected exacerbation (stages of AV) 90.73/patient in affected blood vessels of PSS.*

Involved vessels	Prevalence in %	Severity in %	Stages in %
Arteriole (a)	35,53	35,73	36,47
Small artery (A)	27,29	27,99	28,86
Medium size artery (AA)	12,00	12,77	12,93
Venule (v)	7,53	7,20	6,21
Small vein (V)	9,65	9,10	8,72
Medium size vein (VV)	8,00	7,20	6,81
Total in %	100%	100%	100%

Table 5b: *Prevalence, severity and stages of AV in 11 PSS patients according to the involved blood vessels by size (in percentage of the total sum of prevalence n = 325, severity n = 594 and stages n = 673).*

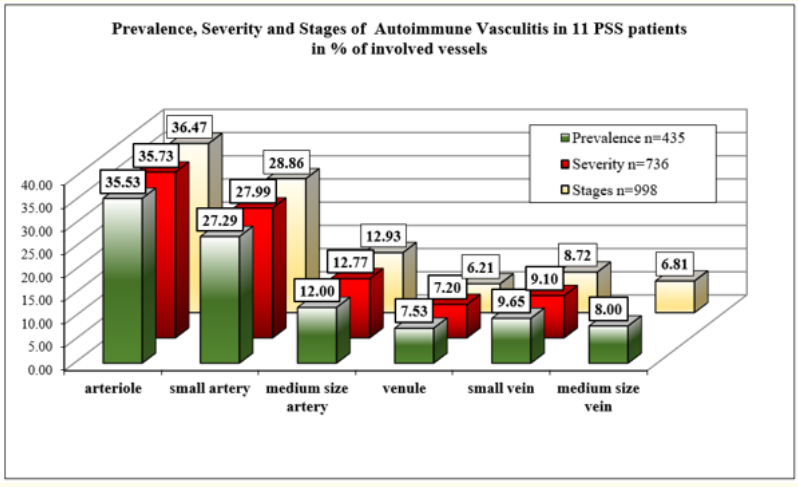

Figure 13b: *Distribution of affected blood vessels by AV in percentage. Prevalence, severity and stages of AV on different size of blood vessels in % of the total number of involved vessels.*

Prevalence, severity and stages of AV changed parallel on arteries and veins.

Veins were relatively more frequently affected comparing to RA.

Multiple (early, advanced, late) stages of inflammation and structural vascular changes existed simultaneously in the same tissue sections.

Changes of capillaries are of electron microscopic dimension, and are not discussed in this light microscopic study.

Different (acute, subacute, subchronic and chronic) stages of inflammation (repeated flare-ups) were present simultaneously in the same tissue slide or on different blood vessels existing side by side at the same time.

Subchronic-chronic stages of inflammation and structural changes of blood vessels dominated the AV in PSS (Table 6a and 6b and figure 14a and 14b).

Table 6a and 6b and figure 14a and 14b demonstrate (show) different (acute, subacute, subchronic and chronic) stages of inflammation according to the type of vasculitis. Phases of inflammation and structural changes in blood vessels tend to be more advanced, chronic in stage, in contrast to those found in RA patients.

Type and stages of AV	Non-specific	Fibrinoid necrotic	Granulomatous	Total
Acute	16	28	0	44
Subacute	78	63	0	141
Subchronic	300	117	0	417
Chronic	289	107	0	396
Total in absolute value	683	315	0	998

Table 6a: *Acute, subacute, subchronic and chronic stages of inflammation according to the type of vasculitis (in absolute value of the total sum of stages n = 998).*

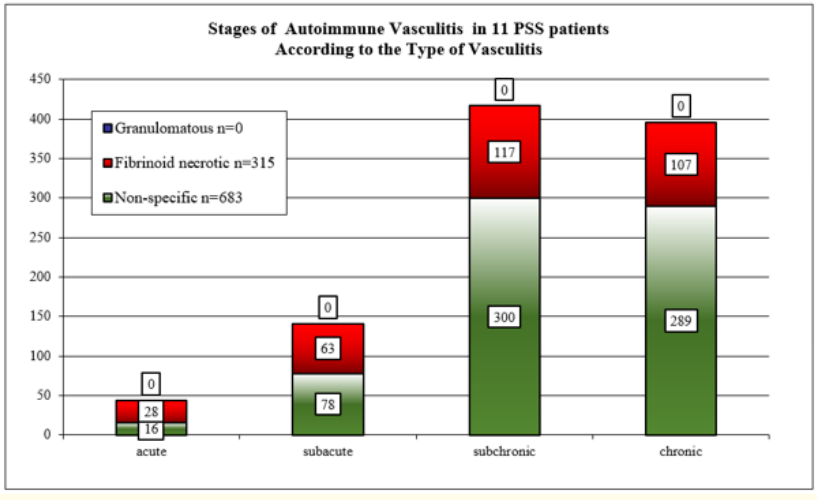

Figure 14a: *Stages of inflammation in absolute number of affected vessels according to the types of AV. Granulomatous type of AV was not found in PSS patients. Subchronic-chronic stages of inflammation dominated the AV in PSS.*

Type and stages of AV	Non-specific	Fibrinoid necrotic	Granulo-matous	Total
Acute	1,60	2,81	0	4,41
Subacute	7,82	6,31	0	14,13
Subchronic	30,06	11,72	0	41,78
Chronic	28,96	10,72	0	39,68
Total in absolute value	68,44	31,56	0	100,00

Table 6b: *Acute, subacute, subchronic and chronic stages of inflammation according to the type of vasculitis (in percentage of the total sum of stages n = 998).*

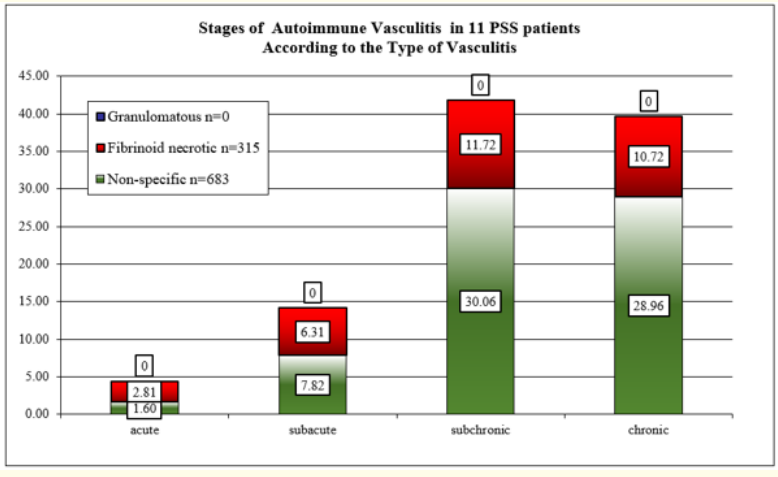

Figure 14b: *Stages of inflammation in % of the total number of involved vessels according to the types of AV. Granulomatous type of AV was not found in PSS patients. Subchronic-chronic stages of inflammation dominated the AV in PSS.*

The prevalence and severity of AV in different organs of 11 PSS patients varied in parallel (See trend lines in figure 15).

Occasional differences were done to random sampling and the semi-objectivity of the method.

Figure 15 shows the prevalence and severity of AV in various organs of PSS patients (in descending order of prevalence).

The lungs, pancreas, kidneys, spleen, and heart were the most commonly affected organs.

The optimal site for early histological diagnosis of AV was to be found the lung, pancreas, and kidney, where AV occurred in nearly nineth % of positive cases (Figure 15).

From a fatality perspective, involvement of the kidneys and heart was most dangerous, with or without cystic lung changes resembling honeycomb spleen ("honeycomb").

Figure 15 show prevalence and severity of AV in various organs of PSS patients.

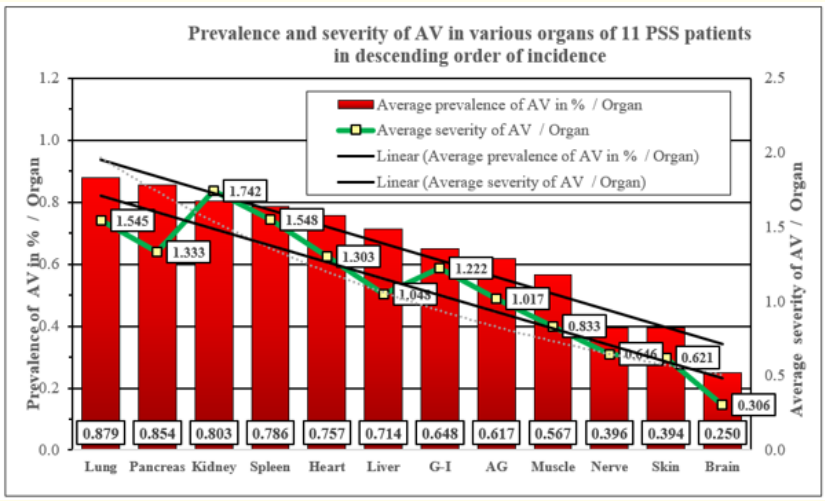

Figure 15: *The prevalence and severity of AV in various organs varied in parallel (see trend lines). Occasional differences were due to the random sampling and the semi-objectivity of the method. The lungs, pancreas, kidneys, spleen, and heart were most commonly affected organs. From a fatality perspective, involvement of the kidneys and heart was most dangerous, with or without cystic lung changes resembling honeycomb spleen ("honeycomb").*

Abbreviations: AG: Adrenal Gland; G-I: Gastrointestinal Tract.

Characteristics of autoimmune vasculitis (AV) in polymyalgia rheumatica (PMR)

In polymyalgia rheumatica (PMR) temporal arteritis (TA) was present in 71 (23.75%) of 299 patients.

TA was accompanied with inflammation of the entire branches temporal blood vessels, including the large and medium-sized arteries, smaller arteries, arterioles, and accompanying veins with different prevalence, severity and stages of inflammation (flare-ups).

Prevalence, severity and stages of TA differed from each other on the branches of the temporal blood vessels.

Three types of autoimmune vasculitis were distinguished in PMR patients with TA (classic, atypical, and healed), according to the description by Allsop and Gallagher (1981) [16] or McMillen B., *et al*. (2025) [17]. Different types of TA existed side by slide in the same tissue slides simultaneously or combined in the same blood vessels at the same time.

TA was basically "non-specific", which existed in different stages of inflammation (flare ups) side by side in blood vessels of the temporal branches.

Penetrating "fibrinoid" necrosis (affecting the entire cross-section of the vessel) or "granulomatous transformation" of the vessels walls was not observed (not found).

TA not existed without PMR.

AbSI of fatal outcome was not detected in PMR.

Figure 16-18 illustrate the atypical, classic and the healed stage of TA.

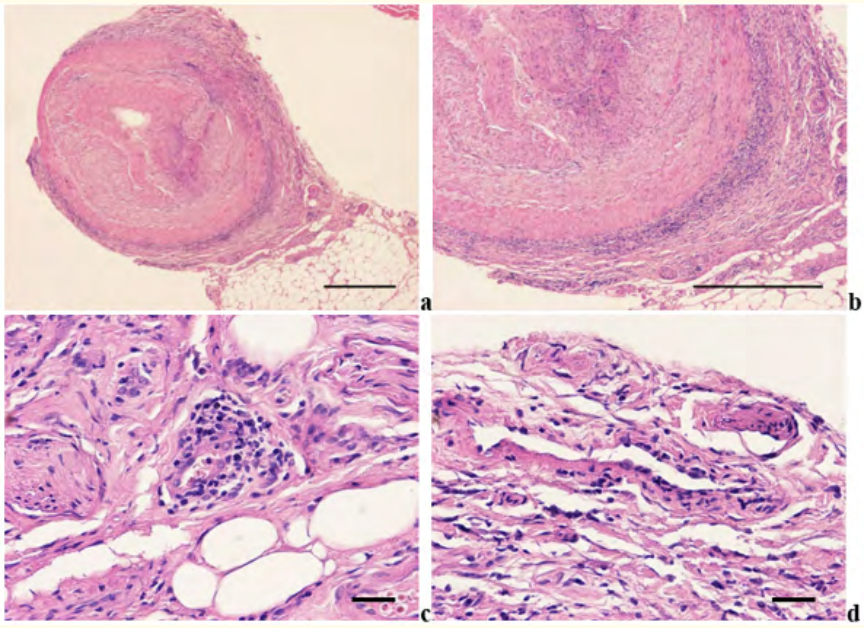

Figure 16a-16d: *Atypical TA, main branch of medium size temporal artery, advanced, chronic stage of inflammation, accompanied with a small artery and vein. Mixed cellular lobular infiltration is primarily affected the outer layer of the vessels, the intima and the adventitia is proliferated and fibrotic, the vessel lumen is narrowed. (a) Medium size artery, HE, scale bar: 1000 [µm], magnification: x20. (b) Detail of image (a), scale bar: 1000 [µm], magnification: x40. (c) Arteriole, non-specific, chronic lobular infiltration, detail of image (a), HE, scale bar: 100 [µm], magnification: x200. (d) Venule, inflammatory infiltration in the vascular wall sector, detail of image (a), HE, scale bar: 100 [µm], magnification: x200.*

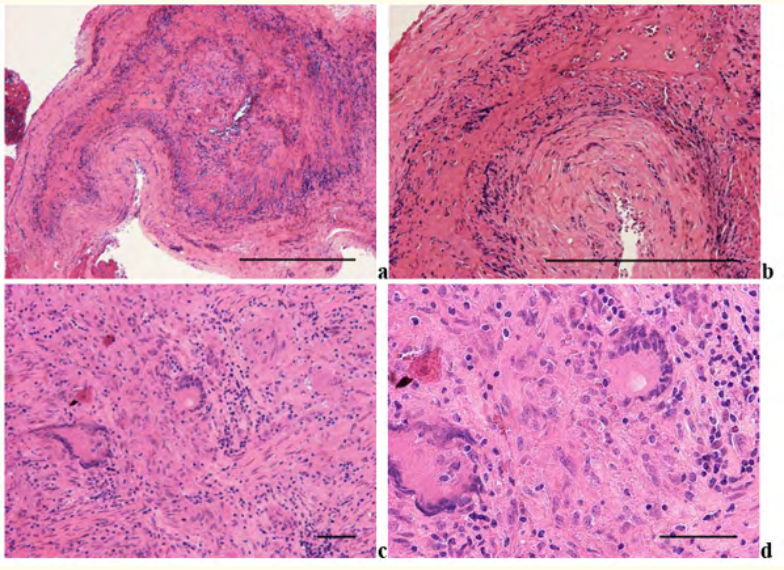

Figure 17a and 17d: *Classic TA, branches of medium-sized arteries and veins, accompanied with arterioles veins and venules, subacute-subchronic cellular infiltration with giant cells. Intensive T lymphocytic inflammatory infiltration in the vessel wall, with histiocytes and multinucleated giant cells. (a) Medium size artery and vein, HE, scale bar: 1000 [µm], magnification: x40. (b) Detail of image (a), scale bar: 1000 [µm], magnification: x100. (c) Giant cell accompanied by phagocytes detail of image (b), HE, scale bar: 100 [µm], magnification: x200. (d) Langhans-type multinucleated giant cell, detail of image (c), HE, scale bar: 100 [µm], magnification: x400.*

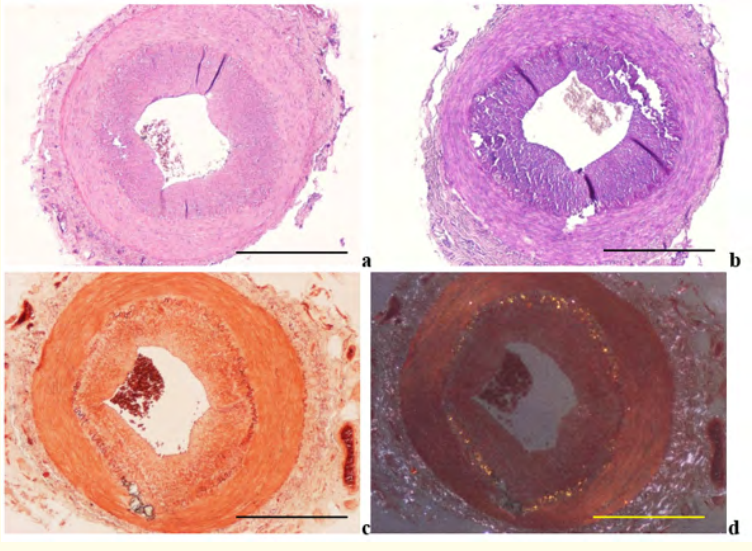

Figure 18a and 18d: *Healed TA, main branch of temporal medium-sized artery, advanced, chronic stage, moderate lobular infiltration. The inner elastic layer is fragmented, degenerated, with intermittent local amyloid deposits, presumably originating from damaged elastic fibers. (a) HE, scale bar: 1000 [µm], magnification: x40. (b) PAS, same as (a), scale bar: 1000 [µm], magnification: x40. (c) Congo red staining, same as (a), scale bar: 1000 [µm], magnification: x40. (d) Congo red staining viewed under polarized light, same as (c), scale bar: 1000 [µm], magnification: x40.*

The vascular inflammation affected the entire vascular network (capillaries, arterioles, small arteries, medium size arteries with the accompanying veins).

The prevalence and severity of atypic, classic and healed form of TA, furthermore the (acute, subacute, subchronic, chronic) stages of inflammation changed parallel on involved blood vessels (Table 7a and 7b and figure 19a and 19b).

Table 7a and 7b and figure 19a and 19b demonstrate (show) the prevalence, severity, and flare-ups of autoimmune vasculitis according to the affected blood vessels (in absolute number and percentage).

Size of involved vessels	Prevalence n = 136	Severity n = 161	Stages n = 370
Medium size artery	55	62	159
Arteriole	44	57	110
Small artery	25	29	67
Venule	8	3	26
Small vein	2	0	4
Medium size vein	2	10	4
Total in absolute value	136	161	370

Table 7a: *Prevalence, severity and stages of TA in 71 PMR patients according to the involved blood vessels by size (in absolute value of the total sum of prevalence n = 136, severity n = 161 and stages n = 370).*

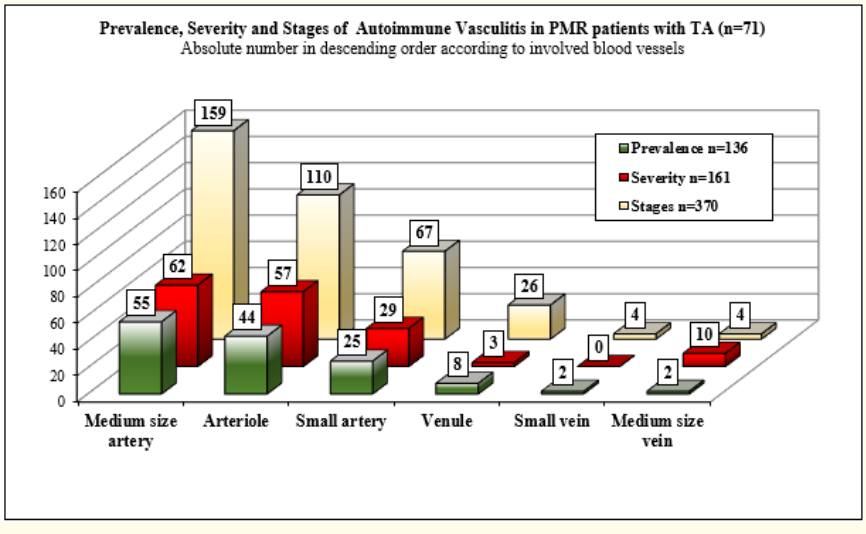

Figure 19a: *Prevalence, severity, and stages of TA in absolute number of affected blood vessels by autoimmune vasculitis in descending order of involved blood vessels. Prevalence was calculated according to the number of inflamed blood vessels. Severity of TA was calculated according to the absolute number of acute and subacute flare-ups. Stages of TA was calculated according to the total (acute, subacute, subchronic and chronic) number of flare-ups. Prevalence, severity and stages of TA existed in the same tissue sections simultaneously and on blood vessels of different size at the same time. Prevalence, severity and staged run parallel to each other's. TA mainly affected the medium-sized arteries compared to the arterioles and small arteries or accompanying veins. The average prevalence of TA was 1.92/patients, the number of inflamed vessels (severity of TA) 2.27/patient, and the detected exacerbation (repeated flare-ups, stages of TA) 5.21/patient in affected blood vessels of PMR.*

Size of involved vessels	Prevalence n = 136	Severity n = 161	Stages n = 370
Medium size artery	40,44	38,51	42,97
Arteriole	32,35	35,40	29,73
Small artery	18,38	18,01	18,11
Venule	5,88	1,86	7,03
Small vein	1,47	0,00	1,08
Medium size vein	1,47	6,21	1,08
Total in absolute value	100.0	100.0	100.0

Table 7b: *Prevalence, severity and stages of TA in 71 PMR patients according to the involved blood vessels by size (in percentage of the total sum of prevalence n = 136, severity n = 161 and stages n = 370).*

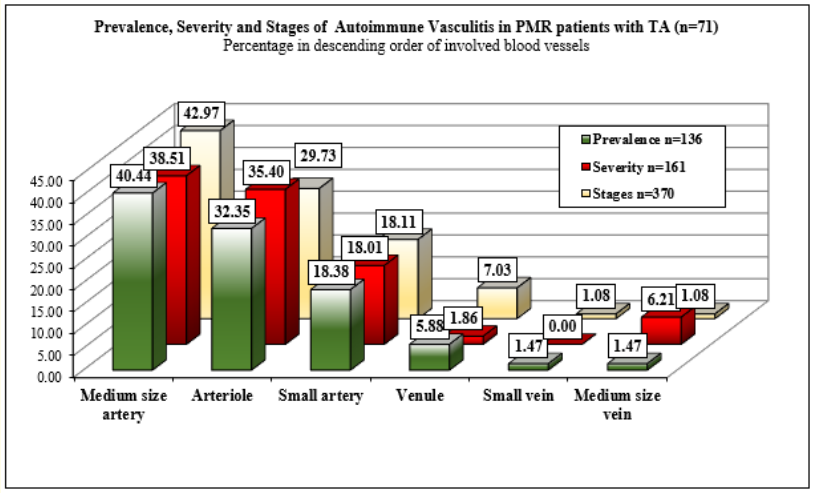

Figure 19b: *Distribution of prevalence, severity and flare-ups of TA according to the descending order of affected vessels in percentage. Prevalence, severity and flare-ups of TA changed parallel on arteries and veins. TA mainly affected the medium-sized arteries. Multiple (early, advanced, late) phases of inflammation and structural vascular changes existed simultaneously in the same tissue sections on different blood vessels.*

Changes of capillaries are of electron microscopic dimension, and are not discussed in this light microscopic study.

Different (acute, subacute, subchronic and chronic) stages of inflammation (repeated flare-ups) were present in the same tissue slide simultaneously or on different blood vessels existing side by side at the same time.

Subacute-subchronic-chronic stages of inflammation and structural changes of blood vessels dominated the TA in PMR (Table 8a and 8b and figure 20a and 20b).

Table 8a and 8b and figure 20a and 20b demonstrate (show) different (acute, subacute, subchronic and chronic) stages of inflammation according to the types of TA. Phases of inflammation and structural changes in blood vessels tend to be more subacute-subchronic-chronic in stage.

Type and stages of AV	Classic TA	Atypic TA	Chronic TA	Total
Acute	19	35	0	54
Subacute	25	72	10	107
Subchronic	22	72	8	102
Chronic	21	60	26	107
Total in absolute value	87	239	44	370

Table 8a: *Acute, subacute, subchronic and chronic stages of inflammation according to the type of vasculitis (in absolute value of the total sum of flare-ups n = 370).*

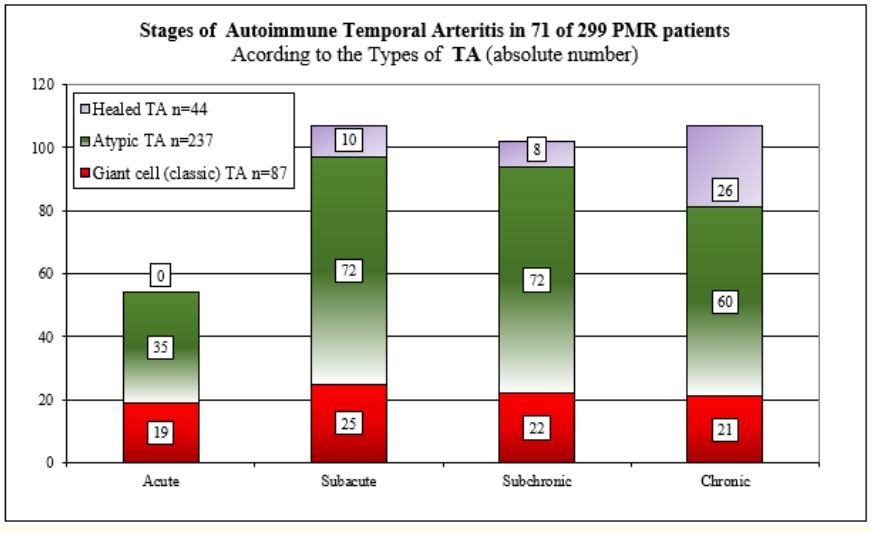

Figure 20a: *Stages of inflammation in absolute number of affected vessels according to the types of TA. Histologically the subacute-subchronic-chronic stages of inflammation were dominant by TA in PMR.*

Type and stages of AV	Non-specific	Fibrinoid necrotic	Granulomatous	Total
Acute	5,14	9,46	0,00	14,59
Subacute	6,76	19,46	2,70	28,92
Subchronic	5,95	19,46	2,16	27,57
Chronic	5,68	16,22	7,03	28,92
Total in percentage	23,51	64,59	11,89	100,0

Table 8b: *Acute, subacute, subchronic and chronic stages of inflammation according to the types of TA (in percentage of the total sum of flare-ups n = 370).*

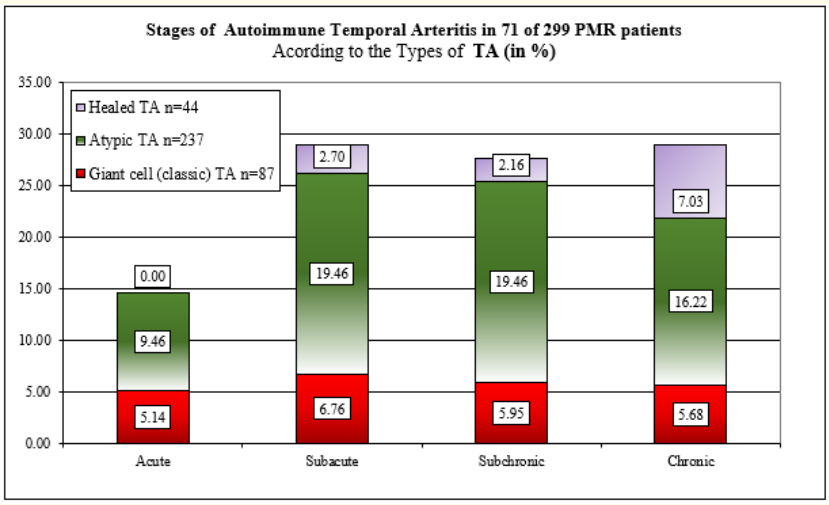

Figure 20b: *Stages of inflammation in % of the total number of involved vessels according to the types of TA. Histologically the subacute-subchronic-chronic stages of inflammation were dominant by TA in PMR.*

In PMR, only the temporal blood vessels was examined; no examination of vascular inflammation affecting individual organs was performed (given that the evaluation was based on sampling from living patients).

Characteristics of systemic septic vasculitis (SV) in rheumatoid arthritis (RA)

Twenty-four (24) of 161 RA patients was complicated by acute bacterial septic infection (AbSI) of fatal outcome. AbSI was accompanied in 3 cases with systemic vasculitis of septic origin (SV).

The clinically identified pathogenic agents (*E. coli, Proteus mirabilis, Pseudomonas aeruginosa*) and the strong, significant and positive correlation between AbSI and SV (association coefficient: 1, c2 = 11.2838, $p < 0.00007$) supported the infectious origin of SV.

AV and SV did not occur together in our patients, and there was no association between these two entities (association coefficient: -1.0, $\chi^2 = 0.0275$, $p < 0.8682$)

SV in RA was less common and less severe than AV in RA.

Vascular inflammation existed in 3 (12.5%) of 24 patients, and only in 9 (75.0%) of 12 organs; the lungs, spleen and the brain were spared.

The average prevalence and severity of AV, furthermore the stages of inflammation (flare-ups) were different among patients and in various organs (differed from each other's).

SV affected the entire vascular network and occurred on all sizes of vessels (capillaries, arterioles, small arteries, medium size arteries) except the veins; the vein were spared.

SV was mostly "non-specific," fibrinoid necrosis occurred in the vessel walls, but granulomatous transformation of the vessel walls was not detected.

Different types of SV existed side by slide in the same tissue slides simultaneously or combined in the same blood vessels at the same time.

Figure 21 illustrates the non-specific, fibrinoid necrotic SV in AbSI of RA patients.

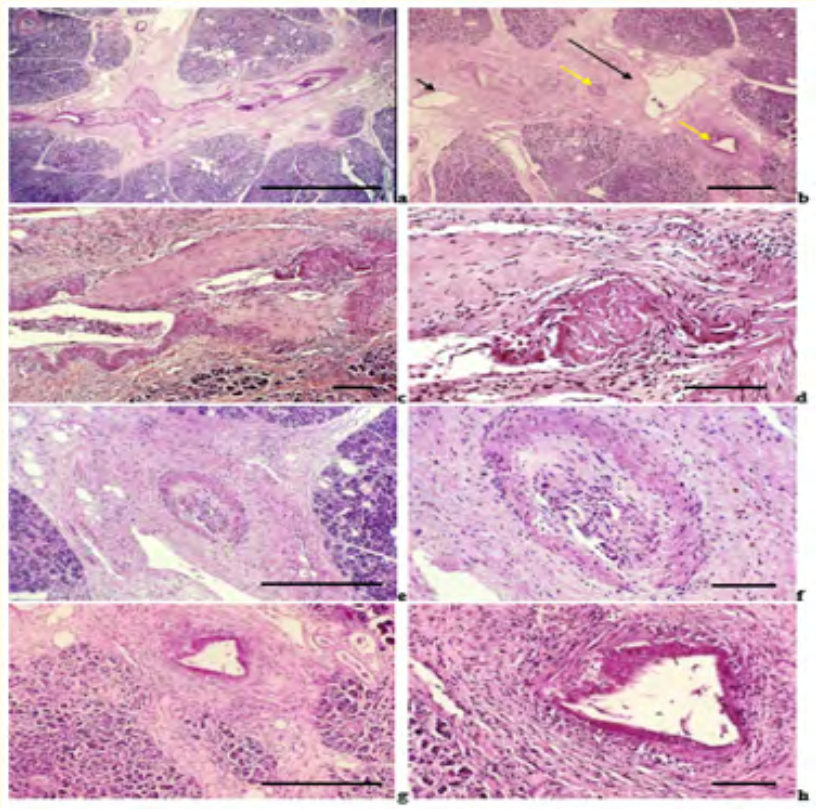

Figure 21a-21h: *SV in AbSI, pancreas, medium size artery, non-specific subchronic-chronic thrombovasculitis. (a) Medium size artery, recanalized recurrent thrombovasculitis, HE, scale bar: 1000 [µm], magnification: x20. (b) Same tissue samples as (a) with surrounding small arteries, arterioles (yellow arrows) and veins, venules (black arrows), HE, scale bar: 1000 [µm], magnification: x20. (c) Same as (a), HE, scale bar: 100 [µm], magnification: x200. (d) Same as (a) HE, scale bar: 100 [µm], magnification: x400. (e) Small artery, non-specific chronic vasculitis, same as (b), HE, scale bar: 1250 [µm], magnification: x50. (f) Small artery, non-specific chronic vasculitis, same as (b), HE, scale bar: 125 [µm], magnification: x125. (g) Small artery, fibrinoid necrotic SV, same as (b), PAS, scale bar: 1250 [µm], magnification: x50. (h) Small artery, fibrinoid necrotic SV, same as (b), PAS, scale bar: 125 [µm], magnification: x125.*

The average prevalence (presence) and severity (number of affected vessels, density of inflamed blood vessels), furthermore the (acute, subacute, subchronic, chronic stages of inflammation (flare-ups) changed parallel on affected blood vessels (Table 9a and 9b and figures 22a and 22b).

Table 9a and 9b and figures 22a and 22b demonstrate (show) the prevalence, severity, and flare-ups of septic vasculitis complicated the AbSI in RA according to the affected blood vessels (in absolute number and in percentage). Prevalence, severity and stages of SV in 3 RA patients according to the involved blood vessels by size (in absolute value of the total sum of prevalence n = 23, severity n = 37 and stages n = 50).

Size of involved vessels	Prevalence of SV	Severity of SV	Stages of SV
Arteriole (a)	10	19	24
Small artery (A)	8	13	15
Medium size artery (AA)	5	5	11
Venule (v)	0	0	0
Small vein (V)	0	0	0
Medium size vein (VV)	0	0	0
Total in absolute value	23	37	50

Table 9a: *Prevalence, severity and stages of SV in AbSI of RA patients according to the involved blood vessels by size (prevalence n = 23, severity n = 37 and stages n = 50).*

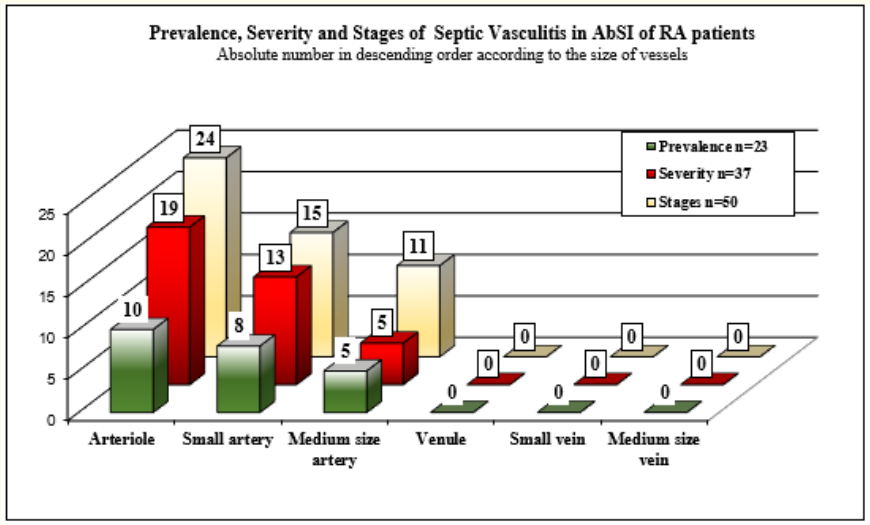

Figure 22a: *Absolute number of affected blood vessels according to the prevalence, severity, and stages of inflammation of septic vasculitis. The affected vessels are arranged in descending order according to the size of arteries and veins; the veins were spared in SV. Granulomatous type of AV was not found in PSS patients. The average prevalence of SV was 7.67/patients, the number of inflamed vessels (severity of SV) 12.3/patient, and the detected exacerbation (stages of SV) 16.67/patient in affected blood vessels of AbSI.*

Involved vessels	Prevalence in %	Severity in %	Stages in %
Arteriole (a)	43,48	51,35	48,00
Small artery (A)	34,78	35,14	30,00
Medium size artery (AA)	21,74	13,51	22,00
Venule (v)	0,0	0,0	0,0
Small vein (V)	0,0	0,0	0,0
Medium size vein (VV)	0,0	0,0	0,0
Total in %	100 %	100 %	100 %

Table 9b: *Prevalence, severity and stages of SV in AbSI of RA patients according to the involved blood vessels by size (in percentage of the total sum of prevalence n = 23, severity n = 37 and stages n = 50).*

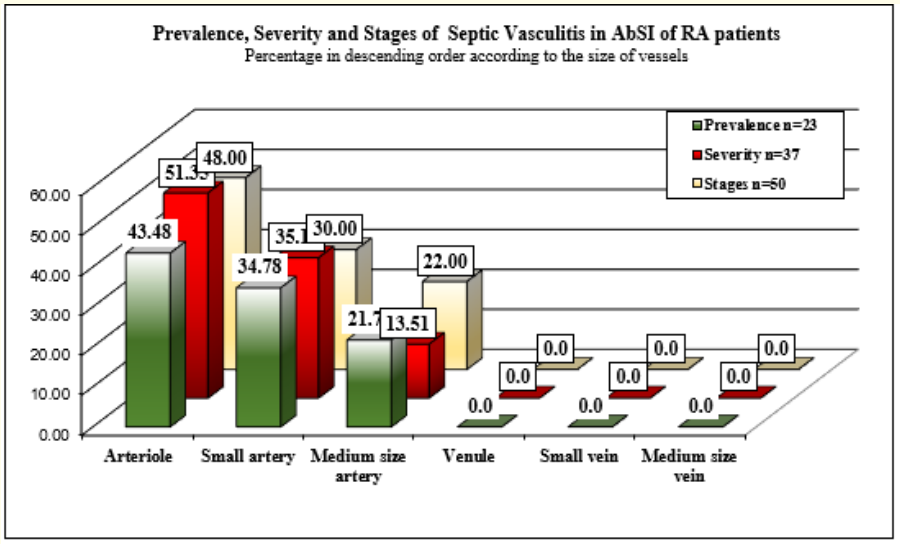

Figure 22b: *Distribution of prevalence, severity and flare-ups of SV according to the size of affected vessels in percentage. Prevalence, severity and flare-ups of AV changed parallel on arteries and veins. The affected vessels are arranged in descending order according to the size of arteries and veins; the veins were spared in SV. Granulomatous type of SV was not found in AbSI in RA patients.*

Different (acute, subacute, subchronic and chronic) stages of inflammation (repeated flare-ups) were present simultaneously in the same tissue slide or on different blood vessels existing side by side at the same time.

Subacute-subchronic stages of inflammation and structural changes of blood vessels dominated the SV in AbSI of RA patients (Table 10a and 10b and figure 23a and 23b).

Table 10a and 10b and figure 23a and 23b demonstrate (show) different (acute, subacute, subchronic and chronic) stages of inflammation according to the type of SV. Phases of inflammation and structural changes in blood vessels tend to be more subacute-subchronic in stage, like stages of AV in RA patients.

Type and stages of AV	Non-specific	Fibrinoid necrotic	Granulomatous	Total
Acute	1	2	0	3
Subacute	13	3	0	16
Subchronic	16	3	0	19
Chronic	10	2	0	12
Total in absolute value	40	10	0	50

Table 10a: *Acute, subacute, subchronic and chronic stages of inflammation according to the type of vasculitis (in absolute value of the total sum of stages n = 50).*

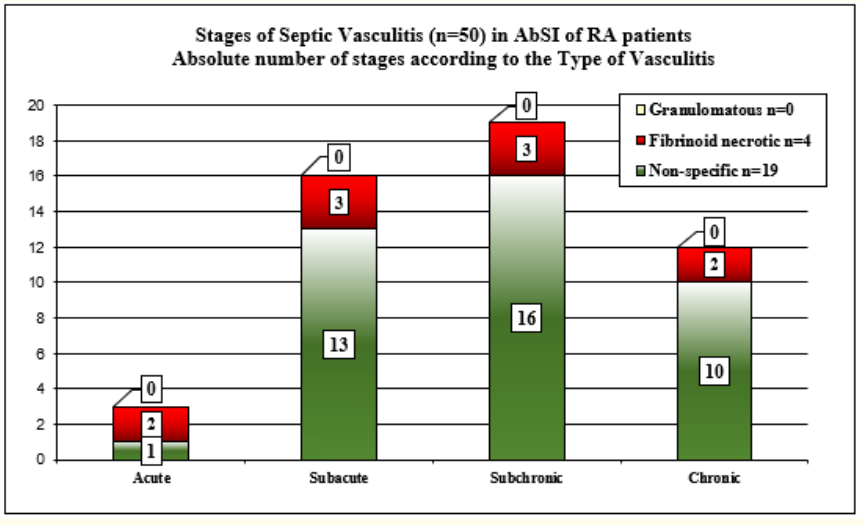

Figure 23a: *Stages of inflammation in absolute number of affected vessels according to the types of SV. Granulomatous vasculitis was not detected in AbSI of RA patients. Subacute-subchronic stages of inflammation dominated the SV in AbSI patients, similarly to AV of RA patients.*

Type and stages of AV	Non-specific	Fibrinoid necrotic	Granulomatous	Total
Acute	2,0	4,0	0,0	6,0
Subacute	26,0	6,0	0,0	32,0
Subchronic	32,0	6,0	0,0	38,0
Chronic	20,0	4,0	0,0	24,0
Total in absolute value	80,0	20,0	0,0	100,0

Table 10b: *Acute, subacute, subchronic and chronic stages of inflammation according to the type of vasculitis (in percentage of the total sum of stages n = 50).*

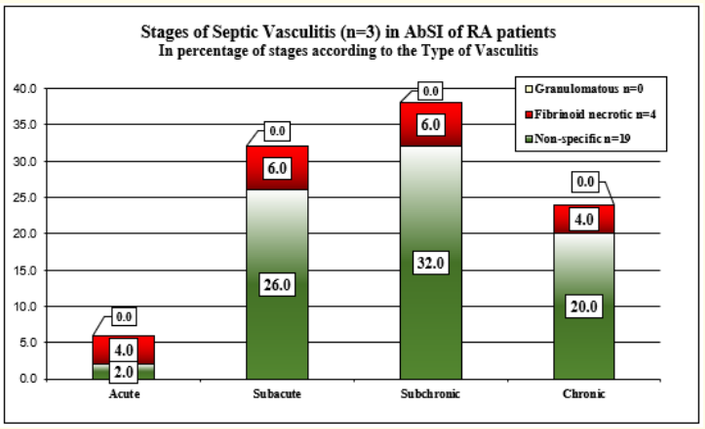

Figure 23b: *Stages of inflammation in % of the total number of involved vessels according to the types of SV. Granulomatous type of SV was not found in AbSI of RA patients. Subacute-subchronic stages of inflammation dominated the SV in RA, similarly to AV of RA patients.*

Figure 24 shows the prevalence and severity of SV in various organs in AbSI of RA patients (in descending order of prevalence).

The heart, pancreas, and G-I tract were the most commonly affected organs; the lungs, spleen and brain were not affected in our patient's cohort.

The optimal site for early histological diagnosis of SV was to be found the G-I tract, and muscle with the surrounding sural nerve, where SV occurred in nearly nineth 70 % of positive cases (Figure 24).

From a fatality perspective, involvement of the heart (resulting cardiac insufficiency), and G-I tract (leading to gastrointestinal ulcer, perforation and peritonitis) were the most dangerous organic involvement.

Figure 24 shows prevalence and severity of SV in various organs of RA patients.

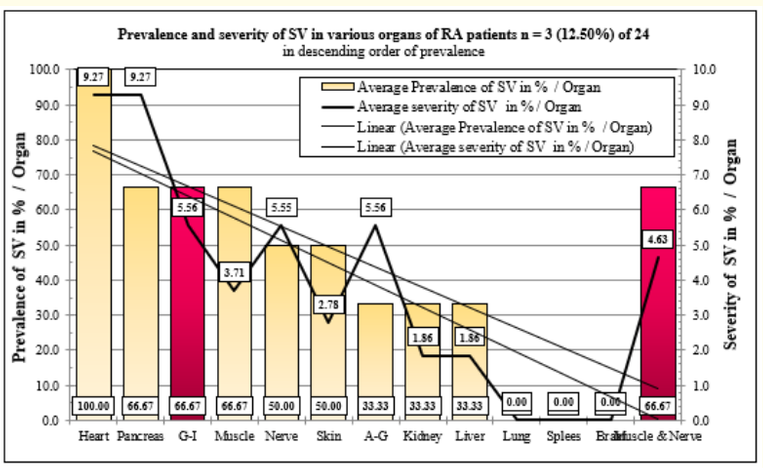

Figure 24: *The prevalence and severity of SV in various organs varied nearly in parallel (see trend lines). Occasional differences were due to the random sampling and the semi-objectivity of the method. The heart, pancreas, G-I tract, muscle and nerve were most commonly affected organs. From a fatality perspective, involvement of the heart, and G-I tract were the most dangerous localization of SV. Based on the coincidence of prevalence and severity, the optimal site for surgical sampling and histological diagnosis of SV appears to be the gastrointestinal tract and/or the sural nerve and surrounding muscle tissue.*

Abbreviations: AG: Adrenal Gland; G-I: Gastrointestinal Tract; M and N: Muscle and Sural Nerve.

Histological differences between autoimmune and septic vasculitis in patients with RA, PSS, PMR, and AbSI

The most severe AV developed in PSS, inflammation was moderate in RA, and mild in PMR patients.

SV was less common and less severe compared to AV of RA.

In PSS the average prevalence of AV was 39.55/patients, the number of inflamed vessels (severity of AV) 66.91/patient, and the detected exacerbation (stages of AV) 90.73/patient in affected blood vessels of PSS.

In RA the average prevalence of AV was 9.85/patients, the number of inflamed vessels (severity of AV) 18.0/patient, and the detected exacerbation (stages of AV) 20.39/patient in affected blood vessels of RA.

In AbSI the average prevalence of SV was 7.67/patients, the number of inflamed vessels (severity of SV) 12.3/patient, and the detected exacerbation (stages of SV) 16.67/patient in affected blood vessels of AbSI.

The average prevalence of TA was 1.92/patients, the number of inflamed vessels (severity of TA) 2.27/patient, and the detected exacerbation (repeated flare-ups, stages of TA) 5.21/patient in affected blood vessels of PMR.

Prevalence (number of affected vessels), severity (density of affected vessels), and stages (number of exacerbations, flare-ups) of AV in patients with RA, PSS, PMR, and of SV in AbSI changed in parallel on blood vessels of different size (Table 11 and figure 25 and 26).

AV and SV affected mainly the arterioles and small arteries in RA, PSS, PMR and in AbSI patients.

TA affected mainly the medium-sized arteries compared to the arterioles and small arteries or accompanying veins.

The veins relatively more frequent involved by AV in PSS than in RA.

The veins remained intact (were spared) by SV in AbSI.

Table 11 and figure 25 and 26 summarize the prevalence, severity and stages of affected blood vessels with AV and SV in RA, PSS, PMR and AbSI patients according to the size of vessels (by number of affected vessels and percentage distribution).

Prevalence of systemic autoimmune and septic vasculitis								
Basic disease	**AV in RA**		**AV in PSS**		**AV in PMR**		**SV in RA**	
Size of vessels	**Absolute n - in %**		**Absolute n - in %**		**Absolute n - in %**		**Absolute n - in %**	
Arteriole	169	52,00	151	35,53	44	32,35	10	43,48
Small artery	106	32,62	116	27,29	25	18,38	8	34,78
Medium size artery	32	9,85	51	12,00	55	40,44	5	21,74
Venule	6	1,85	32	7,53	2	1,47	0	0,00
Small vein	9	2,77	41	9,65	2	1,47	0	0,00
Medium size vein	3	0,92	34	8,00	8	5,88	0	0,00
Total	325	100,0	425	100,0	136	100,0	23	100,0

Severity of systemic autoimmune and septic vasculitis								
Basic disease	**AV in RA**		**AV in PSS**		**AV in PMR**		**SV in RA**	
Size of vessels	**Absolute n - in %**		**Absolute n - in %**		**Absolute n - in %**		**Absolute n - in %**	
Arteriole	204	51,65	263	35,73	57	38,51	19	51,35
Small artery	125	31,65	206	27,99	29	35,40	13	35,14
Medium size artery	51	12,91	94	12,77	62	18,01	5	13,51
Venule	9	2,28	53	7,20	3	1,86	0	0,00
Small vein	6	1,52	67	9,10	0	0,00	0	0,00
Medium size vein	0	0,00	53	7,20	10	6,21	0	0,00
Total	395	100,0	736	100,0	161	100.0	37	100,0
Stages (flare ups) of systemic autoimmune and septic vasculitis								
Basic disease	**AV in RA**		**AV in PSS**		**AV in PMR**		**SV in RA**	
Size of vessels	**Absolute n - in %**		**Absolute n - in %**		**Absolute n - in %**		**Absolute n - in %**	
Arteriole	358	53,19	364	36,47	110	29,73	24	48,00
Small artery	216	32,10	288	28,86	67	18,11	15	30,00
Medium size artery	69	10,25	129	12,93	159	42,97	11	22,00
Venule	11	1,63	62	6,21	4	1,08	0	0,00
Small vein	14	2,08	87	8,72	4	1,08	0	0,00
Medium size vein	5	0,74	68	6,81	26	7,03	0	0,00
Total	673	100,0	998	100,0	370	100,0	50	100,0

Table 11

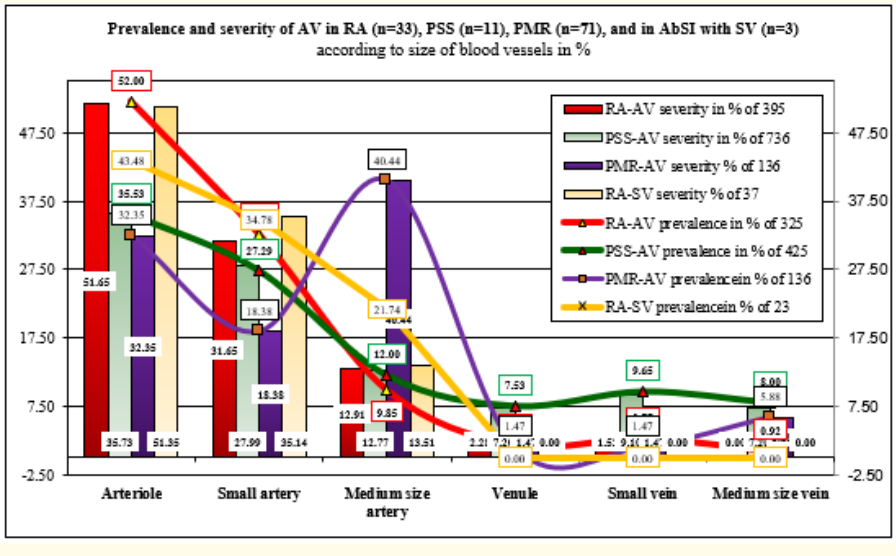

Figure 25: *Prevalence and severity of AV in patients with RA, PSS, PMR and SV in AbSI according to the involved blood vessels by size (in percentage of the total sum of affected blood vessels). AV and SV affected mainly the arterioles and small arteries in RA, PSS, PMR and in AbSI patients, while TA in PMR patients preferred the medium size arteries. In AbSI patients with SV the veins remained intact (were not affected). AV in RA, and SV in AbSI patients was dominated by the subacute-subchronic stages. Stages of AV in PSS were more advanced, and existed in subchronic-chronic stages. Stages of AV in PMR were more monotone, and existed in subacute-subchronic-chronic stages (Figure 26).*

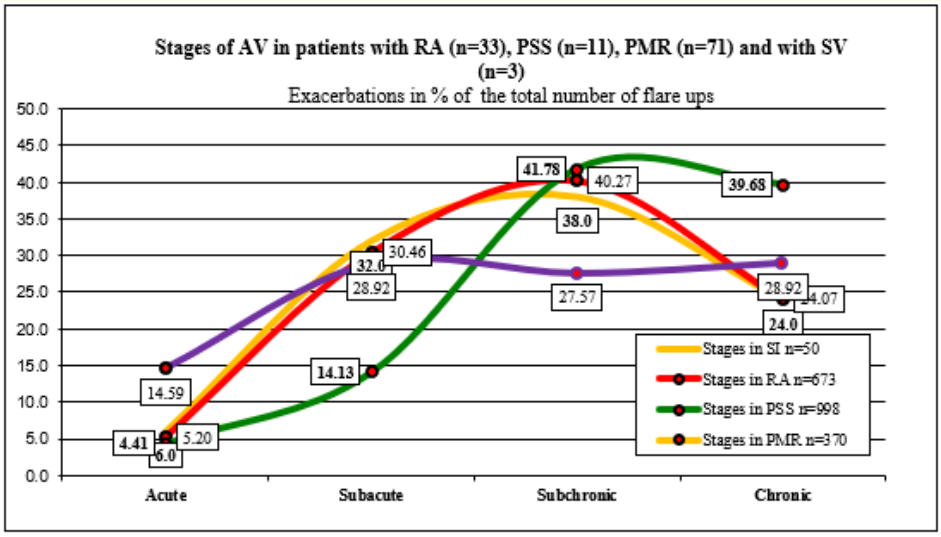

Figure 26: *Flare ups of AV in patients with RA, PSS, PMR and SV in AbSI according to the stages of vasculitis (in percentage of the total sum of prevalence). Flare ups of AV and SV in % of the total number of flare stages of vasculitis were similar in RA and AbSI; AV in PSS, and TA in PMR differed from these.*

In RA three types of AV occurred: non-specific, fibrinoid necrotic, and granulomatous vasculitis; granulomatous type was registered only in RA.

In PSS and AbSI the AV or SV were characterized by non-specific and occasionally by fibrinoid necrotic vasculitis.

In PMR only non-specific vasculitis was registered (Table 10 and figure 25).

Table 12 summarize the involvement of blood vessels with AV and SV in RA, PSS, PMR and AbSI patients (by size of blood vessels, and by types of vasculitis).

Absolute number	Arteriole	Small artery	Medium size artery	Venule	Small vein	Medium size vein	Total
AV in RA							
Ns	110	68	28	6	4	0	216
Fn	37	23	0	0	3	1	64
Gr	22	15	4	0	2	2	45
Total in RA	169	106	32	6	9	3	325
AV in PSS							
Ns	96	81	41	25	32	30	305
Fn	55	35	10	7	9	4	120
Gr	0	0	0	0	0	0	0

Total in PSS	151	116	51	32	41	34	425
TA in PMR							
Ns	44	25	55	2	2	8	136
Fn	0	0	0	0	0	0	0
Gr	0	0	0	0	0	0	0
Total in PMR	44	25	55	2	2	8	136
SV in RA							
Ns	8	6	5	0	0	0	19
Fn	2	2	0	0	0	0	4
Gr	0	0	0	0	0	0	0
Total in AbSI	10	8	5	0	0	0	23
In %							
AV in RA							
Ns	33,85	20,92	8,62	1,85	1,23	0,00	66,46
Fn	11,38	7,08	0,00	0,00	0,92	0,31	19,69
Gr	6,77	4,62	1,23	0,00	0,62	0,62	13,85
Total in RA	52,00	32,62	9,85	1,85	2,77	0,92	100,0
AV in PSS							
Ns	22,59	19,06	9,65	5,88	7,53	7,06	71,76
Fn	12,94	8,24	2,35	1,65	2,12	0,94	28,24
Gr	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Total in PSS	35,53	27,29	12,00	7,53	9,65	8,00	100,0
TA in PMR							
Ns	32,35	18,38	40,44	1,47	1,47	5,88	100,0
Fn	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Gr	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Total in PMR	32,35	18,38	40,44	1,47	1,47	5,88	100,0
SV in RA							
Ns	34,78	26,09	21,74	0,00	0,00	0,00	82,61
Fn	8,70	8,70	0,00	0,00	0,00	0,00	17,39
Gr	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Total in AbSI	43,48	34,78	21,74	0,00	0,00	0,00	100,0

Table 12: *AV and SV according to the size of affected vessels and according to the types of vasculitis. Non-specific and fibrinoid necrotic AV occurred in RA, and in PSS or in AbSI with SV. SV spared the veins. Granulomatous AV was observed only in RA; granulomatous vasculitis was not found in PSS, in PMR or in AbSI with SV.*

Abbreviations to table 12: RA: Rheumatoid Arthritis; PSS: Progressive Systemic Sclerosis; PMR: Polymyalgia Rheumatica; AbSI: Acute Bacterial Septic Infection with Lethal Outcome; AV: Systemic Autoimmune Vasculitis; TA: Temporal Arteritis; SV: Systemic Septic Vasculitis.

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

Discussion

Ad 1.

The PSS patients died earlier than the RA patients (with or without AV), and the PMR patients (with or without TA) died later.

The life expectancy of patients with AbSI was worse than the life expectancy of patients without AbSI, but low or high mean age (early or late death) occurred in all patient groups.

Differences of demographics not helped in differentiation of AV and SV.

Ad 2.

Rheumatoid nodule is the most severe form of necrotic AV in RA [20], and it may be considered as an absolute diagnostic histological sign of RA.

The granulomatous transformation of blood vessels (with or without fibrinoid necrosis) supports the clinical diagnosis of RA, and the autoimmune origin of systemic vasculitis.

Granulomatous transformation may be connected to the altered reactivity of the patients.

Granulomatous autoimmune vasculitis can be regarded as an indirect histological sign of dormant fibro-caseous tuberculosis (TB) with or without miliary dissemination, supported by the close relationship between granulomatous transformation of blood vessels, and epithelioid granulomas [21].

Ad 3

The classic clinical picture of PSS is characteristic and should not cause clinical problems in the diagnosis of the disease.

In the early stages of PSS - before the characteristic clinical symptoms develops - vascular changes responsible for organ symptoms are already present, which can aid in the early recognition of PSS and the establishment of a clinical diagnosis.

Thefibromuscular intimal proliferation (FIP), with or without fibrinoid necrosis of the blood vessels walls, is an absolute diagnostic histological sign of PSS.

Ad 4.

Two types of autoimmune large vessel vasculitis (LVV) are described: TA or cranial giant cell arteritis (GCA) in PMR and Takayasu arteritis (TAK), as independent (distinct) entities [22,23].

Structural changes of blood vessel (with more or less inflammatory infiltration) may be complicate a large number of autoimmune (RA, SLE, Polyarteritis nodosa etc.) and not autoimmune diseases (atherosclerosis, idiopathic aortitis, sarcoidosis etc.) [17,22,24].

Giant cell infiltration of blood vessels can occur in numerous autoimmune diseases, such as RA, SLE etc.; the presence of giant cells in vascular inflammation does not indicate in itself (alone) any of diseases.

We assume that the histological features of TA described in PMR are essentially identical with other LVV, which can be recognized and distinguished based on the characteristics of TA (blood vessel size, severity, and stage of inflammation).

Our study confirmed the systemic nature of TA.

All branches of the temporal blood vessels were affected with varying prevalence, severity, and stages of inflammation (flare-ups).

The close statistical correlations between inflamed arteries and veins of different sizes supported that the inflammation in all of these vessels is the manifestation of the same disease [5].

TA was characterized by the predominant involvement of medium-sized arteries, in contrast to autoimmune or septic vasculitis of RA and PSS.

The predominance of medium-sized arteries - as opposed to small arteries or arterioles, venules, and small and medium-sized veins - is thought to be associated with circulating antigens or immune complexes that are different from those involved in RA and PSS.

Ad 5.

The identification of pathogenic agents, and the strong, significant and positive correlation between AbSI and SV supported the septic origin of the systemic vasculitis.

SV was mostly "non-specific," fibrinoid necrosis occurred in the vessel walls, but granulomatous transformation of the vessel walls was not detected.

The patients probably died earlier, before the infectious agents reached the venous network via the organs and triggered an inflammatory response.

SV in RA was less common and less severe than AV in RA.

The progression of SV and AV run in parallel except the veins; the veins were spared in AbSI.

Granulomatous vasculitis and detection of phlebitis contradict the septic origin of systemic vasculitis, i.e., the absence of granulomatous vasculitis and phlebitis supported the histological diagnosis of SV.

Ad 6.

Vascular inflammation is intermittent or sector-like, i.e. intact and inflamed segments alternate (like beads on a rosary).

In severe vascular inflammation, the abnormal foci are densely interspersed, in mild vascular inflammation they are less frequent.

The AV may remain hidden even by histological examination if the excision involves an intact vascular segment; this may be particularly the case in mild vasculitis or in the early, initial stages of AV, when there are only a few inflamed vascular segments on a few edges.

Table 11 and 12 with figure 25 and 26 summarizes the most important histological sign between autoimmune and septic vasculitis demonstrating the possible histological differential diagnosis between these in RA, PSS or PMR patients.

The limitation of the study (without claiming to be exhaustive) is that despite the detailed dissection and examination of numerous organs, with 100-150 tissue samples taken per patient:

1. Complications may remain undetected, especially in the case of mild lesions or those in their early stages (perfect "processing" would only be ensured by embedding the entire body in paraffin).

2. Vascular inflammation is not continuous, is intermittent or sector-like, i.e. intact and inflamed segments alternate, so AV or SV may remain hidden even by histological examination if the excision involves an intact vascular segment.
3. Value of severity (maximal density of blood vessels /light microscopic field) is subjective (semiobjective only).
4. The examiner "sees what he knows" (the histologist recognizes what he knows).
5. The underlying autoimmune vasculitis often remains hidden, behind the dominant organic and ischemic tissue changes.
6. In cases of infection, aggressive (drastic) antibiotic therapy can eliminate inflammatory infiltration (cellular signs of inflammation), leaving only severe toxic organ and tissue damage visible.

Conclusion

Histological analysis of all available tissue samples of autoimmune diseases is important, and suggested.

Autoimmune and septic vasculitis could be distinguished from each other based on histological examination, based on the size of the affected vessels, on the type of vasculitis, and on the stage of inflammation (flare-ups).

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