

## Systemic and Pulmonary Autoimmune Vasculitis in Rheumatoid Arthritis - A Postmortem Clinicopathologic Study of 147 Autopsy Patients

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### Abstract

**Aim of the Study:** The aim of this study was to determine the incidence of systemic autoimmune vasculitis (sAV) in rheumatoid arthritis (RA), to appraise the involvement of bronchial or pulmonary blood vessels (pAV), and assess the influence of sAV and pAV on lung diseases related [or not related] to RA.

**Patients and Methods:** 147 random autopsy patients with RA were studied. RA was confirmed clinically according to the criteria of the American College of Rheumatology (ARA).

The incidence of sAV and prevalence of pAV was confirmed histologically.

Distinct forms of multifocal inflammation, such as purulent bronchitis or bronchiolitis (purBr), bronchopneumonia (BrPn), infarctpneumonia (InfPn), occlusive (obliterative or obstructive necrotizing) pneumonia (OcclPn), rheumatoid pneumonia (RhPn), furthermore interstitial pneumonia (IPn) were determined at autopsy and analyzed retrospectively, reviewing the clinical and pathological reports.

Demographics of different patient cohorts were compared with the Student (Welch) t-probe. The possible role of sAV or pAV on the prevalence of purBr or BrPn, InfPn, OcclPn, RhPn and IPn was analyzed with Pearson's chi-squared ( $\chi^2$ ) test.

**Results:** sAV complicated RA in 31 (21.08%) of 147 patients. Pulmonary or bronchial arteries and arterioles were involved by vasculitis in 15 (48.39%) of these 31 cases.

PurBr or BrPn were associated with RA in 18 (12.23%), InfPn in 5 (3.4%), OcclPn in 2 (1.4%), RhPn in 3 (2.1%) of 147 patients (only the fatal cases were considered). IPn was present in 35 (23.8% of 147) patients and contributed to the death only in association with cardiac, circulatory or cardio-respiratory insufficiency.

**Discussion and Conclusions:** sAV or pAV may complicate RA in both sexes, and at any time in the course of the disease, elderly (especially female) patients are more likely to be affected than younger or male patients. In elderly female and male patients with autoimmune disease and impaired immune reactivity the risk of purBr or BrPn is increased as well.

The so called rheumatoid pneumonia (RhPn) is a rare lethal complication of RA (n = 3 of 147; 2.4%) mostly generated by autoimmune vasculitis of bronchial arteries. RhPn is accompanied by transient (migratory) multifocal micronodular infiltrates by X ray, react poorly to antibiotics and the patients die suddenly and unexpectedly of rapidly progressive cardio-respiratory insufficiency. It is difficult to recognize clinically the real vasculogenic nature of lethal RhPns. In case of multifocal, transient (migratory) pneumonia which is refractory to antibiotics, RhPn should be considered; existing vasculitis or vasculitis in the medical history supports the vasculogenic origin of inflammation.

**Keywords:** Systemic; Bronchial and Pulmonary Autoimmune (Rheumatoid) Vasculitis; Lung Diseases

## Abbreviations

RA: Rheumatoid Arthritis; sAV: Systemic Vasculitis of Autoimmune Origin; pAV: Pulmonary Manifestation of sAV (Involvement of Bronchial Or Pulmonary Blood Vessels by Autoimmune Vasculitis); ARA: American College of Rheumatology; purBr: Purulent Bronchitis or Bronchiolitis; BrPn: Bronchopneumonia; InfPn -Infarct Pneumonia; OcclPn: Occlusive (Obliterative or Obstructive Necrotizing) Pneumonia; RhPn: Rheumatoid Pneumonia; IPn: Interstitial Pneumonia; SD: Standard Deviation; ND: No Data

## Introduction

Systemic autoimmune vasculitis (sAV) is one of the most important complications of rheumatoid arthritis (RA) [1]. A wide spectrum of lung diseases may complicate RA or is associated with RA [2-4].

## Aim of the Study

The aim of this study was to determine the incidence of sAV in RA, to appraise the involvement of bronchial or pulmonary blood vessels (pAV), and assess the influence of sAV and pAV on lung diseases related [or not related] to RA.

## Patients and Methods

147 random autopsy patients with RA were studied [4]. RA was confirmed clinically according to the criteria of the American College of Rheumatology (ARA) [5].

The incidence of sAV and prevalence of pAV was confirmed by a detailed review of extensive histological material in agreement with the recommendations of the Consensus Conference (2013) [6] and others Scott., *et al.* (1981) [7], Schilling and Fassbender (1988) [8]. From each patient a total of 50 - 100 tissue blocks of 12 organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) were studied microscopically.

Distinct forms of multifocal inflammation, such as purulent bronchitis or bronchiolitis (purBr), bronchopneumonia (BrPn), infarctpneumonia (InfPn), occlusive (obliterative or obstructive necrotizing) pneumonia (OcclPn), rheumatoid pneumonia (RhPn), furthermore interstitial pneumonia (IPn) [1-4] were determined at autopsy and analyzed retrospectively, reviewing the clinical and pathological reports.

Demographics of different patient cohorts were compared with the Student (Welch) t-probe [9]. The possible role of sAV or pAV on the prevalence of purBr or BrPn, InfPn, OcclPn, RhPn and IPn was analyzed with Pearson's chi-squared ( $\chi^2$ ) test [9].

## Glossary of definitions

**“Vasculitis”:** Concerns the presence of inflammatory infiltration and structural changes in blood vessels of different calibers.

**Systemic vasculitis of autoimmune origin (sAV):** Was defined as one of the basic manifestations of RA determined in 12 organs [4], excluding other causes of vasculitis, like hypertension diabetes mellitus, tumors, septic infections, etc.

**Incidence of sAV:** Concerns the average presence of vasculitis determined in 12 organs of RA patients.

**Prevalence of pulmonary vasculitis (pAV):** Means the prevalence of autoimmune vasculitis in the lung of RA patients with sAV, involving bronchial or pulmonary blood vessels of different calibers.

## Size of blood vessels [10]

- **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).

**Results**

sAV complicated RA in 31 (21.08%) of 147 patients. Bronchial or pulmonary arteries and arterioles were involved by vasculitis in 15 (48.39%) of these 31 cases; pAV was histologically excluded in 16 (51.6%) of 31 cases.

sAV led directly to death in 19 (12.92% of 147 and 61.29% of 31) patients due to coronary arteritis and thrombosis of the main coronary artery with a large myocardial infarct in 1, coronary arteriolitis and multiple focal microinfarctions of the myocardium (myocardiocytolysis) in 11, cerebral vasculitis and multifocal brain necrosis in 2, thrombovasculitis of renal artery and renal necrosis in 1 or thrombovasculitis of mesenteric artery and intestinal hemorrhagic necrosis in 1 cases, including 3 cases of bronchial and pulmonary vasculitis and multifocal pneumonia (2.04% of 147, 9.68% of 31 and 20.0% of 15 patients).

PurBr or BrPn were associated with RA in 18 (12.23%), InfPn in 5 (3.4%), OcclPn in 2 (1.4%), RhPn in 3 (2.1%) of 147 patients (only the fatal cases were considered). IPn - characterized by interstitial cellular infiltration with or without edema, fibrinoid deposition, with or without fibrosis, and with or without correspondent pleuritis - was present in 35 (23.8% of 147) patients; IPn alone was not fatal in our cohort and contributed to the death only in association with cardiac, circulatory or cardio-respiratory insufficiency.

In table 1 are summarized the demographics, onset and duration of disease of total population (n = 147), with (n = 31) and without (n = 116) sAV, with (n = 15) and without (n = 16) pAV, with (n = 18) and without (n = 129) PurBr or BrPn, with (n = 3) and without (n = 144) RhPn, with (n = 2) and without (n = 145) OcclPn, furthermore with (n = 35) and without (n = 112) IPn.

Sex	Number of autopsies	Mean age in years at death ± SD	Range (in years)	Mean age at onset of disease ± SD	Disease duration (in years) mean ± SD
RA patients (total)	147	65.63 ± 12.44	16 - 88	51.52 ± 16.63	14.06 ± 10.34
Female	104	65.10 ± 11.74	16 - 87	50.82 ± 15.45	14.29 ± 10.38
Male	43	66.91 ± 13.89	19 - 88	53.31 ± 19.24	13.49 ± 10.23
with sAV	31 of 147	67.35 ± 10.83	32 - 83	56.80 ± 14.86	11.73 ± 10.51
Female	18	67.22 ± 11.48	32 - 82	59.39 ± 10.42	10.67 ± 7.67
Male	13	67.46 ± 9.84	53 - 83	52.92 ± 19.07	13.33 ± 13.55
without sAV	116 of 147	65.17 ± 12.80	16 - 88	49.86 ± 16.81	14.78 ± 10.18
Female	86	64.65 ± 11.75	16 - 87	48.71 ± 15.76	15.16 ± 10.76
Male	30	66.67 ± 15.31	19 - 88	53.52 ± 19.33	13.57 ± 7.96
with pAV	15 of 31	62.20 ± 8.60	50 - 82	52.73 ± 13.88	12.47 ± 9.91
Female	10	67.10 ± 8.87	50 - 82	55.70 ± 7.59	11.40 ± 5.82
Male	5	61.40 ± 6.53	53 - 72	46.80 ± 20.25	14.60 ± 14.83
without pAV	16 of 31	69.38 ± 12.23	32 - 83	60.87 ± 14.68	11.00 ± 11.03
Female	8	67.38 ± 14.07	32 - 80	64.00 ± 11.58	9.75 ± 9.40
Male	8	71.25 ± 9.67	55 - 83	57.29 ± 16.88	12.43 ± 12.48
with purBr or BrPn	18 of 147	71.17 ± 6.12	61 - 83	52.14 ± 15.32	19.43 ± 12.23
Female	11	70.27 ± 6.90	61 - 83	48.11 ± 16.01	22.33 ± 12.76
Male	7	72.57 ± 4.27	64 - 79	59.40 ± 10.67	14.20 ± 9.13
without purBr or BrPn	129 of 147	64.86 ± 12.89	16 - 88	51.44 ± 16.78	13.38 ± 0.88
Female	93	64.48 ± 12.04	16 - 87	51.12 ± 15.36	13.39 ± 9.68
Male	36	65.81 ± 14.82	19 - 82	52.30 ± 20.14	13.37 ± 10.39
with OcclPn	2 of 147	58.50 ± 8.50	50 - 67	40.50 ± 4.50	18.00 ± 13.00
Female	2	58.50 ± 8.50	50 - 67	40.50 ± 4.50	18.00 ± 13.00
Male	0	-	-	-	-
without OcclPn	145 of 147	65.73 ± 12.46	16 - 88	51.69 ± 16.69	13.09 ± 10.28
Female	102	65.23 ± 11.76	16 - 87	51.06 ± 15.33	14.19 ± 10.29

Male	43	66.91 ± 13.89	19 - 88	53.31 ± 19.24	13.49 ± 10.23
with InfPn	5 of 147	68.00 ± 7.80	55 - 78	59.63 ± 15.18	7.13 ± 7.60
Female	5	68.00 ± 7.80	55 - 78	59.63 ± 15.18	7.13 ± 7.60
Male	0	-	-	-	-
without InfPn	142 of 147	65.55 ± 12.56	16 - 88	51.25 ± 16.61	14.28 ± 10.34
Female	99	64.95 ± 11.80	16 - 87	50.42 ± 15.34	14.60 ± 10.37
Male	43	66.91 ± 13.89	19 - 88	53.31 ± 19.24	13.49 ± 10.23
with RhPn	3 of 147	61.67 ± 2.62	58 - 64	53.67 ± 3.30	8.00 ± 3.56
Female	2	63.50 ± 0.50	63 - 64	54.00 ± 4.00	9.50 ± 3.50
Male	1	58.00 ± 0.00	58	53.00 ± 0.00	5.00 ± 0.00
without RhPn	144 of 147	65.72 ± 12.55	16 - 88	51.46 ± 16.82	14.20 ± 10.41
Female	102	65.13 ± 11.85	16 - 87	50.75 ± 15.60	14.38 ± 10.45
Male	42	67.12 ± 13.99	19 - 88	53.32 ± 19.52	13.74 ± 10.27
with IPn	35 of 147	63.63 ± 14.43	19 - 87	48.32 ± 18.12	13.94 ± 10.37
Female	23	62.83 ± 10.73	32 - 87	46.52 ± 13.78	15.67 ± 12.28
Male	12	65.17 ± 19.58	19 - 87	52.10 ± 24.45	10.30 ± 6.86
without IPn	112 of 147	66.33 ± 11.66	16 - 88	52.58 ± 15.96	14.16 ± 10.39
Female	82	65.76 ± 11.86	16 - 84	51.94 ± 15.64	14.04 ± 10.10
Male	30	67.87 ± 10.91	32 - 88	54.46 ± 16.71	14.50 ± 11.20

**Table 1:** Sex, mean age with SD, range, onset and disease duration (in years) of 147 RA patients complicated by or associated with sAV, pAV and lung diseases.

**Glossary to table 1**

RA: Rheumatoid Arthritis; sAV: systemic Autoimmune Vasculitis; pAV: pulmonary Autoimmune Vasculitis; purBr: purulent Bronchitis or Bronchiolitis; BrPn: Broncho Pneumonia; InfPn: Infarct Pneumonia; OcclPn: Occlusive Pneumonia; IPn: Interstitial Pneumonia; SD: Standard Deviation.

Comparing the age, sex, onset of RA, and duration of disease at the time of death, RA started significantly later in patients with sAV (n = 31) in comparison without sAV (n = 116) (56.80 years versus 49.86, p < 0.038); this difference was especially expressed in women (59.39 years versus 48.71, p < 0.002), who died notably earlier (10.67 years versus 15.16, p < 0.054).

There was no significant difference in survival time, onset or duration of RA between patient cohorts with sAV (n = 31) and with pAV (n = 15) (p < 0.48, p < 0.39, p < 0.86), neither between female (p < 0.98, p < 0.31, p < 0.79) and male (p < 0.19, p < 0.62, p < 0.89) or with (n = 15) and without pAV (n = 16) (p < 0.29, p < 0.14, p < 0.71), neither between female (p < 0.96, p < 0.13, p < 0.69) and male (p < 0.07, p < 0.42, p < 0.81).

sAV developed in both sexes, and at any time in the course of the disease, and the pulmonary blood vessels were involved by pAV in both sexes, and at any time in the course of the disease in patient's complicated with sAV (Tables 1 and 2).

The mean age of RA patients was significantly higher with purBr or BrPn (n = 18) in comparison to total population (n = 147) (71.17 years versus 65.63, p < 0.004), either in female (70.27 years versus 65.10, p < 0.052) and male (72.57 years versus 66.91, p < 0.050).

The mean age of RA patients was significantly higher with purBr or BrPn (n = 18) in comparison to patient cohorts without purBr or BrPn (n = 129) (71.17 years versus 64.86, p < 0.002), either in female (70.27 years versus 64.48, p < 0.034) and male (72.57 years versus 65.81, p < 0.034).

Comparing the age, sex, onset of RA, and duration of disease at the time of death there was no significant difference in survival time, onset and duration of disease between RA patients with (n = 2) and without OcclPn (n = 145) (p < 0.55, p < 0.21, p < 0.81), with (n = 5) and without InfPn (n = 142) (p < 0.57, p < 0.41, p < 0.20), with (n = 3) and without RhPn (n = 144) (p < 0.14, p < 0.47, p < 0.11), furthermore with (n = 35) and without IntPn (n = 112) (p < 0.32, p < 0.25, p < 0.91) neither between female (p < 0.27, p < 0.14, p < 0.56) and male (p < 0.67, p < 0.79, p < 0.21) patients.

OcclPn, InfPn, RhPn and IntPn developed in both sexes, and at any time in the course of the disease (Tables 1 and 2).

The relationship (“p” values of correlation) of demographics, onset and duration of disease between RA patients with and without sAV, pAV, purBr-BrPn, OcclPn, InfPn, RhPn or IPn are summarized in table 2.

RA patients (Lung) n = 147	Age	Onset of disease	Disease duration
RA n = 147 versus with sAV n = 31 of 147	p < 0.444	p < 0.098	p < 0.288
Female n = 104 of 147 versus n = 18 of 31	p < 0.488	p < 0.008	p < 0.105
Male n = 43 of 147 versus n = 13 of 31	p < 0.877	p < 0.953	p < 0.973
with sAV n = 31 versus without sAV n = 116 of 147	p < 0.349	p < 0.038	p < 0.175
Female n = 18 of 31 versus n = 86 of 116	p < 0.409	p < 0.002	p < 0.054
Male n = 13 of 31 versus n = 30 of 116	p < 0.844	p < 0.933	p < 0.959
with sAV n = 31 versus with pAV n = 15 of 31	p < 0.482	p < 0.386	p < 0.825
Female n = 18 of 31 versus n = 10 of 31	p < 0.976	p < 0.313	p < 0.787
Male n = 13 of 31 versus n = 5 of 31	p < 0.191	p < 0.616	p < 0.886
with pAV n = 15 of 31 versus without sAV n = 116 of 147	p < 0.992	p < 0.491	p < 0.426
Female n = 10 of 15 versus n = 86 of 116	p < 0.461	p < 0.037	p < 0.122
Male n = 5 of 15 versus n = 30 of 116	p < 0.248	p < 0.898	p < 0.564
with pAV n = 15 vs. without pAV n = 16 of 31	p < 0.294	p < 0.143	p < 0.714
Female n = 10 of 15 versus n = 8 of 16	p < 0.965	p < 0.128	p < 0.691
Male n = 5 of 15 versus n = 8 of 16	p < 0.070	p < 0.418	p < 0.816
with purBr or BrPn n = 18 vs. without purBr or BrPn n = 129	p < 0.002	p < 0.878	p < 0.106
Female n = 11 of 18 versus n = 93 of 129	p < 0.034	p < 0.622	p < 0.686
Male n = 7 of 18 versus n = 36 of 129	p < 0.034	p < 0.305	p < 0.872
with OcclPn n = 2 vs. without OcclPn n = 145	p < 0.550	p < 0.215	p < 0.810
Female n = 2 of 2 versus n = 102 of 145	p < 0.573	p < 0.224	p < 0.819
Male n = 0 of 2 versus n = 43 of 145	-	-	-
with InfPn n = 5 vs. without InfPn n = 142	p < 0.573	p < 0.412	p < 0.201
Female n = 5 of 5 versus n = 99 of 142	p < 0.490	p < 0.373	p < 0.186
Male n = 0 of 5 versus n = 43 of 142	-	-	-
with RhPn n = 3 vs. without RhPn n = 144	p < 0.141	p < 0.473	p < 0.118
Female n = 2 of 3 versus n = 102 of 144	p < 0.213	p < 0.561	p < 0.380
Male n = 1 of 3 versus n = 42 of 144	-	-	-
with IPn n = 35 vs. without IPn n = 112	p < 0.324	p < 0.255	p < 0.919
Female n = 23 of 35 versus n = 82 of 112	p < 0.274	p < 0.141	p < 0.566
Male n = 12 of 35 versus n = 30 of 112	p < 0.672	p < 0.795	p < 0.210

**Table 2:** The statistical correlations (“p” values of significance) between female and male RA patients with and without sAV, pAV, sAAa, pAAa, purBr-BrPn, OcclPn, InfPn, RhPn or IPn.

Glossary to table 2

RA: Rheumatoid Arthritis; sAV: systemic Autoimmune Vasculitis; pAV: pulmonary Autoimmune Vasculitis; purBr: purulent Bronchitis or Bronchiolitis; BrPn: Broncho Pneumonia; InfPn: Infarct Pneumonia; OcclPn: Occlusive Pneumonia; IPn: Interstitial Pneumonia; SD: Standard Deviation.

sAV (n = 31) or pAV (n = 15) was associated with purBr or BrPn in 2 (11.11%) of 18, InfPn in 1 (20.0%) of 5, OcclPn in 1 (50.0%) of 2, RhPn in 3 (100.0%) of 3, IPn in 7 (20.0%) of 35 patients.

The relationship between sAV and purBr or BrPn (\*c = 0.3976,  $\chi^2 = 0.6388$ , p < 0.42), InfPn (\*c = 0.0345,  $\chi^2 = 0.2470$ , p < 0.62), OcclPn (c = 0.5862,  $\chi^2 = 0.0186$ , p < 0.89) or IPn (\*c = 0.0435,  $\chi^2 = 0.0327$ , p < 0.85) was not significant (even in case of purBr or BrPn, InfPn and IPn the relationships were inverse, based on the negative association's coefficients).

The relationship between pAV and purBr-BrPn (c = 0.0545,  $\chi^2 = 0.0783$ , p < 0.77), InfPn (c = 0.3913,  $\chi^2 = 0.00024$ , p < 0.98) or OcclPn (c = 0.8069,  $\chi^2 = 0.4844$ , p < 0.48) was not significant.

There was a significant and positive correlation between sAV and RhPn (c = 1.0,  $\chi^2 = 7.1301$ , p < 0.007) or pAV and RhPn (c = 1.0,  $\chi^2 = 17.8743$ , p < 0.00002), furthermore between pAV and IPn (c = 0.5294,  $\chi^2 = 4.8109$ , p < 0.028).

The statistical link between sAV (n = 31) or pAV (n = 15) and coexistent complications or associated diseases in 147 RA patients is summarized in table 3.

The prevalence of complications or associated diseases in 147 RA patients with or without sAV	The co-existent complications or associated diseases in RA patients with sAV (n = 31) or pAV (n = 15)	The statistical link (with association coefficient - c) between sAV and complications or associated disease in 147 RA patients	The statistical link (with association coefficient - c) between pAV and complications or associated disease in 147 RA patients
purBr or BrPn: n = 18 (12.23 %) of 147	purBr or BrPn: n = 2 (11.1 %) of 18	c*: -0.3976 <b><math>\chi^2 = 0.6388</math>, p &lt; 0.42</b>	c: 0.0545 <b><math>\chi^2 = 0.0783</math>, p &lt; 0.77</b>
InfPn: n = 5 (3.4 %) of 147	InfPn: n = 1 (20.0 %) of 5	c*: -0.0345 <b><math>\chi^2 = 0.2470</math>, p &lt; 0.61</b>	c: 0.3913 <b><math>\chi^2 = 0.00024</math>, p &lt; 0.981</b>
OcclPn: n = 2 (1.4 %) of 147	OcclPn: n = 1 (50.0 %) of 2	c: 0.5862 <b><math>\chi^2 = 0.0186</math>, p &lt; 0.89</b>	c: 0.80691 <b><math>\chi^2 = 0.4844</math>, p &lt; 0.48</b>
RhPn: n = 3 (2.1 %) of 147	RhPn: n = 3 (100.0 %) of 3	c: -1.0 <b><math>\chi^2 = 7.1301</math>, p &lt; 0.007</b>	c: -1.0 <b><math>\chi^2 = 17.3743</math>, p &lt; 0.00002</b>
IPn: n = 35 (23.8 %) of 147	IPn: n = 7 (20.0 %) of 35	c*: -0.0435 <b><math>\chi^2 = 0.0327</math>, p &lt; 0.85</b>	c: 0.5294 <b><math>\chi^2 = 4.8109</math>, p &lt; 0.028</b>

**Table 3:** The influence of sAV or pAV on the prevalence of coexistent complications or associated diseases in 147 RA patients.

**Glossary and legend to table 3**

c: Association Coefficient; \*: Asterisk indicates negative value of association's coefficient (invers relationship between sAV and complications or associated disease in 147 RA patients).

*Bold indicates significant value.*

*There was a significant and positive correlation.*

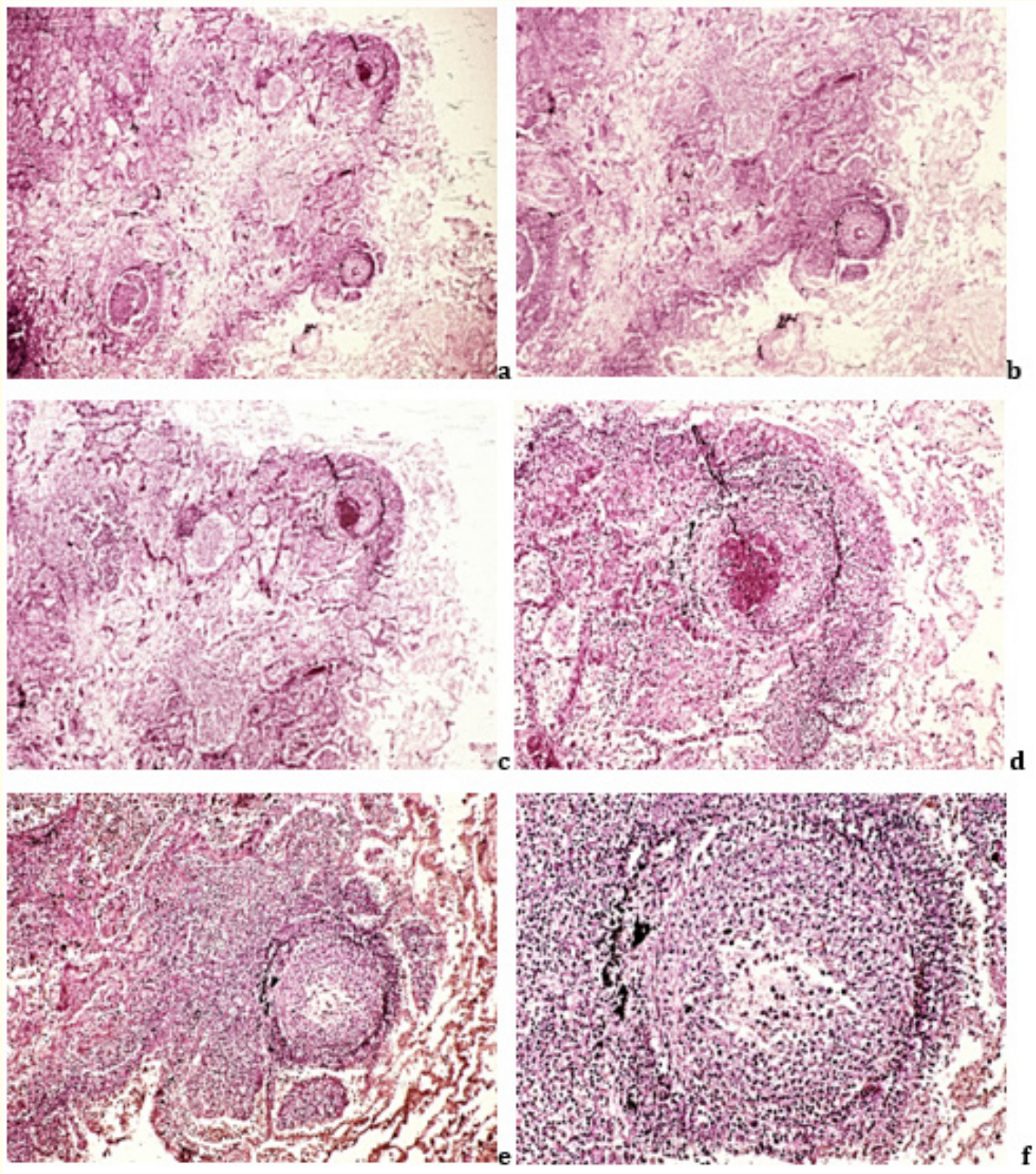
*Between sAV and prevalence of RhPn (c = 1,  $c^2 = 7.1301$ , p < 0.007)*

*Between pAV and prevalence of RhPn (c = 1,  $c^2 = 17.3743$ , p < 0.00002) and*

*Between pAV and prevalence of IPn (c = 0.5294,  $c^2 = 4.8109$ , p < 0.028).*

Figures 1-4 show different types and stages of autoimmune bronchial or pulmonary vasculitis, with or without subsequent (consecutive) sublobular or lobular inflammation.

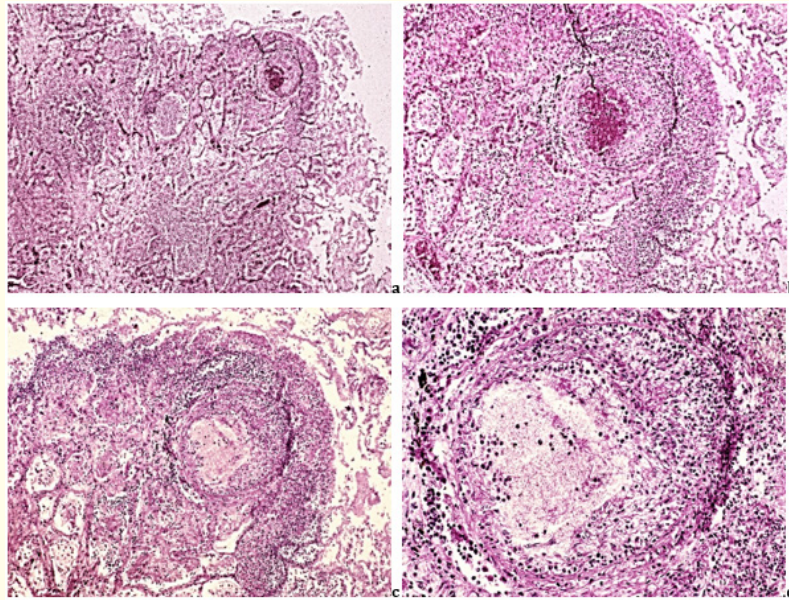
Original magnifications correspond to the 24x36 mm transparency slide; the correct height: width ratio is 2:3. The printed size may be different therefore the original magnifications are indicated.



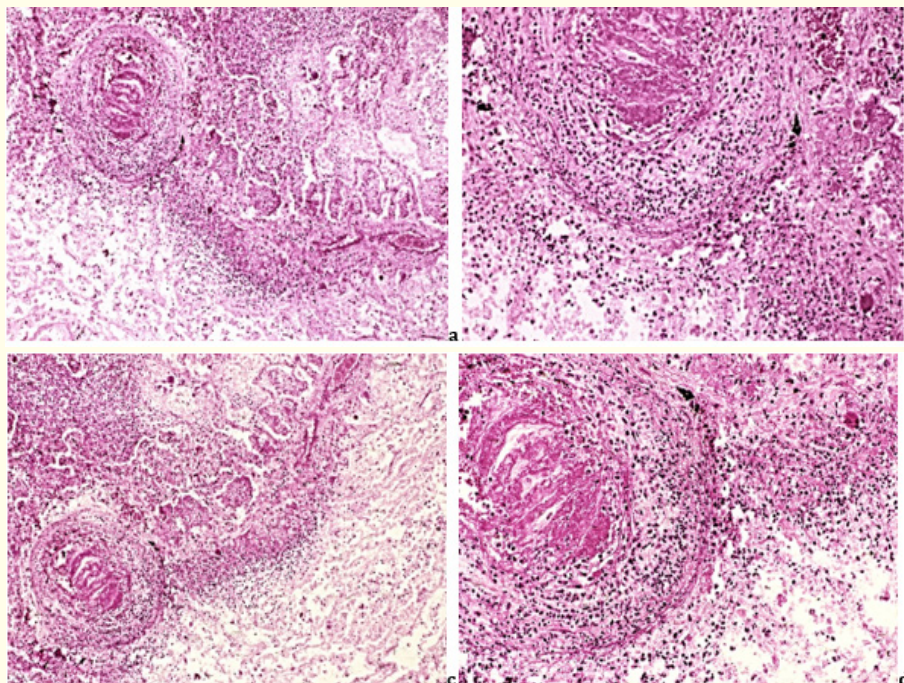
**Figure 1a-1f:** RA, lung, small bronchial arteries.

*Non-specific, subacute necrotizing vasculitis, with incipient sublobular pneumonia.*

*(a) HE, x20 (b) same as (a) x50, (c) same as (a) x50, (d) same as (c) x125, (e) same as (b) x125, (f) same as (e) x200.*

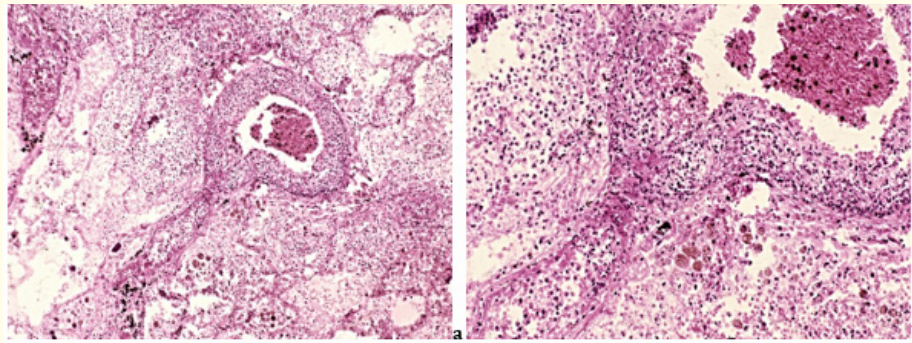


**Figure 2a-2d:** RA, lung, small bronchial artery (same are as figure 1c-d in deeper sections of the tissue blocks)  
Non-specific, subacute necrotizing vasculitis, with sublobular pneumonia.  
(a) HE, x50 (b) same as (a) x125, (c) HE, x125 (d) same as (c) x200.



**Figure 3a-3d:** RA, lung, small bronchial artery and arteriole.  
Non-specific, necrotizing subacute vasculitis, with sublobular pneumonia.  
(a) HE, x125 (b) same as (a) x200, (c) same as (a) rotated 45 degrees, x125 (d) same as (c) x200.





**Figure 4a and 4b:** RA, lung, small pulmonary artery and arteriole junction, non-specific, acute (necrotizing) vasculitis, with incipient regional sublobular pneumonia. (a) HE, x125 (b) same as (a) x200.

**Discussion**

“Systemic vasculitis is a very rare but serious complication of rheumatoid arthritis and may be considered one of the most serious extra-articular consequences of this disease” [11]. Rheumatoid vasculitis usually occurs in patients with severe, longstanding, nodular, destructive RA [12] and usually affects the nail edges and nail folds, and is often accompanied by inflammation of the eyes (iritis, scleritis), polyserositis (pericarditis, pleuritis, fibrosing alveolitis (e.g. interstitial pneumonitis), neuropathy (“mononeuritis multiplex”) [11]. Palpable purpura, cutaneous ulcers (particularly in the malleolar region), digital infarctions are characteristics as well [12]. The majority of RA patients with vasculitis is seropositive and has elevated inflammatory markers [13].

Unfortunately, the classic clinical-laboratory parameters mentioned in the pertinent literature as (Latex, BUN, creatinine, albumin, alfa-2 globulin, CRP, Waaler-Rose, RBC, and ESR) are not specific for vasculitis and do not predict vasculitis. They are related to the basic activity of RA, to renal complications of RA or to the actual intensity of inflammatory processes of the disease [14-16].

For a definite diagnosis of rheumatoid vasculitis muscle biopsies simultaneously with nerve biopsies are suggested which increase the diagnostic yield of the procedure [12,17].

“Treatment of systemic rheumatoid vasculitis is with immunosuppressive drugs, particularly cyclophosphamide accompanied by corticosteroids. Once remission has been achieved, usually within 3 - 6 months, patients may be switched to alternatives such as methotrexate or azathioprine” [11].

The early literature on autopsy of RA patients does not or only sporadically mentions pulmonary vasculitis (involving the bronchial or pulmonal arteries), and without analysis of consequences (Table 4).

Authors	Year of publications [References]	Autopsy n	Prevalence of vasculitis n - %	Mortality of vasculitis n - %	Pulmonary vasculitis n - %
Cruickshank	1954 [18]	72	18*/72-25.0% 11/18-61.1%	ND	ND
Sinclair and Cruickshank	1956 [19]	16	9/16 - 56.3%	3/9 - 33.3%	1/9 - 11.1%
Cruickshank <sup>2*</sup>	1958 [20]	100	20 <sup>2*</sup> /100 - 20.0%	ND	ND
Lebowitz	1963 [21]	62	6/62 - 9.68%	ND	ND
Sokoloff <sup>2*</sup>	1964 [22]	19	2 <sup>2*</sup> /19 - 10.52%	ND	ND
Karten	1969 [23]	102	6/102 - 5.9%	ND	ND

Gardner	1972 [24]	142	7/142 - 4.93%	ND	ND
Davis and Engleman	1974 [25]	62	6/62 - 9.68%	1/62 - 1.6% 1/6 - 16.7%	ND
Eulderink	1976 [26]	111	ND	7/111 - 6.3%	ND
Albada-Kuipers., <i>et al.</i>	1986 [27]	173	17 - 9.83%	ND	ND
Boers., <i>et al.</i>	1987 [28]	132	18/132 - 13.6%	ND	ND
Suzuki., <i>et al.</i>	1994 [29]	81	25 - 30.8%	ND	ND
Bély and Apáthy	1994 [30]	161	36 <sup>3*</sup> - 22.4%	19 - 11.8%	ND
Bély and Apáthy	2005 [31]	234	50 <sup>4*</sup> - 21.4	23 - 9.8%	ND
Bély and Apáthy	2012 [4]	161	33/161 - 20.5%	19/161, 11.8% 19/33, 57.57%	ND
Bély and Apáthy	2018 [32]	234	43/234 - 18.4%	26/234, 11.1% 26/43, 60.5%	ND
Bély and Apáthy	present study	147	31/147 <sup>5*</sup> - 21.08%	19/147, 12.9% 19/31, 61.3%	15/147, 10.2% 15/31, 48.39%

**Table 4:** Prevalence of systemic and pulmonary vasculitis in autopsy material of rheumatoid arthritis (in most cases systemic vasculitis was regarded as a complication of RA).

**Glossary to table 4**

1\*: The origin was not mentioned in 7 of 18 systemic vasculitis; in 11 patients vasculitis was regarded as of autoimmune origin.

2\*: Coronary arteritis.

3\*: Systemic vasculitis of septic origin in 3 of 36 patients (the rest were regarded of autoimmune origin).

4\*: Systemic vasculitis of septic origin in 7 of 50 patients patients (the rest were regarded of autoimmune origin).

5\*: Of 161 patients with RA only 147 lungs were available.

The main complications of RA such as sAV or pulmonary manifestation of sAV (involvement of bronchial or pulmonary blood vessels by autoimmune vasculitis) may be present with higher risk in different patient cohorts, and may influence the prevalence, clinical course and symptoms of associated lung diseases and vice versa. Knowledge of these relationships is important to estimate the relative danger they potentially represent.

In our patient cohorts the risk of autoimmune vasculitis was significantly higher in elderly female RA patients with sAV (n = 18) or pAV (n = 10) than in female RA patients (n = 86) who did not have vasculitis (59.39 years versus 50.82, p < 0.002, resp. 55.70 years versus 50.82, p < 0.037). The chance of survival of female patients with sAV was lower than for female RA patients who did not have vasculitis (10.67 years versus 14.29, p < 0.054); the disease duration in female patients with pAV was also shorter than in female patients without sAV, but this difference was not significant (11.40 years versus 15.16, p < 0.122 - NS). In Vollertsen’s study (1986) patients with rheumatoid vasculitis had a decreased survival in comparison with an age-, sex-, and region-matched general population, and their survival was also decreased in comparison to that of an incidence cohort of community patients with rheumatoid arthritis as well [15].

There was no significant difference in survival time, onset or duration of RA between patient cohorts with sAV (n = 31) and with pAV (n = 15) (p < 0.48, p < 0.39, p < 0.86), neither between female (p < 0.98, p < 0.31, p < 0.79) and male (p < 0.19, p < 0.62, p < 0.89); sAV or pAV may complicate RA in both sexes, and at any time in the course of the disease, and the elderly (especially female) patients are more compromised, than the younger or male patients.

In elderly patients (n = 18) the risk of purBr or BrPn was significantly higher in comparison to total population (n = 147) (71.17 years versus 65.63, p < 0.004), either in female (70.27 years versus 65.10, p < 0.052) and male (72.27 years versus 66.91, p < 0.050) or in comparison to patient cohorts without purBr or BrPn (n = 129) (71.17 years versus 64.86, p < 0.002), either in female (70.27 years versus 64.48, p < 0.034) or male patients (72.57 years versus 65.81, p < 0.034). The high risk of purBr or BrPn in elderly female and male patients may be due to the impaired immune reactivity of senescent patients with autoimmune disease.

Autoimmune vasculitis associated with multifocal inflammation in the lungs (namely RhPn), may be regarded as a special pulmonary manifestation of sAV and pAV or a new vasculogenic entity in RA [33,34]. This possibility is supported by the strong positive statistical correlation between sAV and RhPn ( $c = 1$ ,  $\chi^2 = 7.1301$ ,  $p < 0.007$ ) or pAV and RhPn ( $c = 1$ ,  $\chi^2 = 17.3743$ ,  $p < 0.00002$ ) according to our pertinent study.

The level of significance between pAV and RhPn exceeded the level of significance between sAV and RhPn ( $\chi^2 = 17.3743$ ,  $p < 0.00002$  versus  $\chi^2 = 7.1301$ ,  $p < 0.007$ ), indicating a more direct and closer relationship between pulmonary vasculitis and RhPn than sAV and RhPn.

The significant correlation between pAV and IPn suggests a positive influence of pulmonary vasculitis on IPn ( $c = 0.5294$ ,  $\chi^2 = 4.8109$ ,  $p < 0.02$ ).

The not significant correlations advocate that purBr or BrPn, InPn and OcclPn are independent entities, which are not influenced by sAV or pAV.

Severe necrotizing vasculitis (with or without thrombosis), plays a major role in the pathogenesis of vasculogenic or so-called rheumatoid pneumonia (RhPn). Diminished blood supply due to vasculitis distal to the involved vessels may result in ischemia and develop vulnerable territories (*loci minoris resistentiae*) for a secondary infection (via bronchogenic or hematogenic route). According to the size of involved vessels lobular or sublobular pneumonia may develop, more or less respecting the anatomic borders of pulmonary units (Figures 1-4). The inflammation does not have a hemorrhagic character, in contrast to infarct-pneumonia due to thrombovasculitis with simultaneous venous congestion. Vasculogenic RhPn differs from bronchopneumonia as well, which is bronchocentric, has no sharply demarcated borders at the periphery and is independent of the fine anatomic borders of the lung.

The size of inflammatory foci depends on the size of involved vessels; in most cases lobular or sublobular pulmonary units (supplied by the bronchial or pulmonary small arteries or arterioles) are inflamed and the diameter of the inflamed territories is usually less than 20 - 10 millimeters.

The proper blood supply of the lungs depends primarily on the bronchial arteries via the aorta, whereas the pulmonary arteries transport oxygen deficient blood from right heart. In all of our three patients the inflammatory foci of RhPn were associated mainly with bronchial arteritis, but vasculitis of pulmonary arteries (with or without consecutive distal inflammation) was also present [33,34].

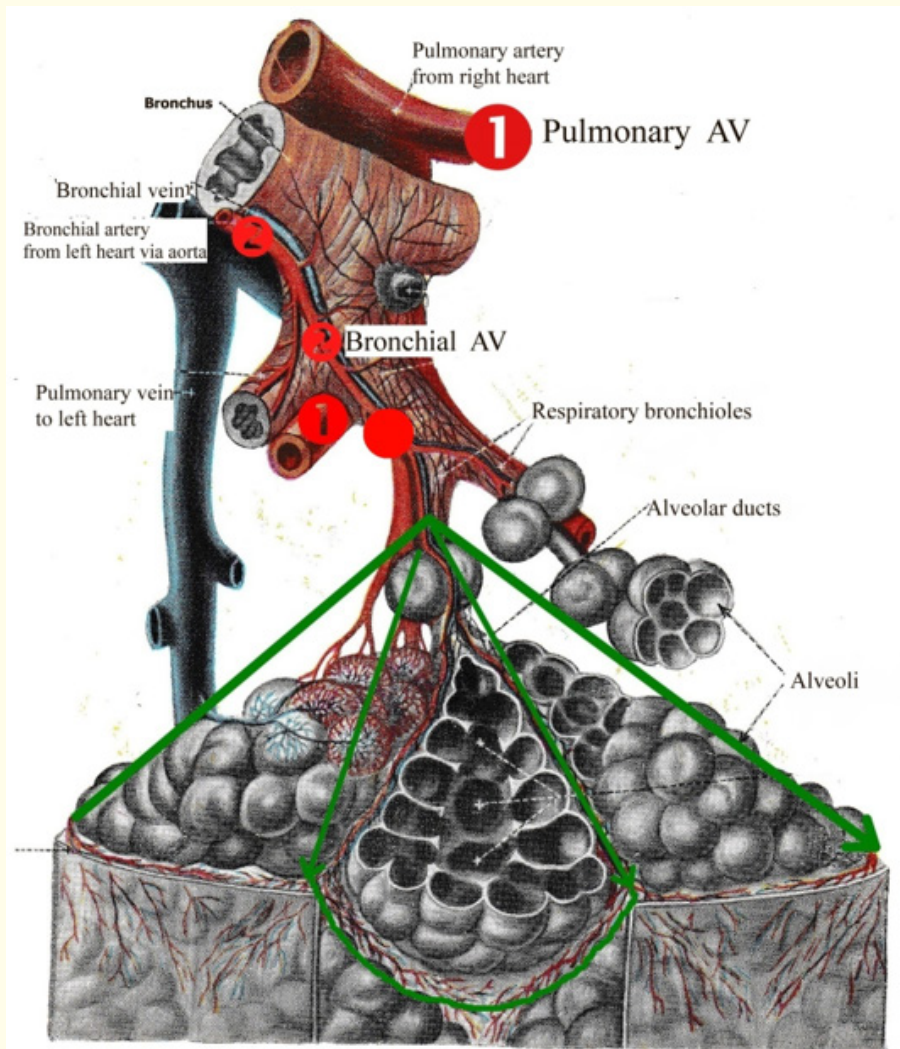
Any forms of immune mediated or autoimmune vasculitis are of a relapsing-recurrent nature [4]. Sectorial or segmental cellular infiltration in different stages of inflammation and chronic structural changes of the vessel wall existing side by side indicate the relapsing nature of autoimmune vasculitis.

The repetitive and progressive process of pAV leads to the silent accumulation of inflammatory foci side by side in different stages of inflammation. The number of inflammatory foci (severity RhPn) depends on the number of involved vessels and on the frequency of repeated exacerbation of vasculitis.

Clinically it is difficult to recognize the pAV and the consequent small, silently accumulating inflammatory foci in the lungs. The history of vasculitis, transient pulmonary complaints with or without fever may help in the diagnosis.

Antibiotics may only temporarily suppress successive bouts of inflammation generated by vasculitis; successful therapeutic effect is expected only from immunosuppressive drugs by controlling the basic process of autoimmune vasculitis.

Schematic portrayal of anatomic background and formal pathogenesis of disseminated (multifocal) lobular-sublobular pneumonia generated by autoimmune bronchial or pulmonary vasculitis (so called rheumatoid pneumonia - RhPn) is demonstrated in figure 5.



**Glossary and legend to figure 5:**

- 1 - Different stages of sectorial or segmental autoimmune vasculitis of pulmonary arteries or arterioles
- 2 - Different stages of sectorial or segmental autoimmune vasculitis of bronchial arteries or arterioles

**Formal pathogenesis of RhPn**

Severe necrotizing vasculitis, with or without thrombosis leads to a diminished blood supply distal to the involved vessel and results in ischemia producing vulnerable territories (*loci minoris resistentiae*) for a secondary infection (via a bronchogenic or hematogenic route). According to the size of involved vessels lobular or sublobular pneumonia may develop (usually less than 10 - 20 millimeters in diameter), more or less respecting the anatomic borders of pulmonary units.

- The inflammation does not have a basically hemorrhagic character, in contrast to infarct-pneumonia due to thrombembolisation with simultaneous venous congestion.
- Vasculogenic RhPn respects the fine anatomic borders of the lung, and differs from bronchopneumonia as well, which is bronchocentric, has no sharply demarcated borders and is independent of the fine anatomic borders of the lung.
- Any forms of autoimmune vasculitis are of a relapsing (recurrent) nature, leading to the silent accumulation of inflammatory foci existing side by side in different stages of inflammation. The number of inflammatory foci (severity RhPn) depends on the number of involved vessels and on the frequency of repeated exacerbation of vasculitis [33,34].

## Conclusions

sAV or pAV may complicate RA in both sexes, and at any time in the course of the disease, elderly (especially female) patients are more likely to be affected than younger or male patients.

In elderly female and male patients with autoimmune disease and impaired immune reactivity the risk of purBr or BrPn is increased as well.

The so called rheumatoid pneumonia (RhPn) is a rare lethal complication of RA (n = 3 of 147; 2.4%) mostly generated by autoimmune vasculitis of bronchial arteries.

RhPn is accompanied by transient (migratory) multifocal micronodular infiltrates by X ray, react poorly to antibiotics and the patients die suddenly and unexpectedly of rapidly progressive cardio-respiratory insufficiency. It is difficult to recognize clinically the real vasculogenic nature of lethal RhPns.

In case of multifocal, transient (migratory) pneumonia which is refractory to antibiotics, RhPn should be considered; existing vasculitis or vasculitis in the medical history supports the vasculogenic origin of inflammation.

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