Research Article

Fatal complications of rheumatoid arthritis and associated diseases of the lungs – A postmortem clinicopathologic study of 147 patients

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Abstract

Background

*Systemic autoimmune vasculitis (**sAV**), systemic AA amyloidosis (**sAAa**) generalized lethal septic infection (**SI**) with or without purulent arthritis (**PA**) are the most important complications of rheumatoid arthritis (**RA**), which may involve the lungs.*
*In addition to these complications of **RA** (**sAV**, **sAAa**, **SI**), a wide spectrum of lung diseases multifocal pneumonia (**mfPn**), tuberculosis (**TB**) or malignant tumors (**mTu**) may associate with **RA**.*

*This study aimed to determine that group of patients in which the risk of complications and associated diseases is the highest based on the age, sex of patients, onset and duration of **RA**, furthermore to evaluate the proportion of mortality and missed diagnosis.*

Patients and Methods

147 *random autopsy patients with* ***RA*** *were studied.* ***RA*** *was confirmed clinically according to the criteria of the* ***ACR****.*

The prevalence of complications and associated diseases of the lungs was confirmed by a detailed review of extensive histological material.

Results

Elderly (especially female) patients were more likely to be affected by ***sAV*** *than younger or male patients.* ***sAV*** *complicated* ***RA*** *in* ***31*** *(****21.08****%) of* ***147*** *patients and led directly to death in* ***19*** *(12.92% of 147).* ***sAV*** *was clinically* ***recognized*** *in* ***5*** *(****16.13*** *%) of 31 patients.*

The ***ratio*** *of* ***diagnosed*** *(n=5) and* ***missed*** *(n=26) cases of* ***sAV*** *was:* ***0.19*** *(5:26 of 31).*

Amyloidosis developed in both sexes, and at any time in the course of the disease. ***sAAa*** *complicated* ***RA*** *in* ***34*** *(****23.13****%) of* ***147*** *patients and was fatal in* ***17*** *(11.56 % of 147) patients.* ***sAAa*** *with uremia was clinically diagnosed in* ***9*** *(****26.47*** *%) of 34 patients.*

The ***ratio*** *of* ***diagnosed*** *(n=9) and* ***missed*** *(n=25) cases of* ***sAAa*** *was:* ***0.36*** *(9:25 of 34).*

Fatal ***SI*** *with or without* ***PA*** *developed in both sexes, and at any time in the course of the disease.* ***SI*** *complicated* ***RA*** *in* ***22*** *(****14.97*** *%) of* ***147*** *patients, in association with* ***PA*** *in* ***11*** *(50.0 %) of* ***22*** *patients.* ***SI*** *was clinically diagnosed in* ***9*** *(****0.41*** *%) of 22, and* ***PA*** *in* ***5*** *(****45.45*** *%) of 11 cases. The* ***ratio*** *of* ***diagnosed*** *(n=9) and* ***missed*** *(n=13)* ***fatal*** *cases of* ***SI*** *was:* ***0.69*** *(9:13 of 22), and it was:* ***0.83*** *(5:6 of 11) in cases of* ***PA****.*

The prevalence of ***mfPn*** *was higher in our elderly female and male autoimmune patients with impaired immune function than in younger.*

Distinct forms of ***mfPn*** *with fatal outcomes were detected in* ***28*** *(****19.05*** *%) of 147 patients.* ***mfPn*** *was clinically diagnosed in* ***19*** *(****67.86*** *%) of 28 patients.*

The ***ratio*** *of* ***diagnosed*** *(n=19) and* ***missed*** *(n=9)* ***fatal*** *cases of* ***mfPn*** *was:* ***2.11*** *(19:9 of 28).*

Conclusions:

*Complications of **RA** (**sAV**, **sAAa**, **SI**) and/or allied disorders of the lungs (**mfPn**, **TB**, **mTu**) were present in **111** (75.51 % of 147) patients, accompanying **RA** in both sexes and at any time in the course of **RA**.*

*Only **36** (24.49 % of 147) patients were found without complications or allied disorders of the lungs, which died of consequences of atherosclerosis (**Ath**) or accidental (post-operative embolia in one case).*

*The ratio of **diagnosed** and **missed** cases was very bad in case of **sAV** (0.19) in contrast to **sAAa** (0.36), **SI** (0.69) or **PA** (0.83).*

*Between associated diseases of the lungs, the **TB** (0.11) topped the list as the most dangerous and life-threatening diseases compared to the **mTu** (0.75) or **mfPn** (2.11).*

Keywords

Rheumatoid arthritis, autoimmune vasculitis, AA amyloidosis, lethal septic infection, purulent arthritis, multifocal pneumonia, tuberculosis malignant tumors.

Abbreviations:

RA – Rheumatoid **A**rthritis

ACR – American **C**ollege of **R**heumatology

sAV – systemic **A**utoimmune **V**asculitis

pAV – pulmonary **A**utoimmune **V**asculitis

sAAa – systemic **AA a**myloidosis

pAAa – pulmonary **AA a**myloidosis (amyloid A deposits in the lungs)

RhV – Rheumatoid **V**asculitis

SI – Septic **I**nfection with fatal outcome

PA – Purulent **A**rthritis

IPn – Interstitial **Pn**eumonitis

mfPn – multifocal **Pn**eumonia with fatal outcome

purBr – purulent **B**ronchitis or **br**onchiolitis

BrPn – Broncho**Pn**eumonia

InfPn – Infarct**Pn**eumonia

OcclPn – Occlusive**Pn**eumonia

TB – Tuberculosis

fTB – fibrous TB (inactive tuberculotic scar without miliary dissemination)

fcTB – fibrocaseous TB (fibrocaseous tubercle with or without miliary dissemination)

mTB – miliary TB (active TB with miliary dissemination)

mTu – **m**alignant **Tu**mor

CaBrAlv – **Br**ongho**alv**eolar **Ca**rcinoma

Ath – **A**therosclerosis

HT – Hyper**t**ension

c – Coefficient of colligation (coefficient of association); range of values from"-1" to "+1": „-1" indicates a perfect inverse (negative) relationship, „0" indicates no relationship, and „+1" means a perfect positive correlation

SD – Standard **D**eviation

ND – No **D**ata

NS – Not **S**gificant

HE – **H**ematoxylin-**E**osin staining

Introduction

Systemic autoimmune vasculitis (**sAV**), systemic AA amyloidosis (**sAAa**) generalized lethal septic infection (**SI**) are the most important complications of rheumatoid arthritis (**RA**), which may involve the lungs **(**1**)**.

In addition to these complications of **RA** (**sAV**, **sAAa**, **SI**), a wide spectrum of lung diseases may associate with **RA (**2**)**.

The **aim** of this study was to determine the prevalence of **sAV**, **sAAa**, and lethal **SI** in **RA**, to appraise the involvement of bronchial or pulmonary blood vessels by autoimmune vasculitis (**pAV**), to identify the amyloid A deposition on different tissue structures of the lungs (**pAAa**), and to characterize the histological features of **SI** in lungs.

The authors estimated the spectrum of associated diseases **(**related or not related to **RA)** in the lungs and identified the group of patients in which the risk of complications and associated diseases is the highest, compared to the patient cohort's without complications and/or associated diseases, based on

the age, sex of patients, onset and duration of **RA**.

Patients and Methods

147 random autopsy patients with **RA** were studied **(**3,4**)**. **RA** was confirmed clinically according to the criteria of the American College of Rheumatology (**ACR**) **(**5**)**.

The prevalence of **sAV** and **pAV** was confirmed by a detailed review of extensive histological material in agreement with the recommendations of the Consensus Conference (2013) **(**6**)**.

Amyloid A deposition was diagnosed histologically according to Romhányi **(**7**)** by a modified (more sensitive) Congo red staining **(**8**)**. Amyloid A deposits were identified in serial sections by immunohistochemical and histochemical methods **(**9, 10**)**. The prevalence and severity of amyloid A deposition were evaluated microscopically with an Olympus BX51 polarizing microscope.

Lethal cases of **SI** and distinct forms of ***multifocal inflammation*** (mfPn) of the lungs, such as ***purulent bronchitis*** *or* ***bronchiolitis*** (**purBr**), ***bronchopneumonia*** (**BrPn**), ***infarctpneumonia*** (**InfPn**), ***occlusive*** (obliterative or obstructive necrotizing) ***pneumonia*** (**OcclPn**), ***rheumatoid pneumonia*** (**RhPn**), ***interstitial pneumonia*** (**IPn**), ***tuberculosis*** (**TB**) **(**2**)**, furthermore primary ***malignant tumors*** of the lungs (**mTu**) were determined at autopsy and analyzed retrospectively, confirmed microscopically by a detailed review of extensive histological material, reviewing retrospectively all available clinical and pathological reports.

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.

Demographics of different patient cohorts were compared with the Student (Welch) t-probe **(**11**)**.

Glossary of definitions

"Vasculitis" – concerns the presence of inflammatory infiltration and structural changes in blood vessels of different calibers **(**12**)**

Systemic vasculitis of autoimmune origin (**sAV**) or **rheumatoid vasculitis** – was defined as one of the basic manifestations of **RA** determined in 12 organs **(**3**)**, excluding other causes of vasculitis, like hypertension, diabetes mellitus, tumors, septic infections, etc.

Prevalence of **sAV** concerns the presence of vasculitis determined in 12 organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) 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 (13**) in tissue samples**:

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)

"**Prevalence of sAAa**" concerns the proportion of amyloid A deposits in various organs of our autopsy population, and conveys information about the risk of complications.

Prevalence of **sAAa** was specified histologically based on the presence of amyloid A in blood vessels of different calibers or different tissue structures of the aforementioned 12 organs in each patient **(**1**)**.

"**Prevalence of pAAa**" concerns how widespread the amyloid A deposits are in pulmonary or bronchial blood vessels of different calibers or in different tissue structures of the lungs.

Blood vessels of different caliber as aforementioned **(**13**)** and further

tissue structures of the lungs:

Interstitial collagen fiber (**I**)

reticulin fiber *(collagen IV)* (**ret**)

Basement membrane – (**BM**) *peribronchial,* (br**BM**), *peritubular* (lob**BM**) *or panlobular* (plob**BM**) *of the lung* ***nerve*** (**n**) in the lung

The presence of septic infection (**SI**) with or without purulent arthritis (**PA**) was determined at autopsy; only fatal cases were considered. The pathogenic agents were detected by bacteriologic culture in vivo and/or post mortem (occasionally the infective agents were identified by bacteriologic culture post mortem only). Concomitant infective agents (e.g. fungi, parasites) were sometimes identified only histologically.

Only **RA** related interstitial pneumonitis (**IPn**) was considered; **IPn** was listed in association

with **sAV**, **sAAa**, **SI**, or with **RA** related further complications (glomerulonephritis, poliserositis, etc.). **IPn** was characterized by interstitial cellular infiltration with or without hyperemia, edema, fibrinoid or amyloid A deposition, with or without fibrosis, and with or without corespondent pleuritis. **IPn** alone was not fatal in our cohort and contributed to the death only in association with the aforementioned **RA** related complications.

Distinct forms of multifocal inflammatory processes of the lungs (**purBr**, **BrPn**, **OcclPn**, **InfPn**, and **RhPn**) were detected at autopsy and/or histologically; only the fatal cases of multifocal pneumonia (**mfPn**) were considered.

Results

1. Complications of RA (sAV n=31, sAAa n=34 or SI n=22)

1.1 Systemic autoimmune vasculitis (sAV)

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.

There was a very strong positive relationship between **sAV (n=31)** and **pAV** (**n=15**) (c=1.0, c^2=57.3381, p <0.0000).

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 arterioles and multiple focal microinfarctions of the myocardium (myocardiocytolysis) in **11**, cerebral vasculitis and multifocal brain necrosis in **2**, thrombovasculitis of the renal artery and renal necrosis in **1** or thrombovasculitis of the mesenteric artery and intestinal hemorrhagic necrosis in **1** case, including **3** cases of bronchial and pulmonary vasculitis and multifocal pneumonia.

In **12** (8.16 % of 147 and 38.71 % of 31) cases **sAV** had no direct role in the death, and the patients died of circulatory failure due to endo-myo-epi- or pancarditis, **sAAa**, pneumonia, etc.

sAV was clinically **recognized** in **5** (**16.13** %) and was **missed** in **26** (**83.87** %) of 31 patients. There was a significant and positive correlation between **clinical diagnosis** of **sAV** and **prevalence** of **sAV** (c=1.0, c^2=14.7706, p <0.00012).

Four (**21.05** %) of 19 **fatal sAV** were diagnosed, and **15** (**78.95** %) were not.

One (**8.33** %) of 12 **non -fatal sAV** were noticed, and **11** (**91.67** %) were not.

The correlation was also significant and positive between **clinical diagnosis** of **sAV and mortality sAV** ($c=0.88764$, $c^2=11.4601$, $p<0.00071$).

Figures 1-3 show different types of **pAV** involving pulmonary blood vessels.

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...

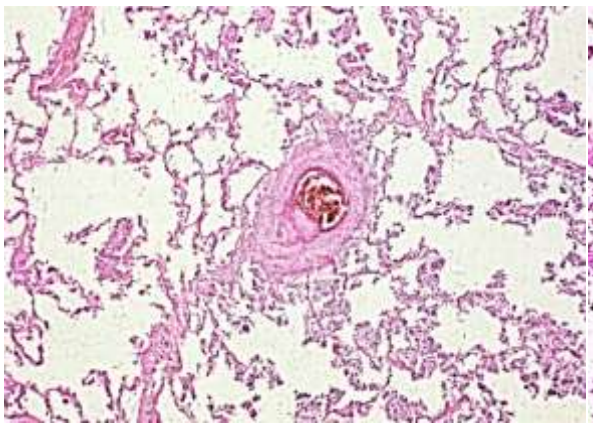


Figure 1a

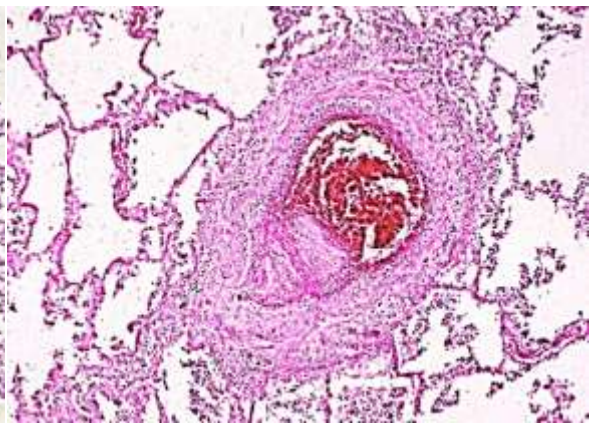
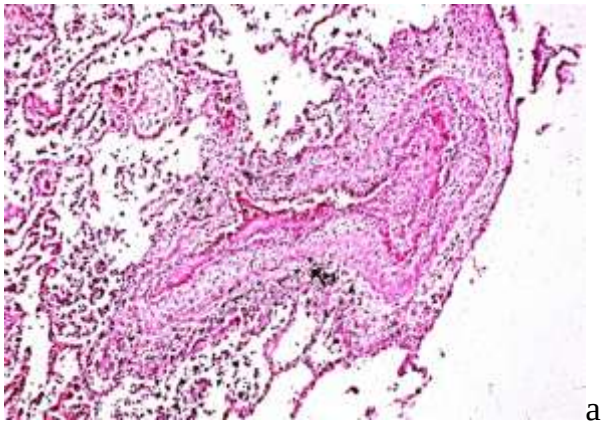


Figure 1b

Figure: 1a-b

RA, lung, small pulmonary artery, non-specific, acute (necrotizing) vasculitis

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



a

Figure 2a

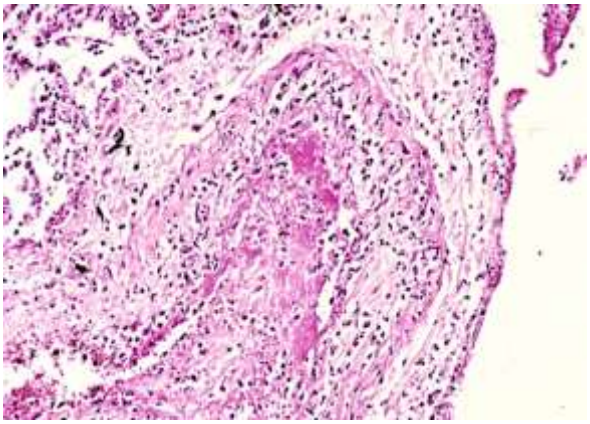
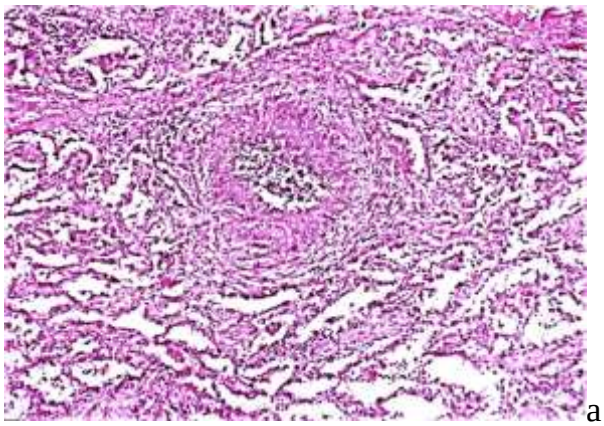


Figure 2b

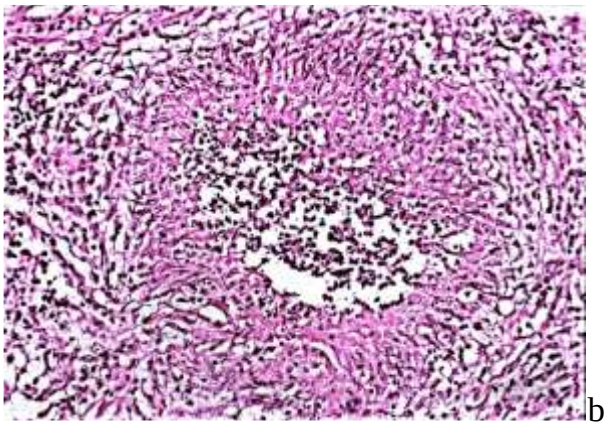
Figure 2a-b

RA, lung, small pulmonary artery and arteriole junction, fibrinoid necrotic, acute vasculitis

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



a



b

Figure 3a Figure 3b

Figure 3a-b

RA, lung, small pulmonary artery, granulomatous, acute (necrotizing) vasculitis

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

1.2 Systemic AA amyloidosis (sAAa)

sAAa complicated **RA** in **34** (**23.13**%) of **147** patients. Branches of pulmonary and bronchial blood vessels of different calibers and various tissue structures of the lungs were involved in **25** (73.53 % of 34, 17.01 % of 147) cases; pulmonary amyloid A deposits (**pAAa**) was histologically excluded in **9** (**26.47** % of 34) of 34 cases.

There was a very strong positive relationship between **sAAa** (**n=34**) and **pAAa** (**n=25**) (c=1.0, c^2=94.9228, p <0.0000).

Systemic **AAa** was fatal in **17** (50.0 % of 34, 11.56 % of 147) patients due to renal insufficiency and uremia. **Seventeen** (50.0 % of 34, 11.56 % of 147) patients with **sAAa** died of other causes, such as circulatory failure (due to cardiac amyloidosis, rheumatoid vasculitis, carditis, or atherosclerosis), peritonitis, lethal septic infection etc. Systemic **AAa** with uremia was clinically diagnosed in **9** (26.47 %) and missed in **25** (73.53 %) of 34 patients. There was a significant and positive correlation between **clinical diagnosis** of **sAAa** and **prevalence** of **sAAa** (c=1.0, c^2=27.4235, p <0.00000).

Fatal cases of **sAAa** were diagnosed clinically in **9** (**52.94 %** of 17) patients, and in **8** (**47.06** % of 17) were not. The non-fatal cases of **sAAa** were not recognized clinically (0 % of 17). The correlation was very strong and positive between the **clinical diagnosis** of **sAAa** and **mortality** of **sAAa** (c=0.1, c^2=64.3903, p <0.00000).

Figures 4-5 show centrilobular peribronchial (subepithelial) amyloid A deposit of **pAAa**.

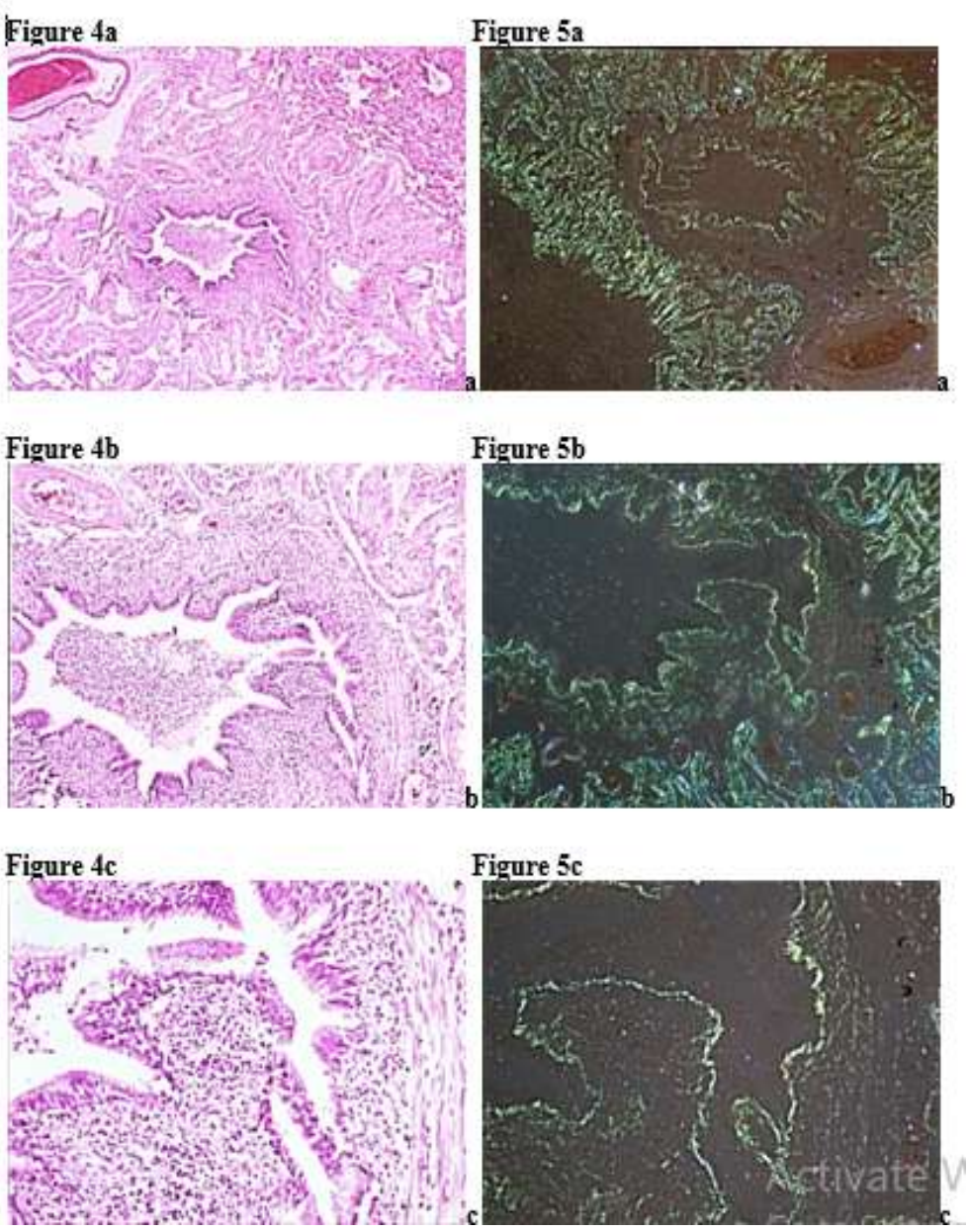


Figure 4a-c

RA, lung, centrilobular peribronchial amyloid A deposit (along subepithelial basal lamina) of **pAAa** Amyloid deposited within interstitial reticular and collagen fibers, and along alveolar basal membranes

(**a**) HE, x 50, (**b**) same as (a) x125, (**c**) same as (a) x200

Legend to Figure 5a-c

RA, lung, centrilobular peribronchial amyloid A deposit (along subepithelial basal lamina) of **pAAa**
Same as Figure 4a-c, Congo red staining, without alcoholic differentiation, covered with gum arabic. Viewed under polarized light
(**a**) x50, (**b**) x125, (**c**) x200

1.3 Lethal septic infection (SI) with or without purulent arthritis (PA)

Generalized septic infections were registered only with fatal outcomes. Generalized **SI** with fatal outcome complicated **RA** in **22** (**14.97** %) of **147** patients.
SI was histologically excluded in **125** (**85.03** %) of 147 RA patients
The lungs were involved by septic infection (**pSI**) in **6** (**27.27** %) of these 22 cases. There was a very strong positive relationship between **SI** (**n=22**) and pulmonary manifestation of **SI** (**n=6**) (c=1.0, c^2=28.9168, p <0.0000).

Lethal **SI** was complicated by purulent (suppurative) arthritis (**PA**) in **11** (50.0 %) of **22** patients (purulent gonarthritis n=7, omarthritis n=2, coxitis n=2), and it was not in **11** (50.0 %) cases. **PA** did not complicate **RA** without **SI**. The relationship was very strong and positive between **SI** and **PA** (c=1.0, c^2=60.5259, p <0.0000).

SI was clinically diagnosed in **9** (**40.91** %) and missed in **13**(**59.09** %) of 22 patients.
There was a very strong positive relationship between **clinical diagnosis** of **SI** and **prevalence** of **SI** (c=1.0, c^2=47.5863, p <0.0000) (**only fatal cases of SI were considered**, so the prevalence or mortality of **SI** is identical, all detected **SI** were fatal.
PA was clinically diagnosed in **5** (**45.45** %) and missed in **6** (**54.55** %) of 11 cases. The relationship between **clinical diagnosis** of **PA** and **prevalence** of **PA** was also significant (c=1.0, c^2=50.9083, p <0.0000).

The histology of purulent arthritis and osteomyelitis are demonstrated on Figures 6a-b.

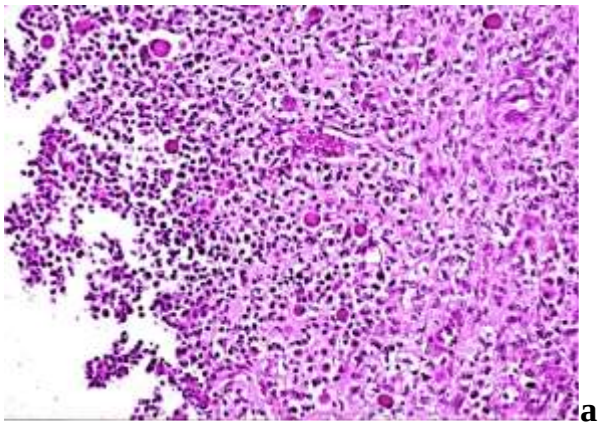


Figure 6a

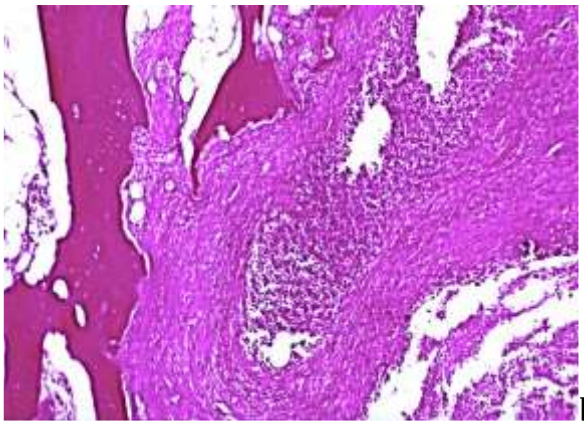


Figure 6b

Figure 6a-b

RA, purulent gonarthitis

(**a**) Synovial membrane, purulent synovialitis, HE, x 50

(**b**) Osteomyelitis, HE, x50

1.4 Interstitial pneumonitis (IPn) related to complications of RA

RA related interstitial pneumnitis (**IPn**) existed only in association with complications of **RA** in **30** (**20.41**%) of **147** patients.

IPn alone was not fatal in our cohort and contributed to the death only in association with **sAV** (n=7), **sAAa** (n=7), **SI** (n=3), endo-myo- or epicarditis (n=1), polyserositis (n=2) or glomerulonephritis (n=1) in **21** (70.0 %) of 30 patients.

IPn itself was diagnosed in **none** (0 %) of 30 patients or was mentioned only as cardial or cardiorespiratory insufficiency.

1.5 Complications of RA (n=87)

Aforementioned **87** (**sAV**: n=31, **sAAa**: n=34 and **SI**: n=22) complications were present in **79** patients; in 63 patients only one and in 8 patient 2 complications existed at the same time; **68** patients were not complicated by **sAV**, **sAAa**, or **SI**.

Fifty eight patients died of **RA** related complication; **sAV led to death** in **19** (32.76

%), **sAAa** in **17** (29.31 %), and **SI** in **22** (37.93 %) of 58 cases.
sAV was **diagnosed** clinically in **4** (**21.05** % of 19) **sAAa** in **9** (**52.94** % of 17), and **SI** in **9** (**40.91** % of 22) patients with fatal outcome of these complications.

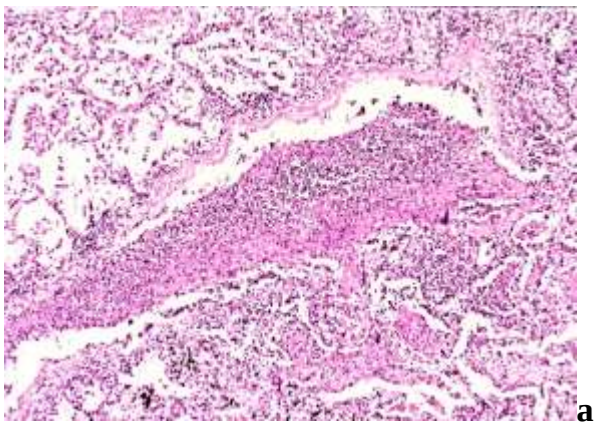
2. Associated diseases of the lungs (mfPn n=28, TB n=21 or mTU n=14)

2.1 Multifocal inflammatory processes of the lungs with fatal outcome (mfPn)*

***Footnote**: Six patients of 28 clinically **mfPn** were associated with fatal **sAV** (**BrPn**, **OcclPn** or **InfPn** in 1-1, and **RhPn** in 3 cases.

Distinct forms of multifocal inflammatory processes of the lungs (**mfPn**) were detected in **28** (**19.05** %) of 147 patients; **PurBr** or **BrPn** were associated with **RA** in **18** (**12.25** %), **OcclPn** in **2** (**1.36** %), **OcclPn** in **2** (**1.36** %), **InfPn** in **5** (**3.40** %), **RhPn** in **3** (**2.04** %) of **147** patients; only the fatal cases were considered.

Multifocal pneumonia (**purBr**-**BrPn**, **OcclPn**, **InfPn** or **RhPn**) was clinically diagnosed in **19** (**67.86** %), and missed in **9** (**32.14** %) of 28 patients.
There was a very strong positive relationship between **clinical diagnosis** and **prevalence** of (multi)focal pneumonia ($c=1.00$, $c^2=86.8050$, $p<0.0000$) (**only the fatal cases of multifocal pneumonia were considered**, so the prevalence or mortality of **mfPn** are identical, all detected **mfPn** was fatal per definitionem.
The most important **mfPn** are demonstrated in Figures 7-8 including but not limited to all possibilities.



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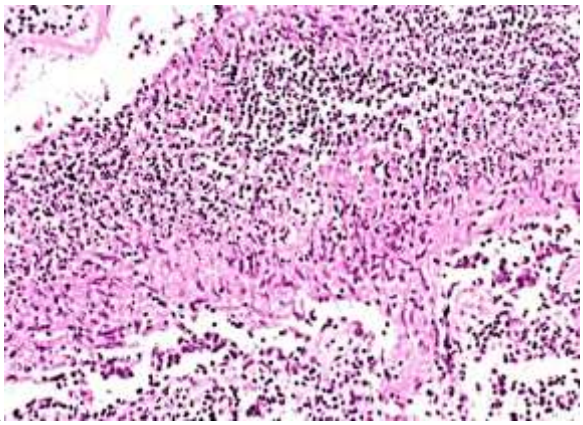

Figure 7a

Figure 7b

Figure 7a-b

RA, lung, purulent bronchiolitis with incipient bronchopneumonia

(**a**) HE, x 50, (**b**) Same as (a) x125

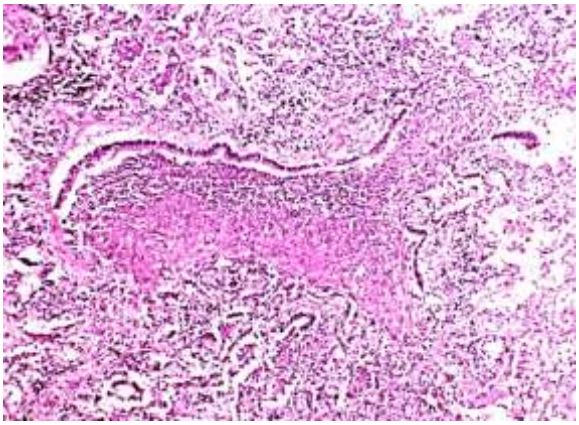

Figure 8a

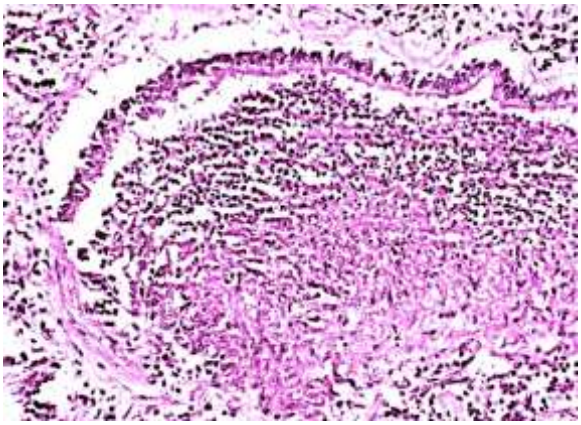

Figure 8b

Figure 8a-b

RA, lung, occlusive (obliterative or obstructive necrotizing) bronchiolitis with bronchopneumonia

(**a**) HE, x 50, (**b**) Same as (a) x125

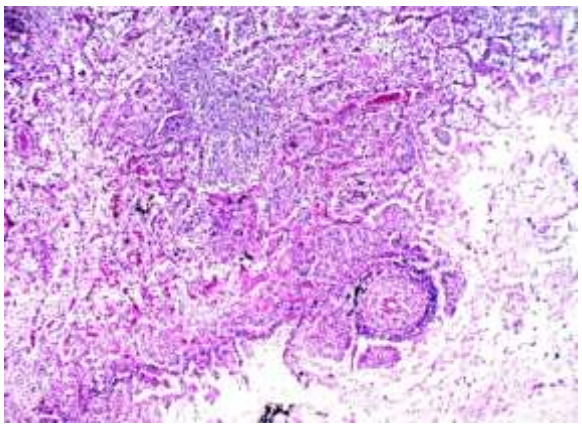

Figure 9a

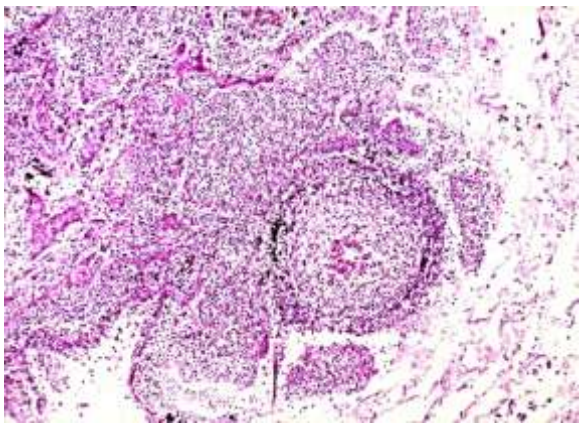

Figure 9b

Figure 9a-b

RA, lung, small bronchial artery, non-specific, subacute necroziting vasculitis, with sublobular pneumonia (with so called rheumatoid pneumonia, i.e. vasculitis associated lobular-sublobular

pneumonia **(**1, 3**)**)
(**a**) HE, x 50, (**b**) Same as (a) x125

2.2 Tuberculosis (fTB, fcTB or mTB)

Post-primary **TB** was associated with **RA** in **21** (**14.29** %) of 147 patients.
Post-primary **TB** was localized to the lung. **Twelve** (57.14%) of 21 **TB** were histologically only fibrous, antracothic tuberculotic scars (**fTB**), and **9** (42.86%) of 21 revealed a fibrocaseous tubercle (**fcTB**). **One** of 12 **fTB** and **5** of 9 **fcTB** were associated with miliary tuberculosis (**mTB**) in **6** (4.08 % of 147; 28.57 % of 21) **RA** patients with **fTB** or **fcTB**.

There was a strong positive correlation between: **TB** and **fTB** (c=1, c^2=70.9630, p<0.00000001), **TB** and **fcTB** (c=1, c^2=50.3069, p<0.00000001), **TB** and **mTB** (c=1, c^2=30.5888, p<0.00000001).
The correlation was also significant and positive between **fibrocaseous** character of post-primary tuberculotic foci and **mTB** (c=0.9884, c^2 =51.6319, p < 0. 00000001).
The **fTB** did not promote the miliary dissemination; the link between **fTB** and **mTB** was not significant (c=0.4064, c^2 = 0.0002, p <0.9876 – NS).

fcTB complicated by **mTB** led to death in **2** (9.52 % of 21; 1.36 % of 147) female patients; **TB** without **mTB** was not fatal. There was a significant correlation between **TB** and **mortality** of TB (c=1, c^2=6.1039, p<0.013), **fcTB** and **mortality** of **TB** (c=1, c^2=16.7359, p<0.000043) or **mTB** and **mortality** of **TB** (c=1, c^2=26.0472, p<0.00000033); the chance of fatal outcome increased significantly in **RA** patients with **TB**, **fcTB** or **mTB**.
In 19 (90.48 % of 21) patients **TB** was not recognized clinically.

There was no relation between **fTB** and **mortality** of **TB** (c=**-1***, c^2=0.7667, p<0.3812 – NS); the **fTB** did not influence statistically the lifespan of **RA** patients, even the relationship was inverse.

fTB was mentioned only in **2** (9.52 % of 21; 1.36 % of 147) patients with consolidated fibrous tubecrculotic scars.
There was a positive and significant relationship between clinical diagnosis and prevalence of **fTB** (c=1, c^2=12.0817, p<0.0005).
fTB or **fcTB** with or without **mTB** was clinically latent (not recognized and/or not mentioned in clinical reports) in **19** (90.48 % of 21; 12.92 % of 147) patients.

The **two** cases of **fcTB** complicated by **mTB** with fatal outcome were not diagnosed clinically. The links between **clinical diagnosis** and **mortality** of **fcTB** (c=**-1***, c^2=1.2571, p<0.2621 – NS) or **mTB** (c=**-1***, c^2=2.2662, p<0.1322 – NS) were not significant; the histological appearance or characteristics of **fcTB** or **mTB** did not influence statistically the clinical recognition of **TB**.

Figure 10a-b show miliary disseminated tuberculosis in the lungs.

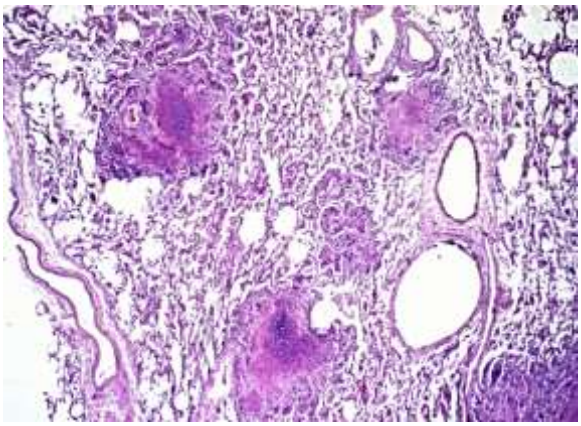

Figure 10a

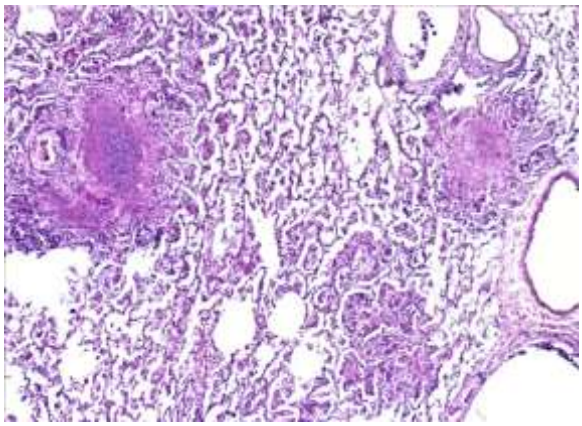

Figure 10b

Figure 10a-b

RA, Disseminated coalescent, moderately caseous and proliferative miliary granulomas in the lungs (**a**) HE, x 50, (**b**) Same as (a) x125

2.3 Malignant tumors (mTu)

Malignant tumors (**mTu**) were associated with **RA** in **14** (**9.52** %) of 147 patients. **Five** (35.71 %) of 14 **mTu** were primary bronchoalveolar cancer (**CaBrAlv**).

In **5** (35.71 % of 14; 3.40 % of 147) patients the **mTu** was the basic disease, and led directly to death; **4** patients died of cachexia due to multiple metastases, and **one** of thyroid cancer by massive internal bleeding due to erosion of laryngeal artery.

In **9** (64.29 % of 14; 6.12 % of 147) patients **mTu** was only accompanied to **RA** (without the direct causal role of death).

Bronchoalveolar cancer (**CaBrAlv**) was **fatal** in **one** (20 %) of 5 patients caused by cerebral metastasis, and was **not fatal** in **4** (80 %).

Clinically only **5** (35.71 %) of 14 **mTu** were diagnosed, including **one CaBrAlv** with cerebral metastasis; **9 mTu** (64.29 % of 14; 6.12 % of 147) were not recognized clinically.

There was a significant correlation between **prevalence** of **mTu** (n=14) and **mortality** of **mTu** (n=5 of

14) (c=1, c^2=38.9035, p <0.00000) or **clinical diagnosis** of **mTu** (n=5 of 14) and **mortality** of **mTu** (n=5 of 14) (c=1, c^2=118.1401, p <0.00000).

The correlations were also significant between **prevalence** of **CaBrAlv** (n=5) and **mortality** of **CaBrAlv** (n=1 of 5) (c=1, c^2=6.6541, p <0.00989) or **clinical diagnosis** of **CaBrAlv** (n=1 of 5) and **mortality** of **CaBrAlv** (n=1 of 5) (c=1, c^2=6.6541, p <0.00989).

Figure 11a-b demonstrates undifferentiated bronchoalveolar carcinoma of the apical region of the lung.

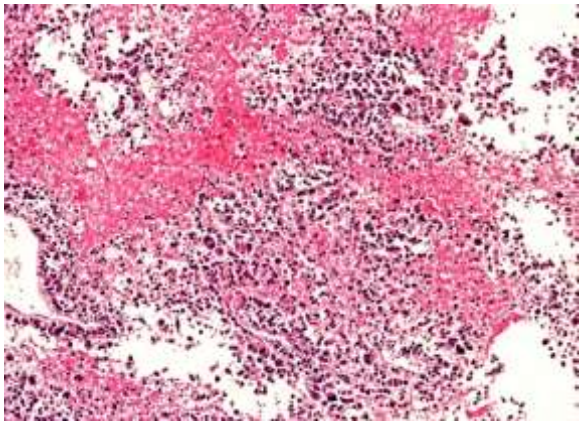

Figure 11a

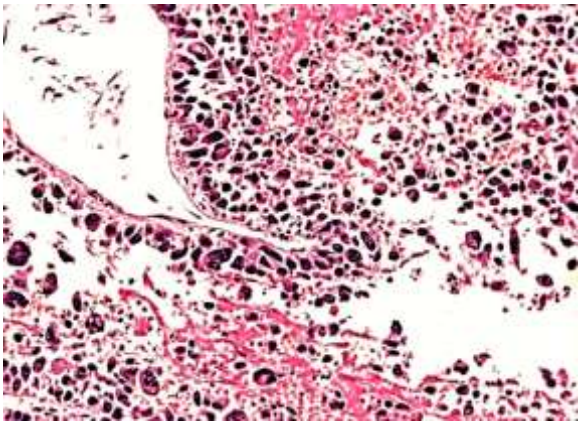

Figure 11b

Figure 11a-b

RA, lung, undifferentiated bronchoalveolar carcinoma

Irregular spaces separated by fibrotic septa, and enveloped by tall columnar epithelium

(**a**) HE, x 40, (**b**) Same as (a) x100

2.4 Associated diseases of the lungs (n=63)

The aforementioned **63** (**mfPn**: n=28, **TB**: n=21 and **mTu**: n=14) associated diseases were present in **56** patients; in 49 patients only one and in 7 patients 2 associated disease existed at the same time; **91** patients were not accompanied with **mfPn**, **TB**, or **mTu**.

Thirty-five patients died of associated diseases of the lungs; **mfPn led to death** in **28** (80.0 %), **TB** in **2** (5.71 %), and **mTu** in **5** (14.29 %) of 35 cases.

Associated diseases with **fatal** outcome were diagnosed in **19** (**67.86** % of 28) patients with **mfPn**, in **none** (**0.0** % of 2) with **TB**, and in **5** (**35.71** % of 14) with **mTu** (in one patient the not

fatal **CaBrAlv** was also diagnosed).

There was a significant correlation between **prevalence** (n=63) and **mortality** of **allied disorders** (n=35 of 63) (c=1, c^2=58.22585, p <0.00000) or **clinical diagnosis** (n=19) and **mortality** of **allied disorders** (n=35 of 63) (c=1, c^2=65.0849, p <0.00000).

2.5 Complications of RA (n=87) and/or associated diseases of the lungs (n=63)

Complications of **RA** (n=87) and **associated diseases** of the **lungs** (n=63) were present in **111** (75.51 %) of 147 patients.

We found in our patients' cohort only **36** (24.49 % of 147) patients without aforementioned complications **RA** or allied disorders of the lungs; **35** of these patients died of consequences of atherosclerosis (**Ath**) with or without hypertension (**HT**), and **one** patient died of a postoperative complication (pulmonary embolim) after prostatectomy.

Severe atherosclerotic changes were not detected in the pulmonary blood vessels, so in this study we do not discuss the role of **Ath** in lung diseases; despite **Ath** is the most important allied disease of **RA** per factum.

Table 1 summarizes the demographics, onset and duration of disease of **total population with** and **without complication** of **RA** or **associated diseases** of the lungs.

Table 1: Sex, mean age with SD, range, onset and disease duration (in years) of 147 RA patients with and without complication of RA or associated diseases of the lungs

Sex	**Number of autopsies**	**Mean age in years at death ± SD**	**Range (in years)**	**Mean age at onset of RA ± SD**	**Duration of RA (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	50.53±15.29	14.37±10.40
Male	43	66.91±13.89	19 – 88	53.97±19.37	13.28±10.16

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	58.35±9.78	10.94±7.80
Male	13	67.46±9.84	53 – 83	54.72±19.42	12.77±13.16
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 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 sAAa	**34 of 147**	**62.41±15.59**	**19 – 88**	**47.61±18.04**	**15.58±9.36**
Female	29	64.34±11.07	32 – 83	48.56±15.25	15.70±9.88
Male	5	51.20±28.18	19 – 88	41.25±30.07	14.75±4.44
with pAAa	**25 of 34**	**61.72±17.16**	**19 – 88**	**47.14±20.11**	**15.59±9.77**
Female	20	64.35±11.62	32 – 83	48.44±16.86	15.78±10.59
Male	5	51.20±28.18	19 – 88	41.25±30.07	14.75±4.44
without sAAa	**113 of 147**	**66.60±11.14**	**16 – 87**	**52.79±15.94**	**13.56±10.59**
Female	75	65.39±11.98	16 – 87	51.38±15.22	13.79±10.56

Male	38	68.97±8.78	52 – 87	55.56±16.92	13.09±10.65
with SI	**22 of 147**	**62.27±7.74**	**51 – 83**	**48.63±11.73**	**12.95±9.81**
Female	15	61.80±8.31	51 – 83	50.08±12.96	11.08±10.21
Male	7	63.29±6.20	52 – 70	45.50±7.59	17.00±7.39
with PA	**11 of 22**	**59.09±5.90**	**51 – 68**	**42.60±10.30**	**16.40±11.47**
Female	7	58.71±5.80	51 – 68	42.83±12.18	15.67±12.92
Male	4	59.75±6.02	52 – 67	42.25±6.50	17.50±8.76
with pSI	**6 of 22**	**61.00±5.77**	**52 – 68**	**43.67±12.06**	**17.33±12.72**
Female	5	59.80±5.60	52 – 68	43.00±13.11	16.80±13.88
Male	1	67.00±0.00	67	47.00±0.00	20.00±0.00
without SI	**125 of 147**	**66.30±12.90**	**16 – 88**	**52.11±17.36**	**14.25±10.47**
Female	88	65.74±12.08	16 – 87	50.71±15.72	14.92±10.39
Male	37	67.62±14.63	19 – 88	55.67±20.53	12.53±10.47
IPn associated with complications of RA (sAV, sAAa, SI, etc.)	**30 of 147**	**61.00±14.00**	**19 – 87**	**46.36±17.98**	**14.43±10.36**
Female	19	60.53±9.79	32 – 73	45.11±13.66	15.89±11.43
Male	11	61.82±19.58	19 – 87	48.60±23.70	11.80±7.37
without IPn	**117 of 147**	**66.82±11.72**	**16 – 88**	**52.99±15.92**	**13.95±10.33**

Female	85	66.12±11.90	16 – 87	51.89±15.37	13.99±10.08
Male	32	68.66±11.00	32 – 88	56.04±16.97	13.85±10.99
with complications of RA (sAV, sAAa or SI) – n of Pts.	**79 of 147**	**63.61±12.53**	**19 – 88**	**50.39±16.39**	**13.92±10.32**
Female	55	64.18±10.65	32 – 83	50.80±14.05	13.90±9.96
Male	24	62.25±15.92	19 – 88	49.45±20.71	13.95±11.08
without complications of RA (sAV, sAAa or SI) – n of Pts.	**68 of 147**	**67.99±11.91**	**16 – 87**	**53.02±16.83**	**14.24±10.37**
Female	49	66.12±12.78	16 – 87	50.20±16.70	14.95±10.88
Male	19	72.79±7.40	60 – 87	61.07±14.43	12.21±8.41
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
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	–	–	–	–
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	–	–	–	–
with RhPn	**3 of 147**	**61.67±2.62**	**58 –**	**53.67±3.30**	**8.00±3.56**

			64		
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
with multifocal Pn	**28of 147**	**68.43±7.85**	**50 – 83**	**51.15±14.41**	**15.85±12.01**
Female	20	67.50±8.22	50 – 83	49.97±15.07	16.97±12.71
Male	8	70.75±6.26	58 – 79	58.33±10.03	12.67±9.01
without multifocal Pn	**119of 147**	**64.92±13.22**	**16 – 88**	**51.27±17.07**	**13.69±9.86**
Female	84	64.44±12.39	16 – 87	50.51±15.31	13.82±9.64
Male	35	66.03±14.97	19 – 88	53.10±20.63	13.40±10.37
with TB	**21 of 147**	**69.00±9.70**	**50 – 84**	**54.19±16.39**	**14.81±12.41**
Female	15	70.20±10.18	50 – 84	54.53±17.88	15.67±13.82
Male	6	66.00±7.59	56 – 78	53.33±11.80	12.67±7.45
with fTB	**12 of 21**	**70.92±8.48**	**59 – 84**	**52.33±16.01**	**18.58±12.76**
Female	7	73.00±8.98	62 – 84	51.14±17.85	21.86±14.60
Male	5	68.00±6.72	59 – 78	54.00±12.82	14.00±7.48
with fcTB	**9 of 21**	**66.44±10.59**	**50 – 80**	**56.67±16.55**	**9.78±9.91**
Female	8	67.75±10.53	50 – 80	57.50±17.38	10.25±10.41
Male	1	56.00±0.00	56	50.00±0.00	6.005±0.00
with mTB	**6 of 21**	**68.33±11.09**	**50 –**	**58.67±8.24**	**9.67±4.85**

			82		
Female	6	68.33±11.09	50 – 82	58.67±8.24	9.67±4.85
Male	0	–	–	–	–
without TB	**126 of 147**	**65.31±12.45**	**16 – 88**	**51.17±16.43**	**14.00±9.88**
Female	88	64.58±11.38	16 – 87	50.08±14.37	14.16±9.60
Male	38	66.97±14.47	19 – 88	53.77±20.29	13.61±10.51
with malignant Tu	**14 of 147**	**65.50±13.75**	**34 – 87**	**53.46±19.09**	**12.08±8.85**
Female	12	62.58±12.58	34 – 80	49.00±17.22	13.36±9.04
Male	2	83.00±4.00	79 – 87	78.00±5.00	5.00±1.00
with alveolar CA	**5 of 147**	**70.40±11.34**	**50 – 80**	**59.00±17.27**	**11.40±6.62**
Female	5	70.40±11.34	50 – 80	59.00±17.27	11.40±6.62
Male	0	–	–	–	–
without malignant Tu	**133 of 147**	**65.65±12.29**	**16 – 88**	**51.29±16.31**	**14.28±10.47**
Female	92	65.42±11.59	16 – 87	50.75±14.98	14.51±10.56
Male	41	66.12±13.72	19 – 88	52.56±18.97	13.76±10.24
with allied disorders of the lungs:mfPn, TB, mTu – n of Pts.	**56 of 147**	**67.89±9.93**	**34 – 87**	**52.95±15.85**	**14.75±11.43**
Female	40	66.85±10.30	34 – 84	50.60±16.19	15.99±12.27
Male	16	70.50±8.39	56 – 87	59.00±13.11	11.57±8.12

without allied disorders of the lungs:mfPn, TB, mTu – n of Pts.	**91 of 147**	**64.24±13.57**	**16 – 88**	**50.57±17.06**	**13.60±9.52**
Female	64	64.00±12.43	16 – 87	50.49±14.65	13.29±8.77
Male	27	64.78±15.92	19 – 88	50.77±21.87	14.36±11.13
with complication of RA and allied disorders of the lungs.	**111 of 147**	**65.16±12.35**	**19 – 88**	**50.86±16.43**	**14.49±10.82**
Female	76	64.79±11.01	32 – 84	50.20±14.71	14.75±10.92
Male	35	65.95±14.81	19 – 88	52.33±19.66	13.90±14.44
without complication of RA and allied disorders of the lungss.	**36 of 147**	**67.50±12.83**	**16 – 87**	**53.73±17.39**	**12.55±8.53**
Female	27	65.89±13.74	16 – 87	51.43±17.19	13.20±8.58
Male	9	72.33±7.79	60 – 82	62.17±15.40	10.17±7.92

Glossary to Table 1

RA – Rheumatoid **A**rthritis

sAV – systemic **A**utoimmune **V**asculitis

pAV – pulmonary **A**utoimmune **V**asculitis

sAAa – systemic **AA a**myloidosis

pAAa – pulmonary **AA a**myloidosis (amyloid A deposits in the lungs)

SI – Septic **I**nfection with fatal outcome

PA – Purulent **A**rthritis

IPn – Interstitial **Pn**eumonitis

mfPn – multifocal **Pn**eumonia

purBr – purulent **B**ronchitis or **br**onchiolitis

BrPn – Broncho**Pn**eumonia

InfPn – Infarct**Pn**eumonia

OcclPn – Occlusive**Pn**eumonia

RA – Rheumatoid **A**rthritis

TB – tuberculosis

fTB – fibrous tuberculosis (inactive tuberculosis)

fcTB – fibrocaseous tuberculosis (inactive tuberculosis)

mTB – miliary tuberculosis (active tuberculosis with miliary dissemination)

mTu – **m**alignant **Tu**mor

CaBrAlv – **Br**ncho**alv**eolar **Ca**rcinoma

SD – Standard **D**eviation

1. Demographics of complications of RA

1.1 Demographics of 31 RA patients with sAV

Comparing the **mean age, sex** of the patients, **onset**, and **duration of RA** 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** (58.35 years versus 48.71, p <**0.003**), who died notably earlier (10.94 years versus 15.16, **p**< 0.175 – NS).

The risk of **pAV** was also higher in **women** at late **onset** of **RA** (55.75 years) compared to the **onset** of **RA** (48.71 years) in **women without sAV** (n=86); the difference was significant (**p <0.037**).

There was **no significant difference in lifespan, onset** or **duration of RA** between patient cohorts **with sAV** (n=31) and **with pAV** (n=15) (p< 0.48, p< 0.39, p< 0.83), neither between **female** (p< 0.98, p< 0.46, p< 0.87) and **male** (p< 0.19, p< 0.52, p< 0.83); **pAV** complicated **sAV** in **both sexes** and **at any time** in the course of the disease (Tables 1 and 2).

1.2 Demographics of 34 RA patients with sAAa

Comparing the **mean age, sex** of the patients, **onset**, and **duration of RA** at the time of death there was **no significant** between patient cohorts **with** (n=34) and **without sAAa** (n=113) (p< 0.16, p< 0.17, p< 0.32), neither between **females** (p< 0.68, p< 0.37, p< 0.39) and **males** (p< 0.27, p< 0.49, p< 0.67), **with sAAa** (n=34) and **with pAAa** (n=25) (p< 0.88, p< 0.93, p< 0.99), neither between **females** (p< 0.99,

p< 0.98, p< 0.98) and **males** (p< 1.00, p< 1.00, p< 1.00) or between patient cohorts **with pAAa** (n=25) and **without sAAa** (n=113) (p< 0.19, p< 0.24, p< 0.40), neither between **females** (p< 0.73, p< 0.52, p< 0.499), and **males** (p< 0.27, p< 0.47, p< 0.62).

Amyloidosis developed in both sexes, and **at any time in the course of the disease** (Tables 1 and 2).

1.3 Demographics of 22 RA patients with SI with (n=11) or without PA (n=11)

There was no significant difference in **mean age** of patients at death, and **onset** or **disease duration** of **RA** between patient cohorts **with SI** (n=22) and **with PA** (n=11) (p< 0.228, p< 0.19, p< 0.45), neither between **females** (p< 0.36, p< 0.299, p< 0.50) and **males** (p< 0.44, p< 0.54, p< 0.94).
Fatal septic infection with or without purulent arthritis developed in both sexes, and **at any time in the course of the disease** (Tables 1 and 2).

There was **no significant difference in mean age, onset** or **duration of RA** between patient cohorts **with SI** (n=22) and **with pSI** (n=6) (p< 0.69, p< 0.44, p< 0.499) or **women with SI** (n=15) and **women with pSI** (n=5) (p< 0.59, p< 0.38, p< 0.48) furthermore **with pSI** (n=6) and **without SI** (n=125) (p< 0.10, p< 0.19, p< 0.62) or **women with pSI** (n=5) and **women without SI** (n=88) (p< 0.10, p< 0.31, p< 0.80) (correlations were not calculated in **males** because of zero divisor).
Pulmonary involvement (**pSI**) **occurred at any time in the course** of generalized septic infection (**SI**).

The early onset of **RA** increased the risk of suppurative arthritis (**PA**), in comparison to the patients **without SI** (42.60 years versus 52.11 years; **p< 0.026**), and the septic patients **with PA** died earlier, than the patients **without SI** (59.09 at death years versus 66.30 years at death; **p< 0.004**).
RA started earlier in **males with PA** (42.25 years), than in **males without SI** (55.67 years); the difference was significant (**p< 0.029**).
The septic **women** died earlier with **PA** (mean age at death: 58.71 years), than the **women without SI** (mean age at death: 65.74 years); the difference was also significant (**p< 0.026**).

1.4 Demographics of 30 RA patients with IPn

Five diffuse interstitial fibrotic processes (associated with atherosclerosis in 3, **TB in 1 and **mTu** in 1 patient) were excluded in this study

The **lifespan** of **RA** patients (the **mean age** at death) **with IPn** decreased significantly compared to the patients **without IPn** (61.00 years versus 66.82 years; **p< 0.045**), and the **women with IPn** died also earlier, than the **women without IPn** (60.53 years versus 66.12 years; **p< 0.043**).

1.5 Demographics of 79 RA patients with sAV, sAAa or SI

The **lifespan** of patients **with sAV**, **sAAa** and/or **SI** (n=79) decreased significantly compared to the patients **without complications** of **RA** (n=68) (63.61 years versus 67.99 years; **p< 0.033**), and this tendency was similar in **males** as well (62.25 years versus 72.79 years; **p< 0.008**).

2. Demographics of allied disorders of the lungs

2.1 Demographics of 28 RA patients with mfPn (BrPn, OcclPn, InfPn or RhPn)

The **mean age** of **RA** patients was significantly higher **with purBr** or **BrPn** (n=18) compared to the patients **without multifocal Pn** (n=119) (71.17 years versus 64.92, **p <0.002**), either in **females** (70.27 years versus 64.44, **p <0.035**) and **males** (72.57 years versus 66.03, **p <0.043**).

Comparing the **age**, **sex** of patients, **onset** and **duration** of **RA** at the time of death, there was no significant difference between **RA** patients **with OcclPn** (n=2), **InfPn** (n=5) or **RhPn** (n=3), and **without multifocal Pn** (n=119); neither in females (the differences were not calculated in males because of the zero divisor).
Onset and **duration** of **RA** did not influence the prevalence of **BrPn**, **OcclPn**, **InfPn**, **RhPn**; multifocal **inflammatory processes of the lungs any time in the course of RA** (Tables 1 and 2).

2.2 Demographics of 21 RA patients with TB (fTB, fcTB or mTB)

There was no significant difference in **mean age** at death, and **onset** or **disease duration** of **RA** between patient cohorts **with TB** (n=21), **fTB** (n=12), **fcTB** (n=9) or **mTB** (n=6) compared to patients **without TB**

(n=126); **TB** (**fTB**, **fcTB**, **mTB**) **developed in both sexes,** and **at any time in the course of the disease** (Tables 1 and 2).

The **mean age** of **RA** patients (especially females) was **higher with TB** (n=21), **fTB** (n=12), **fcTB** (n=9) or **mTB** (n=6) in comparison to patients **without TB** (n=126), but these differences were not significant. Survival of **RA** patients was shorter with **fcTB** (9.78 years) or **mTB** (9.67 years) in comparison to the patients **without TB** (14.0 years), but these differences were also not significant (p <0.274, p <0.110 resp.).

In our autopsy population only females had miliary dissemination of **TB** (all of **6 RA** patients with **mTB** were women). The elderly **females with mTB** (n=6) died earlier than females **without TB**, but the difference was not significant (n=88) (9.67 years versus 14.16, p <0.103 – NS).

2.3 Demographics of 14 RA patients with mTu and CaBrAlv

There was **no significant difference in mean age** of patients (including females) **with mTu** (n=14) and **without mTu** (n=133) (p< 0.97, p< 0.48) or **with mTu** (n=14) and **with CaBrAlv** (n=5) (p< 0.49, p< 0.28) furthermore **with CaBrAlv** (n=5) and **without mTu** (n=133) (p< 0.45, p< 0.43).

The **onset** and **duration** of **RA** in patients (including females) did not influence the prevalence of coexistent **mTu** or **CaBrAlv**; the difference was not significant between patient cohorts **with mTu** (n=14) and **without mTu** (n=133) or **with mTu** (n=14) and **with CaBrAlv** (n=5), furthermore **with CaBrAlv** (n=5) and **without mTu** (n=133).
RA started later in **males with mTu**, in comparison to the **males without mTu** (78.00 years versus 51.29 years; **p< 0.049**), and the **males with mTu** died earlier, than the **males without mTu** (5.00 years versus 14.28 years; **p< 0.001**).

2.4 Demographics of 56 RA patients with allied disorders of the lungs (mfPn, TB or mTu)

Comparing the **mean age, sex** of the patients, **onset**, and **duration of RA** at the time of death there was **no significant** difference between patient cohorts **with** (n=56) and **without allied disorders** (n=91) (p< 0.064, p< 0.43, p< 0.56), neither between **females** (p< 0.21, p< 0.98, p< 0.27) and **males** (p< 0.14, p< 0.18, p< 0.41).

Allied disorders accompanied RA in both sexes, and **at any time in the course of the disease** (Tables 1 and 2).

2.5 Demographics of 111 patients with complications of RA (with sAV, sAAa or SI) and/or associated diseases of the lungs (mfPn, TB or mTu)

Comparing the **mean age, sex** of patients, **onset**, and **duration of RA** at the time of death there was **no significant** difference between patient cohorts **with complications** of **RA** (**sAV**, **sAAa**, **SI**) and/or **allied disorders** of the **lungs** (**mfPn**, **TB**, **mTu**) (n= 111) and **without complications** of **RA** (**sAV**, **sAAa**, **SI**) and/or **allied disorders** of the **lungs** (**mfPn**, **TB**, **mTu**) (n=36) ($p< 0.35$, $p< 0.48$, $p< 0.33$), neither between **females** ($p< 0.71$, $p< 0.77$, $p< 0.51$) and **males** ($p< 0.10$, $p< 0.24$, $p< 0.38$)

Complications of **RA** (**sAV**, **sAAa**, **SI**) and **allied disorders** of the **lungs** (**mfPn**, **TB**, **mTu**) **accompanied RA in both sexes** and **at any time in the course of RA** (Tables 1 and 2).

Table 2 summarizes the statistical correlations ("p" values) of female and male patients **with** and **without complication** of **RA** or **with** and **without associated diseases** of the lungs.

Table 2: The statistical correlations ("p" values) between female and male patients with and without complications of RA or associated diseases of the lungs

p < 0.05 at an alpha level of 0.05	**Age**	**Onset of disease**	**Disease duration**
with sAV n=31 versus **without sAV n=116** of 147	**0,349**	**0,038**	**0,175**
Female n=**18** of 31 versus n=**86** of 116	0,409	**0,003**	0,079
Male n=**13** of 31 versus n=**30** of 116	0,844	0,859	0,851
with sAV n=31 versus **with pAV n=15 of 31**	**0,482**	**0,386**	**0,825**
Female n=**18** of 31 versus n=**10** of 31	0,976	0,459	0,869
Male n=**13** of 31 versus n=**5** of 31	0,191	0,515	0,833
with pAV n=15 vs**. without sAV n=116** of 147	**0,992**	**0,491**	**0,426**
Female n=**10** of 15 versus n=**86** of 116	0,461	**0,037**	0,122
Male n=**5** of 15 versus n=**30** of 116	0,248	0,564	0,898

with sAAa n=34 versus **without sAAa n=113** of 147	**0,157**	**0,166**	**0,323**
Female n=**29** of 34 versus n=**75** of 113	0,680	0,431	0,421
Male n=**5** of 34 versus n=**38** of 113	0,277	0,473	0,620
with sAAa n=34 versus **with pAAa n=25 of 34**	**0,877**	**0,931**	**0,997**
Female n=**29** of 34 versus n=**20** of 25	0,999	0,983	0,982
Male n=**5** of 34 versus n=**5** of 25	1,000	1,000	1,000
with pAAa n=25 versus **without sAAa n=113** of 147	**0,193**	**0,238**	**0,402**
Female n=**20** of 25 versus n=**75** of 113	0,733	0,522	0,499
Male n=**5** of 25 versus n=**38** of 113	0,277	0,473	0,620
with SI n=22 versus **without SI n=125** of 147	**0,056**	**0,291**	**0,612**
Female n=**15** of 22 versus n=**88** of 125	0,139	0,881	0,244
Male n=**7** of 22 versus n=**37** of 127	0,232	0,060	0,275
with SI n=22 versus **with PA n=11 of 22**	**0,218**	**0,186**	**0,451**
Female n=**15** of 22 versus n=**7** of 11	0,356	0,299	0,500
Male n=**7** of 22 versus n=**4** of 11	0,441	0,541	0,937
with SI n=22 versus **with pSI n=6 of 22**	**0,689**	**0,437**	**0,499**
Female n=**15** of 20 versus n=**5** of 6	0,589	0,381	0,479
Male n=**7** of 20 versus n=**1** of 6	-	-	-
with PA n=11 versus **without SI n=125** of 147	**0,004**	**0,026**	**0,598**
Female n=**7** of 11 versus n=**88** of 125	**0,026**	0,218	0,904
Male n=**4** of 11 versus n=**37** of 125	0,109	**0,029**	0,412
with pSI n=6 versus **without SI n=125** of 147	**0,102**	**0,186**	**0,615**
Female n=**5** of 6 versus n=**88** of 125	0,104	0,312	0,802
Male n=**1** of 6 versus n=**37** of 125	-	-	-
with IPn n=30verssus **without IPn n=117** of 147	**0,045**	**0,090**	**0,832**
Female n=**19** of 30 versus n=**85** of 117	**0,043**	**0,084**	**0,535**
Male n=**11** of 30 versus n=**32** of 117	**0,304**	**0,403**	**0,541**
with sAV, sAAa or SI n=79 vs. **without complications n=68**	**0,033**	**0,386**	**0,863**
Female n=**55** of 79 versus n=**49** of 68	0,410	0,858	0,642
Male n=**24** of 79 versus n=**19** of 68	**0,008**	**0,063**	**0,608**
with purBr or **BrPn n=18** vs**. without mfPn n=119** of 147	**0,002**	**0,850**	**0,125**
Female n=**11** of 18 versus n=**84** of 119	**0,035**	0,695	0,100
Male n=**7** of 18 versus n=**35** of 119	**0,043**	0,363	0,877

with OcclPn n=2 versus **without mfPn n=119**	**0,587**	**0,218**	**0,796**
Female n=**2** of 2 versus n=**84** of 119	0,611	0,233	0,802
Male n=**0** of 2 versus n=**35** of 119	-	-	-
with InfPn n=5 versus **without mfPn n=119**	**0,485**	**0,414**	**0,232**
Female n=**5** of 5 versus n=**84** of 119	0,428	0,378	0,226
Male n=**0** of 5 versus n=**35** of 119	-	-	-
with RhPn n=3 versus **without mfPn n=119**	**0,216**	**0,446**	**0,137**
Female n=**2** of 3 versus n=**84** of 119	0,520	0,536	0,421
Male n=**1** of 3 versus n=35 of 119	-	-	-
with mfPn n=28 versus **without mfPn n=119** of 147	**0,075**	**0,438**	**0,802**
Female n=**20** of 28 versus n=**84** of 119	0,195	0,361	0,898
Male n=**8** of 28 versus n=**35** of 119	0,188	0,874	0,390
with TB n=21 versus **without TB n=126** of 147	**0,140**	**0,457**	**0,785**
Female n=**15** of 21 versus n=**88** of 126	0,074	0,391	0,702
Male n=**6** of 21 versus n=**38** of 1260	0,819	0,947	0,811
with fTB n=12 versus **without TB n=126**	**0,062**	**0,823**	**0,270**
Female n=**7** of 12 versus n=**88** of 126	0,064	0,891	0,249
Male n=**5** of 12 versus n=**38** of 126	0,809	0,977	0,929
with fcTB n=9 versus **without TB n=126**	**0,778**	**0,388**	**0,274**
Female n=**8** of 9 versus n=**88** of 126	**0,467**	**0,306**	**0,367**
Male n=**1** of 9 versus n=**38** of 126	-	-	-
with mTB n=6 versus. **without TB n=126**	**0,575**	**0,104**	**0,110**
Female n=**6** of 6 versus n=**88** of 126	0,492	0,070	0,103
Male n=**0** of 6 versus n=**38** of 126	-	-	-
with mTu n=14 versus **without mTu n=133** of 147	**0,971**	**0,710**	**0,433**
Female n=**12** of 14 versus n=**92** of 133	0,488	0,765	0,718
Male n=**2** of 14 versus n=**41** of 133	0,086	**0,049**	**0,001**
with mTu n=14 versus **with AlvCa n=5** of 14	**0,494**	**0,604**	**0,875**
Female n=**12** of 14 versus n=**5** of 5	0,286	0,359	0,663
Male n=**2** of 14 versus n=**0** of 5	-	-	-
with AlvCa n=5 of **14** pts. versus **without mTu n=133** of 147	**0,453**	**0,426**	**0,444**
Female n=**5** of 5 versus n=**92** of 133	0,435	0,398	0,417
Male n=**0** of 5 versus n=**41** of 133	-	-	-

with allied disorders (mfPn, TB, mTu) n=56 versus **without n=91** of 147	**0,064**	**0,430**	**0,560**
Female n=**40** of 56 versus n=**64** of 91	0,213	0,975	0,265
Male n=**16** of 56 versus n=**27** of 91	0,140	0,179	0,405
with complications of RA (sAV, sAAa, SI) and/or **allied disorders of the lungs (mfPn, TB, mTu) n=111** versus **without complications of RA** and/or **allied disorders of the lungs n=36** of 147	**0,347**	**0,447**	**0,332**
Female n=**76** of 111 versus n=**27** of 36	0,714	0,770	0,506
Male n=**35** of 111 versus n=**9** of 36	0,101	0,242	0,381

Glossary to Table 2

RA – Rheumatoid **A**rthritis

sAV – systemic **A**utoimmune **V**asculitis

pAV – pulmonary **A**utoimmune **V**asculitis

sAAa – systemic **AA a**myloidosis

pAAa – pulmonary **AA a**myloidosis (amyloid A deposits in the lungs)

SI – Septic **I**nfection with fatal outcome

PA – Purulent **A**rthritis

IPn – Interstitial **Pn**eumonitis

mfPn – multifocal **Pn**eumonia

purBr – purulent **B**ronchitis or **br**onchiolitis

BrPn – Broncho**Pn**eumonia

InfPn – Infarct**Pn**eumonia

OcclPn – Occlusive**Pn**eumonia

RA – Rheumatoid **A**rthritis

TB – tuberculosis

fTB – fibrous tuberculosis (inactive tuberculosis without miliary dissemination)

fcTB – fibrocaseous tuberculosis (inactive tuberculosis with or without miliary dissemination)

mTB – miliary tuberculosis (active tuberculosis with miliary dissemination)

mTu – **m**alignant **Tu**mor

CaBrAlv – **Br**ongho**alv**eolar **Ca**rcinoma

SD – Standard **D**eviation

Discussion

1. Complications of RA

1.1 Systemic autoimmune vasculitis (sAV)

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 **(**12**)**. Rheumatoid vasculitis usually occurs in patients with severe, longstanding, nodular, destructive **RA (**14**)**.
In Vollertsen's study (1986) in-patients with rheumatoid vasculitis had a decreased survival in comparison with an age-, sex-, and region-matched general population or in comparison with **RA** community people **(**15**)**.

In our autopsy population the **sAV** complicated **RA** in **31** (**21.08**%) of **147** patients, and led directly to death in **19** (61.29% of 31) cases, furthermore only **4** (21.05 %) of 19 **fatal sAV** were diagnosed, so **sAV** should be regarded one of the main life threatening (and highly dangerous) complication of **RA**. The risk of **sAV** was higher at late onset of **RA** especial in females.
The **ratio** of **diagnosed** (n=4) and **missed** (n=15) **fatal** cases of **sAV** was: **0.26** (4:15 of 19), and it was: **0.19** (5:26 of 31) in the total population of **sAV**.

There was a very clouse relationship between systemic and pulmonary vasculitis. The **pAV** resulted in three patients multifocal pneumonia, the so called rheumatoid pneumonia (**RhPn**), which should be regarded a special vasculogenic **RA** related complication, a new entity. The prevalence of **RhPn** was 2.04% of 147, 9.68% of 31 **sAV**. All three cases of **RhPn** were fatal (15.79 % of 19 fatal **sAV** cases), and none of tham were recognized clinically (0 % of 19) **(**3**)**.

1.2 Systemic AA amyloidosis (sAAa)

Systemic AAa (**sAAa**) is related to the cardiovascular system, and pulmonay AAa (**pAAa**) is connected with it **(**1**)**. From a prognostic point of view, amyloid A deposition in the lungs did not prove to be a very serious, life-threatening complication of **RA (**4**)**. It can be asymptomatic or may present nonspecific symptoms such as progressive dyspnea, cough, wheezing and rarely respiratory failure **(**16**)**, by blocking gas exchange in alveolar structures **(**17**)**.

In our autopsy population the **sAAa** complicated **RA** in **34** (**11.56**%) of **147** patients. Half of the patients

(17 of 34) died of uremia caused by massive amyloid A deposition in the kidneys (50.0 % of 34), and only **9** (52.94 %) of these 17 fatal cases were recognized clinically.
Amyloidosis may develope in both sexes, and at any time in the course of **RA**.

From a prognostic point of view, **sAAa** is a very serious, life-threatening complication of **RA**, but appears to be less decisive or critical than **sAV**, based on the **prevalence** (**sAV** n=31, **21.04** % versus **sAAa** n=34, **23.12** % of 147), **fatal outcome** (**sAV** n=19, **12.92** % versus **sAAa** n=17, **11.56** %) and **missed diagnosis** (**sAV** n=26, **17.69** % versus **sAAa** n=25, **17.01** % of 147).
All cases of **sAAa** were clinically diagnosed based on uremia, in an advanced stage of amyloidosis indeed, **sAAa** is one of the most insidious complications of **RA**, which may furtively lead to death.

The **ratio** of **diagnosed** (n=9) and **missed** (n=8) **fatal** cases of **sAAa** was: **1.125** (9:8 of 17), and it was: **0.36** (9:25 of 34) in the total population of **sAAa**.

1.3 Septic infection with or without purulent arthritis

SI with or without **PA** may be considered as a severe indirect consequence of **RA** caused by any bacteriemia **(**18**)**. Staphylococcal infection and infection of multiple joints were associated with higher mortality rates in Dubost's study **(**19**)**.
Generalized fatal infection may exist in **RA** without the classical clinical symptoms of sepsis, and occasionally clinically latent suppurative arthritis may be found at autopsy **(**19**)**. On the other hand clinically recognized and treated septic infection may have no histological evidence at autopsy **(**1, 18**)**.

According to Dubost et all (1994) one-third of infected joints were the knee, and the elbows and wrists were also more often infected in **RA** patients with septic arthritis than in septic patients without **RA**. *Staphylococcus aureus* was recovered in 80% of **RA** patients versus only 60% of septic patients without **RA**, more over Staphylococcal infection and multiple joint involvement were associated with higher mortality rates **(**19**)**.

In agreement with Dubost et all (1994) we also found that the knee joints are the most frequently involved joint, and *Staphylococcus aureus* (in 13) *E. coli* (in 10), *Proteus mirabilis* (in 5), *Pseudomonas aeruginosa* (in 5), *Klebsiella* (in 2), *Streptococcus haemolyticus* (in 2), *Streptococcus pyogenes* and *fecalis* (in 1-1) of 21 cultured cases are the most frequent pathogenic agents. In some cases fungi (Candida albicans, Aspergillus) and parasites were found only histologically, and were regarded as concomitant infection

(20**)**.

Maximal association coefficient: 1 of **SI** and **PA** refers to a very close connection between fatal **SI** and suppurative arthritis. The close connection implies that **SI** may be caused or complicated by **PA.**
In **RA** the active inflammation of the joints with swollen, hyperemic synovial membranes represent a favorable target (locus minoris resistentiae) for secondary bacterial inflammation, and **PA** in these cases may be regarded as a complication of general **SI (**21**)**. After intraarticular intervention **PA** should be regarded as a primary source of lethal **SI**, supported statistically by the close connection between intraarticular intervention and **PA (**21**)**.

There was no significant difference in the mean age of patients at death, onset or duration of **RA** between patients with and without **SI** (complicated or not by **PA**).
Fatal septic infection with or without purulent arthritis may develop in both sexes, and at any time in the course of the disease.
Septic complications of **RA** reduced the life expectancy of patients, especially women, and the shorter lifespan was strongly expressed in septic patients (inclusive females) complicated by **PA**.

SI complicated **RA** in 22 (14.97 %) of 147 patients (versus **sAV**: n=31, 21.08 % or **sAAa**: n=34, 23.13 %). All cases were fatal (14.97 %) of 147 patients (versus **sAV**: n=19, 12.92 % or **sAAa**: n= 17, 11.47 %), and was clinically missed in 13 (8.84 %) of 147 patients (versus **sAV**: n=5, 17.69 % or **sAAa**: n=9, 17.02 %); **SI** represents also a very serious complication, but seems to be less critical based on prevalence (fatal outcome), and missed diagnosis.
The **ratio** of **diagnosed** (n=9) and **missed** (n=13) **fatal** cases of **SI** was: **0.69** (9:13 of 22), and in cases of **PA** was: **0.83** (5:6 of 11).

1.4 Interstitial pneumonitis related to complications of RA

IPn itself was not fatal (led to death only in association with complications of **RA** as cardial or circulatory failure), and was diagnosed in **none** (0 %) of 30 patients.

1.5 Complications of RA (n=87)

Eighty seven (87) (**sAV**: n=31, **sAAa**: n=34 and **SI**: n=22) complications were present in **79** patients.
The **ratio** of **diagnosed** (n=22) and **missed** (n=36) **fatal complications** (n=58) was **0.61** (22:36 of 58), and it was: **0.36** (23:64 of 87) in total population of complications (one of not fatal **sAV** was clinically recognized).

2. Allied disorders of the lungs

2.1 Multifocal pneumonia with fatal outcome (BrPn, OcclPn, InfPn or RhPn)

In elderly patients (n=18) the **risk of purBr** or **BrPn** was **significantly higher** in comparison with 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.

Comparing the **age**, **sex** of patients, **onset** and **duration** of **RA** at the time of death, there was no significant difference between **RA** patients **with OcclPn** (n=2), **InfPn** (n=5) or **RhPn** (n=3), and **without multifocal Pn** (n=119); neither in females (the differences were not calculated in males because of the zero divisor).
OcclPn, **InfPn** or **RhPn** may develope in both sexes, and at any time in the course of the **RA**.

The **ratio** of **diagnosed** (n=19) and **missed** (n=9) **fatal** cases of **mfPn** was: **2.11** (19:9 of 28).

2.2 Tuberculosis (fTB, fcTB or mTB)

The prevalence and mortality of **TB** is much higher in an autopsy population compared to the general population **(**22**)**. The risk of encountering **TB** is reduced with decreasing incidence in the general population; however, it still can be found at autopsy**(**23**)**. Histopathology remains one of the most important methods for diagnosing tuberculosis **(**24**)**.

The diagnosis of latent **TB** in **RA** is a great challenge for the rheumatologist mainly due to the limited response in elderly autoimmune patients. Despite the presence of **TB**, patients may have no clinical complaints or radiological abnormalities, and the value of the tuberculin skin test may be also limited due to inadequate or poor response of the patients **(**25 – 26**)**, as well as the QuantiFERON blood test **(**27 – 28**)**. A positive **I**nterferon-**G**amma (**γ**) **R**elease **A**ssays (**IGRA**) result may not necessarily indicate **TB** infection with tuberculous mycobacteria **(**27**)**. A negative **IGRA** does not rule out active **TB** disease **(**28**)**.

Detailed medical history and targeted X-ray examination, as well as the tuberculin skin test, and the QuantiFERON blood test (despite their limitations) are key factors in the clinical diagnosis of latent **TB** with or without subclinical or atypical miliary exacerbation **(**29 – 31**)**.

Microbiologic culture may be necessary, but takes time (may be critical premortem), the results are often false negative, and in clinically latent **TB** it appears not indicated.

The clinically latent **TB** (**fTB**, **fcTB**, **mTB**) involved both genders, and developed at any time in the course of the disease.
The **onset** and **disease duration** of **RA** did not influence basically the prevalence and features of coexistent **TB** (**fTB**, **fcTB**, **mTB**).
The risk of **TB** was higher in elderly **RA** patients than in younger ones, especially elderly **females** were more likely to be affected by **TB**.
The risk of miliary dissemination (**mTB**) was particularly high in elderly **women**; females **with mTB** die earlier than females **without mTB**.

TB with **fatal** outcome (n=2) was not diagnosed, and the **ratio** of clinically **diagnosed** not fatal (n=2) and **missed** (n=19) cases of **TB** was: **0.11** (2:19 of 21).

2.3 Malignant tumors and bronchoalveolar cancer of the lungs

The malignant tumors (**mTu**) are of special clinical significance because of paraneoplastic symptoms can mimic rheumatic disease or because of cancer genesis in connection with immunomodulatory effect of immunosuppressive therapy.
Paraneoplastic syndromes with rheumatoid complaints may be excluded by the onset and duration of **RA** and tumors.
Bronchoalveolar carcinomas (5 of 14) were relatively numerous in comparisons to other carcinomas (9 of 14). The relatively high incidence of bronchoalveolar tumors is interesting and remains unexplained for the time being.

mTu with **fatal** outcome was diagnosed without exception (5 of 5=**1.0**); in total population the **ratio** of clinically **diagnosed** (n=6) and **missed** (n=8) cases was: **0.75** (6:8 of 14).

2.4 Associated diseases of the lungs (n=63)

Sixty three (**mfPn**: n=28, **TB**: n=21 and **mTu**: n=14) associated diseases were present in **56** patients.
The **ratio** of **diagnosed** (n=24) and **missed** (n=39) **associated diseases** of the lungs with **fatal** outcome was: **0.61** (24:27 of 63), and it was: **0.75** (27:36 of 63) in total population of associated diseases (one of

not fatal **mTu** was clinically recognized).

2.5 Complications of RA (with sAV, sAAa or SI) and/or associated diseases of the lungs (mfPn, TB or mTu) (n=111)

Comparing the **ratio** of **diagnosed** (n=22) and **missed** (n=36) **fatal complications** [**0.61** (22:36 of 58)] with **diagnosed** (n=26) and **missed** (n=37) **fatal associated diseases** of the lungs [**0.71** (24:39 of 63)], it was confirmed, that **fatal** complications of **RA** were often missed, than allied disorders.

This tendency was more pronounced comparing the **diagnosed** and **missed complications** [**0.36** (23:64 of 87)] with the **diagnosed** and **missed associated diseases** [**0.66** (27:36 of 63)] in the total population; **TB** from this point of view was exceptional.

Conclusions:

Complications of **RA** (**sAV**, **sAAa**, **SI**) and/or allied disorders of the lungs (**mfPn**, **TB**, **mTu**) were present in **111** (75.51 % of 147) patients, accompanying **RA** in both sexes and at any time in the course of **RA**. Only **36** (24.49 % of 147) patients were found without complications or allied disorders of the lungs, which died of consequences of atherosclerosis (**Ath**) or accidental (post-operative embolia in one case).

Elderly (especially female) patients were more likely to be affected by **sAV** than younger or male patients. The so called rheumatoid pneumonia (**RhPn**) is a rare lethal complication of **RA**, and may be regarded a vasculogenetic entity in **RA**.

The reactivation of latent **TB** was extremely high in elderly **RA** patients, compared to the younger ones; especially elderly **females** were more likely to be affected by **TB**.

The prevalence of **purBr** or **BrPn** was also higher in our elderly female and male autoimmune patients with impaired immune function, with or without conventional or biological treatment.

The ratio of **diagnosed** and **missed fatal** cases was very bad in case of **sAV** (0.26) in contrast to **SI** (0.69), **PA** (0.83) or **sAAa** (1.13).

Between associated diseases of the lungs, the **TB** (0.0) topped the list as the the most dangerous and life threatening diseases compared to **mTu** (1.0) or the **mfPn** (2.11) based on the proportion of diagnosed and missed cases.

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Volume 2 Issue 3 March 2021