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Research Article

Tuberculosis and Associated Complications and Comorbidities of Rheumatoid Arthritis - A Retrospective Clinicopathologic Study of 234 Autopsy Patients

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Abstract

Introduction: Coexisting complications and comorbidities modify each other and the underlying disease, producing atypical clinical manifestations.

The risk of post-primary tuberculosis (TB) is high in rheumatoid arthritis (RA).

The diagnosis of inactive or active clinically latent TB in RA is a great challenge for the rheumatologist mainly due to the limited response and treatment of elderly autoimmune patients.

This study discusses the characteristics of tuberculosis and the interactions with the coexistent complications and associated diseases on a large autopsy population with rheumatoid arthritis.

Patients (Autopsy Population) and Methods: The patients were treated and died at the National Institute of Rheumatology, Budapest, Hungary, between 1969 and 1999 in the era of steroid and conventional synthetic disease modifying anti-rheumatic drug treatment (csDMARDs), before the introduction of biological therapy (boDMARDs).

RA was confirmed clinically according to the criteria of the American College of Rheumatology (ACR).

The post-primary fibrous (fTB) or fibro-caseous (fcTB) tuberculosis with or without active miliary dissemination (mTB) was diagnosed at autopsy, confirmed and characterized microscopically by a detailed review of extensive histological material, reviewing all available clinical and pathological reports.

Results: Inactive or active TB (fTB, fcTB, mTB) developed in both sexes, and at any time in the course of RA.

The morbidity of tuberculosis was higher in elderly people with RA than in younger ones, especially aged women had a higher susceptibility for TB.

TB, especially fcTB, represented a high risk for miliary dissemination in RA.

The presence of fcTB or mTB increased the risk for mortality of RA patients, especial of women, while consolidated anthracotic scars (fTB) did not.

Women with mTB died earlier then women without mTB.

The onset, and duration of RA did not influence the prevalence and mortality of inactive or active TB.

Discussion and Conclusion: Our results suggest that the clinical diagnosis of TB with or without lethal outcome is incidental.

A detailed medical history and targeted X-ray examination, as well as the tuberculin skin test (despite its limitations) are key factors in diagnosing clinically latent TB with or without subclinical atypical miliary exacerbation.

The value of inflammatory clinical-laboratory parameters is limited; none of them is specific for tuberculosis and indicates only actual inflammatory activity.

(Based on our previous study, the decreased albumin/globulin quotient and elevated α1 and α2 globulin % of patients with moderate clinical activity of RA may indicate the reactivation of a dormant inactive tuberculotic process excluding other causes of inflammatory activity).

Histopathology remains one of the most important methods for diagnosing tuberculosis.

Granulomatous autoimmune vasculitis can be regarded as an indirect histological sign of dormant TB with or without miliary dissemination, supported by the close relationship between epithelioid granulomas and granulomatous transformation of blood vessels, independently of the origin of the tissue samples.

Keywords: *Rheumatoid Arthritis; Latent Tuberculosis; Demographics; Clinical Diagnosis; Comorbidities*

Abbreviations

RA: Rheumatoid Arthritis; ACR: American College of Rheumatology; TB: Tuberculosis; fTB: Fibrous Tuberculosis; fcTB: Fibro-Caseous Tuberculosis; mTB: Miliary Tuberculosis; cDMARDs or csDMARDs: Conventional (Synthetic) Disease Modifying Antirheumatic Drugs (Methotrexate, Leflunomide, Sulfasalazine, Hydro Chloroquine, Chloroquine); bDMARDs or boDMARDs: Biological (Original) Disease Modifying Antirheumatic Drugs (TNF-α Inhibitors: Adalimumab, Certolizumab, Pegol, Etanercept, Golimumab, Infliximab, and Others); IGRAs: Interferon-Gamma (γ) Release Assays (QuantiFERON Blood Test); AV: Autoimmune (Rheumatoid) Vasculitis; NsAV: Nonspecific AV; FnAV: Fibrinoid Necrotic AV; GrAV: Granulomatous AV; AAa: Systemic AA Amyloidosis; AbSI: Acute Bacterial Septic Infection with Lethal Outcome; PA: Purulent Septic Arthritis; Ath: Atherosclerosis; LyIPn: Lymphocytic Interstitial Pneumonia; ILyH: Interstitial Nodular Lymphoid Hyperplasia; HE: Hematoxylin Eosin Staining; PAS: Periodic Acid Schiff Reaction; Pr. n^0/y: Protocol Number/Year; Cl+: Clinically Diagnosed; Cl-: Clinically Not Recognized; SD: Standard Deviation; NS: Not Significant; 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; CDAI: Clinical Disease Activity Index for Rheumatoid Arthritis (Smolen JS, Aletaha D); SDAI: Simple Disease Activity Index for Rheumatoid Arthritis (Smolen JS, Aletaha D); DAS28-CRP: Disease Activity Score-28 for Rheumatoid Arthritis with CRP (Fransen J)

Introduction

The risk of tuberculosis (TB) is higher in rheumatoid arthritis (RA) compared to the general population due to the impaired immune reactivity of elderly patients with autoimmune disease [1-6], and especially high when the patients are treated with steroids, and conventional or biological disease-modifying antirheumatic drugs (cDMARDs or bDMARDs) [6].

Introduction of bDMARDs (TNF inhibitors, etc.) increases the risk of reactivation of dormant TB with miliary dissemination (mTB) in RA [7,8].

TB is one of the most important diseases accompanying RA [9-11].

Aim of the Study

The aim of this study was:

1. To determine the prevalence of post-primary TB in RA patients.
2. To characterize histologically the post-primary fibrous (fTB) or fibro-caseous (fcTB) tuberculotic processes, with or without active miliary dissemination (mTB).
3. To determine the proportion between inactive TB and active miliary disseminated TB.
4. To ascertain the origin (endogenous exacerbation or exogenous reinfection) of tuberculotic processes statistically, based on the relationships between TB and fTB, fcTB or mTB.
5. To register the organ involvement by TB and mTB.
6. To review the demographics of RA patients with and without tuberculotic processes.
7. To identify those groups of RA patients which are at a high risk of latent and active TB (based on the age, sex of patients, onset and duration of RA).
8. To assess the mortality due to TB or miliary disseminated tuberculosis (mTB).
9. To detect the incidence of clinically latent (not diagnosed) indolent TB or mTB in the era of steroid and cDMARDs, before introduction of the bDMARDs; to estimate the real danger of dormant TB or mTB in RA.
10. To analyze the relationship between mortality and clinical diagnosis of TB, fTB, fcTB or mTB.
11. To establish the most important complications and associated diseases of RA in patients with TB.
12. To prove the possible influence of fTB, fcTB or mTB on the prevalence and mortality of complications of RA.
13. To appraise the possible influence of fTB, fcTB or mTB on the prevalence and mortality of comorbidities of RA.

Patients (Autopsy Population) and Methods

Two hundred thirty-four (234) non-selected autopsy patients with RA were studied.

RA was confirmed clinically according to the criteria of the American College of Rheumatology (ACR) [12].

The patients were treated and died at the National Institute of Rheumatology, Budapest, Hungary, between 1969 and 1999 in the era of steroid and conventional synthetic disease modifying anti-rheumatic drug treatment (csDMARDs), before the introduction of biological therapy (boDMARDs).

The post-primary fibrous (fTB) or fibro-caseous (fcTB) tuberculosis with or without active miliary dissemination (mTB) was diagnosed at autopsy, confirmed and characterized microscopically by a detailed review of extensive histological material, reviewing all the available clinical and pathological reports retrospectively.

From each patient a total of 50-100 tissue blocks of 16 organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal gland, skeletal muscle, peripheral nerve, skin, brain, bone and synovial membrane of hip- and knee-joint) were studied microscopically.

The tissue blocks were fixed in an 8% aqueous solution of formaldehyde at pH 7.6 for > 24 hours at room temperature (20 C^{o}) and embedded in paraffin.

Serial sections (5 microns) were stained with hematoxylin-eosin (HE) [13].

In case of fTB, fcTB or mTB additional histological sections were stained according to Ziehl-Neelsen [14] using positive control.

Standard sections were examined with a professional high-brightness (100-Watt) microscope (Olympus BX51).

Demographics of different patient cohorts were compared with the Student (Welch) T-probe [15]. The difference between two samples was regarded "significant" at an alpha level of 0.05.

The relationships were analyzed with Pearson's chi-squared (χ^2) test between tuberculotic processes (TB, fTB, fcTB, mTB, active and inactive TB, with or without lethal outcome), furthermore between TB and complications or comorbidities of RA [15].

Glossary of TB

- TB: Post-primary tuberculosis localized to the lungs.
- Prevalence of TB: The number of autopsy patients with TB who died at the National Institute of Rheumatism, Budapest Hungary between 1969 and 1999.
- fTB: Fibrous TB, anthracotic tuberculotic scar (inactive, without miliary dissemination or active, with miliary dissemination).
- fcTB: Fibro-caseous TB, characterized by fibrous and caseous tubercule (inactive, without miliary dissemination or active, with miliary dissemination).
- mTB: Miliary TB (active fTB or fcTB tuberculosis with miliary dissemination); the hematogenous dissemination of exudative or proliferative granulomas in late (Ranke III) stage of TB may involve different organs.
- mTB exudative: Miliary granulomas characterized by exudative (serous), paucicellular, without epithelioid histiocytes and without Langhan's type giant cells; exudative mTB corresponds to the poor response (limited reactivity) of the patients.
- mTB proliferative: Miliary granulomas characterized by proliferative histiocytes and multinucleated giant cells of Langhans; proliferative mTB corresponds to a relative better response (reactivity) of the patients.

Glossary of RA complications and accompanying disease (definitions)

- Basic disease: Underlying disease related to death.
- Complication: Consequence of basic disease leading directly to death.
- Cause of death: Fatal outcome of basic disease.
- Associated (Accompanying) disease: Important disorder without direct causal role in death.
- AV: Autoimmune (rheumatoid) Vasculitis means presence of inflammatory infiltration and structural changes in blood vessels of different calibers.
- Systemic vasculitis of autoimmune origin (AV): Defined as one of the basic manifestations of RA determined in 12 organs [9], excluding other causes of vasculitis, like hypertension, diabetes mellitus, tumors, septic infections etc.
- AAa: Systemic AA amyloidosis was specified histologically, based on evaluation of 5 organs (heart, lung, liver, kidney, and pancreas).
- Amyloid A deposition was diagnosed histologically with a modified (more sensitive) Congo red staining [17] of Romhányi [16]. Amyloid A deposits were identified in serial sections by immunohistochemical and histochemical methods [18,19].
- AbSI: Acute bacterial septic infection with a lethal outcome (only infections with clinically identified pathogenic agents were considered).
- PA: Purulent arthritis.

- Atherosclerosis: Atherosclerosis was diagnosed in RA patients only in cases when it was present macroscopically as a "severe" atherosclerotic process (characterized by occlusive thrombosis or sclerotic ulcers) or when it was the basic disease leading to death. Moderate changes like hyaline or sclerotic plaques without causal role in death were not mentioned as "atherosclerosis" since such changes are frequent in elderly RA patients [9].
- Myocardiocytolysis: Multifocal microinfarction of myocardium.
- LyIPn: Lymphocytic interstitial pneumonia is characterized by interstitial nodular lymphoid hyperplasia (ILyH). It is a rare form of compressive bronchial obstruction complicating RA [9]. LyIPn sometimes also called as obliterative bronchiolitis and confused with the organizing pathological processes.

Results

Prevalence and characteristic of post primary TB in RA

Post-primary TB localized to the lungs accompanied RA in 28 (11.96%) of 234 autopsy patients. Sixteen (57.14%) of 28 TB were histologically only fibrous, anthracotic tuberculotic scars (fTB), and 12 (42.86%) of 28 revealed a fibro-caseous tubercle (fcTB).

Two of 16 fTB and 7 of 12 fcTB were complicated by active disseminated miliary tuberculosis (mTB) in 9 (3.84% of 234; 32.14% of 28) RA patients; fTB or fcTB was inactive in 19 (8.12% of 234; 67.86% of 28) RA patients.

TB was histologically excluded in 206 (88.03%) of 234 RA patients.

There was a strong positive correlation between: TB and fTB ($c = 1$, $\chi^2 = 117.5726$, $p < 0.0000000$), TB and fcTB ($c = 1$, $\chi^2 = 84.4575$, $p < 0.00000001$), TB and mTB ($c = 1$, $\chi^2 = 63.029$, $p < 0.0000000$) or fcTB and mTB ($c = 0.9871$, $\chi^2 = 86.6046$, $p < 0.0000000$). The link between fTB and mTB was not significant ($c = 0.6231$, $\chi^2 = 1.4196$, $p < 0.2334$ - NS).

Proliferative and exudative epithelioid granulomas (mTB) existed side by side in the same or in different organs, such as lungs, liver, spleen, adrenal glands, synovial membrane, vertebrae, pituitary gland, and lymph nodes.

The organs involved in disseminated military tuberculosis are listed in table 1.

	Pr. n /year	Post-primary tuberculotic focus	Histological character of TB: fibrous (fTB) or fibro caseous (fcTB)	Disseminated miliary TB (mTB) exudative or proliferative granulomas side by side
1	61/70	Lung	fcTB	Lung, liver, spleen, adrenal gland, synovial membrane, vertebrae
2	140/70	Lung	fcTB	Lung, pituitary gland
3	287/75	Lung	fcTB	Lung
4	395/76	Lung	fcTB	Lung, liver
5	240/88	Lung	fTB	Lung, spleen
6	227/89	Lung	fcTB	Lung, lymph node, liver
7	87/90	Lung	fcTB	Lymph node
8	375/95	Lung	fcTB	Lymph node
9	155/97	Lung	fTB	Lung, liver

Table 1: *Organs involved in disseminated miliary tuberculosis.*

Glossary to table 1: TB: Tuberculosis; fTB: Fibrous Tuberculosis; fcTB: Fibro-Caseous Tuberculosis; mTB: Miliary Tuberculosis; Pr. n0/y: Protocol Number/Year.

Demographics of patients with or without tuberculosis in RA

The mean age of RA patients was high with TB (68.93 years), inactive TB (69.37 years), or active mTB (68.00 years) in comparison with the total population of RA (66.25 years) or with patients without TB (65.89 years), but these differences were not significant (Table 2 and 3).

The mean age of female RA patients with TB was also higher than the mean age of females without TB (69.76 years versus 65.82, $p < 0.142$ - NS).

The mean age of RA patients with anthracotic tuberculotic scar (fTB) was especial high compared to the patients without TB (70.81 years versus 65.89, $p < 0.566$ - NS), and particular high comparing the females (72.09 years versus 65.82, $p < 0.590$ - NS) (Table 2 and 3).

Miliary dissemination of TB was more common in females than males (8 of 9 RA patients with mTB were women) and led to death only in females (3 of 3) in our autopsy population (Table 2).

Sex, mean age (range) with SD, duration, and onset of RA (in years) with or without tuberculosis are summarized in table 2.

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) ± SD
RA patients	234	66.25 ± 13.15	16- 88	51.02 ± 16.58	14.76 ± 10.79
Female	170	66.31 ± 12.82	16 - 88	50.46 ± 15.92	15.42 ± 11.12
Male	64	66.08 ± 13.97	19 - 88	52.55 ± 18.18	12.96 ± 9.60
With TB	28 of 234	68.93 ± 10.10	47 - 84	54.96 ± 15.66	14.33 ± 12.14
Female	21	69.76 ± 10.78	47 - 84	55.00 ± 16.87	15.30 ± 13.28
Male	7	66.43 ± 7.11	56 - 78	54.86 ± 11.54	11.57 ± 7.40
With fTB	16 of 28	70.81 ± 10.09	47 - 84	53.44 ± 15.64	17.38 ± 12.93
Female	11	72.09 ± 11.06	47 - 84	53.18 ± 17.03	18.91 ± 14.49
Male	5	68.00 ± 6.72	59 - 78	54.00 ± 12.82	14.00 ± 7.48
With fcTB	12 of 28	66.43 ± 9.54	50 - 80	57.18 ± 15.15	9.91 ± 7.27
Female	10	67.20 ± 9.86	50 - 80	57.22 ± 16.40	10.89 ± 9.98
Male	2	62.50 ± 6.50	56 - 69	57.00 ± 7.00	5.50 ± 0.50
With inactive TB	19 of 28	69.37 ± 10.22	47 - 84	53.11 ± 17.73	16.25 ± 15.67
Female	13	70.92 ± 10.89	47 - 84	53.00 ± 19.88	17.92 ± 15.45
Male	6	66.00 ± 7.59	56 - 78	53.33 ± 11.80	12.67 ± 7.45
With active mTB	9 of 28	68.00 ± 9.75	50 - 82	59.38 ± 7.35	9.75 ± 4.89
Female	8	67.88 ± 10.34	50 - 82	58.71 ± 7.63	10.43 ± 4.87
Male	1	69.00 ± 0.00	69 - 69	64.00 ± 0.00	5.00 ± 0.00
Without TB	206 of 234	65.89 ± 13.46	16 - 88	50.34 ± 16.64	14.83 ± 10.53
Female	149	65.82 ± 12.99	16 - 88	49.65 ± 15.61	15.44 ± 10.69
Male	57	66.04 ± 14.59	19 - 88	52.17 ± 19.03	13.19 ± 9.90

Fatal fcTB with mTB	3 of 28	67.670 ± 5.91	58 - 71	57.00 ± 7.00	7.50 ± 0.50
Female	3	67.670 ± 5.91	58 - 71	57.00 ± 7.00	7.50 ± 0.50
Male	-	-	-	-	-
Not fatal fTB, fcTB or mTB	25 of 28	69.68 ± 10.23	47 - 84	54.80 ± 16.19	14.88 ± 12.46
Female	18	70.94 ± 10.96	47 - 84	54.78 ± 17.61	16.17 ± 15.72
Male	7	66.43 ± 7.11	56 - 78	54.86 ± 11.54	11.57 ± 7.40

Table 2: *Sex, mean age (range) with SD, onset and disease duration of RA with (inactive fTB, fcTB and active mTB) and without TB, furthermore with or without fatal outcome.*

Legend to table 2: Fourteen of 16 fTB and 5 of 12 fcTB were inactive (dormant) in 19 (8.12% of 234; 67.86% of 28) RA patients. TB (2 of 16 fTB and 7 of 12 fcTB) was active, complicated by miliary dissemination (mTB) in 9 (3.84% of 234; 32.14% of 28) RA patients. mTB led to death in 3 of these 9 patients.

Glossary to table 2: RA: Rheumatoid Arthritis; TB: Tuberculosis; fTB: Fibrous TB (with or without miliary dissemination, n = 16); fcTB: Fibro-Caseous TB (with or without miliary dissemination, n = 12); mTB: Miliary Tuberculosis (Active tuberculosis with miliary dissemination, n = 9); SD: Standard Deviation.

There was no significant difference in the lifespan, onset and disease duration of RA between patient cohorts with TB (n = 28) and fTB (n = 16), fcTB (n = 12) or mTB (n = 9).

The difference was also not significant between

- TB (n = 28) and without TB (n = 206),
- TB (n = 28) and inactive TB (n = 19),
- fTB (n = 16) and fcTB (n = 12),
- fTB (n = 16) and mTB (n = 9) or
- fcTB (n = 12) and mTB (n = 9).

Inactive or active TB (fTB, fcTB, mTB) developed in both sexes, and at any time in the course of the disease (Table 2 and 3).

Elderly females with mTB (n = 8) died earlier than females without mTB (n = 13) (67.88 years versus 70.92, $p < 0.552$ - NS).

RA in male patients with fcTB started later in comparison to the total autopsy population (66.08 years versus 62.50 years), and their chance of survival decreased significantly (5.50 years versus 12.96; $p < 0.000014$); the fTB did not influence statistically the lifespan of RA patients.

RA started later in patients with active mTB in comparison to the total autopsy population (59.38 years versus 51.02 years; $p < 0.020$), and the patients died earlier; the duration of RA decreased significantly in patients with mTB (9.75 years versus 14.76; $p < 0.033$).

Similar significant relationships were found comparing the onset of disease (58.71 years versus 50.46 years; $p < 0.050$) or disease duration (10.43 years versus 15.42; $p < 0.040$) in the female patients.

Table 3 summarizes the statistical correlations ("p" values) between female and male RA patients with and without TB, fTB, fcTB, or mTB, furthermore with or without fatal outcome.

RA patients n = 234 with and without TB, fTB, fcTB or mTB	Age p <	Onset of disease p <	Disease duration p <
RA patients n = 234 versus pts. with TB n = 28 of 234	0,212	0,242	0,867
Female n = 170 of 234 versus n = 21 of 28	0,193	0,280	0,970
Male n = 64 of 234 versus n = 7 of 28	0,920	0,678	0,686
RA patients n = 234 versus pts. with fTB n = 16 of 28	0,112	0,579	0,456
Female n = 170 of 234 versus n = 11 of 16	0,137	0,634	0,472
Male n = 64 of 234 versus n = 5 of 16	0,629	0,842	0,804
RA patients n = 234 versus pts. with fcTB n = 12 of 28	0,957	0,238	0,138
Female n = 170 of 234 versus n = 10 of 12	0,800	0,286	0,246
Male n = 64 of 234 versus n = 2 of 12	0,679	0,639	0,000014
RA patients n = 234 versus pts. with inactive TB n = 19 of 28	0,234	0,637	0,655
Female n = 170 of 234 versus n = 13 of 19	0,181	0,674	0,593
Male n = 645 of 234 versus n = 6 of 19	0,984	0,898	0,938
RA patients n = 234 versus pts. with active mTB n = 9 of 28	0,634	0,020	0,033
Female n = 170 of 234 versus n = 8 of 9	0,708	0,040	0,050
Male n = 64 of 234 versus n = 1 of 9	-	-	-
RA patients n = 234 versus pts. without TB n = 206 of 234	0,762	0,706	0,949
Female n = 170 of 234 versus n = 149of 206	0,677	0,646	0,970
Male n = 64 of 234 versus n = 57 of 206	0,987	0,923	0,912
TB n = 28 of 234 pts. versus without TB n = 206	0,163	0,176	0,845
Female n = 21 of 28 versus n = 149 of 206	0,142	0,209	0,965
Male n = 7 of 28 versus n = 57 of 206	0,912	0,638	0,644
TB n = 28 of 234 pts. versus fTB n = 16	0,566	0,768	0,464
Female n = 21 of 28 versus n = 11 of 16	0,590	0,787	0,520
Male n = 7 of 28 versus n = 5 of 16	0,732	0,917	0,626
TB n = 28 of 234 pts. versus fcTB n = 12	0,477	0,701	0,253
Female n = 21 of 28 versus n = 10 of 10	0,537	0,754	0,356
Male n = 7 of 28 versus n = 2 of 2	0,655	0,823	0,092
TB n = 28 of 234 pts. versus inactive TB n = 19	0,888	0,722	0,633
Female n = 21 of 28 versus n = 13 of 19	0,772	0,775	0,632
Male n = 7 of 28 versus n = 6 of 19	0,925	0,834	0,812
TB n = 28 of 234 pts. versus active mTB n = 9	0,818	0,297	0,140
Female n = 21 of 28 versus n = 8 of 9	0,688	0,463	0,193
Male n = 7 of 28 versus n = 1 of 9	-	-	-
fTB n = 16 of 28 pts. versus fcTB n = 12	0,268	0,558	0,105

Female n = 11 of 16 versus n = 10 of 12	0,321	0,616	0,183
Male n = 5 of 16 versus n = 2 of 12	0,548	0,774	0,085
fTB n = 16 of 28 pts. versus mTB n = 9	0,524	0,242	0,059
Female n = 11 of 16 versus n = 8 of 9	0,433	0,388	0,113
Male n = 5 of 16 versus n = 1 of 9	-	-	-
fcTB n = 12 of 28 pts. versus mTB n = 9	0,729	0,697	0,964
Female n = 10 of 12 versus n = 8 of 9	0,897	0,825	0,911
Male n = 2 of 12 versus n = 1 of 9	-	-	-
inactive TB n = 19 of 28 pts. versus mTB n = 9	0,749	0,223	0,092
Female n = 13 of 19 versus n = 8 of 9	0,552	0,394	0,144
Male n = 6 of 19 versus n = 1 of 9	-	-	-
TB n = 28 of 234 pts. vs. TB fatal n = 3 of 28	0,269	0,823	0,009
Female n = 21 of 28 versus n = 3 of 28	0,225	0,830	0,020
Male n = 7 of 28 versus n = 0 of 28	-	-	-
TB n = 28 of 234 pts. vs. TB not-fatal n = 25 of 28	0,793	0,971	0,876
Female n = 21 of 28 versus n = 18 of 25	0,744	0,969	0,849
Male n = 7 of 28 versus n = 7 of 25	1,000	1,000	1,000
TB fatal n = 3 of 28 pts. vs. TB not-fatal n = 25 of 28	0,227	0,811	0,009
Female n = 3 of 3 versus n = 18 of 25	0,172	0,813	0,019
Male n = 0 of 3 versus n = 7 of 25	-	-	-

Table 3: *Relationship between patient cohorts with and without TB, fTB, fcTB or mTB.*

Legend to table 3: There was no significant difference in mean age of patients comparing the total autopsy population (n = 234) and the patient cohorts with and without TB, fTB, fcTB or with and without fatal outcome; p values were higher than 0.05. RA in male patients with fcTB started later comparing with the total autopsy population (66.08 years versus 62.50 years), and the chance of survival decreased significantly (5.50 years versus 12.96; p < 0.000014); the fTB did not influence statistically the lifespan of RA patients. RA started later in patients with active mTB comparing to the total autopsy population (59.38 years versus 51.02 years; p < 0.020), and the patients died earlier; the duration of RA decreased in patients with mTB (9.75 years versus 14.76; p < 0.033). The relationships were similar comparing the onset of disease (58.71 years versus 50.46 years; p < 0.050) or disease duration (10.43 years versus 15.42; p < 0.040) in the female patients.

Glossary to table 3: RA: Rheumatoid Arthritis; TB: Tuberculosis; fTB: Fibrous Tuberculosis; fcTB: Fibro-Caseous Tuberculosis; mTB: Miliary Tuberculosis (Active tuberculosis with miliary dissemination); inactive TB: Inactive Tuberculosis Without Miliary Dissemination.

Mortality of post primary TB, fTB, fcTB or mTB in RA

Tuberculosis (fcTB complicated by mTB) led to death in 3 female patients.

TB influenced notable the mortality of RA patients; the correlation between TB and mortality was significant (c = 1, χ^2 = 14.6938, p < 0.00012).

There was a strong positive correlation between mTB and mortality (c = 1, χ^2 = 51.9190, p < 0.0000), and fcTB and mortality (c = 1. χ^2 = 38.2026, p < 0.0000). The link between or fTB and mortality was not significant, it was negative (c = -1*. χ^2 = 0.8316, p < 0.3618 - NS).

Clinical diagnosis of TB, fTB, fcTB or mTB

TB was clinically diagnosed only in 4 (14.28% of 28; 1.71% of 234) patients: 1 fatal fcTB with disseminated mTB (3.57% of 28; 0.43% of 234), and 3 not fatal inactive fTB (10.71% of 28; 1.28% of 234) with consolidated fibrous tubercular.

fTB or fcTB was clinically latent (not recognized and/or not mentioned in clinical reports) in 24 (85.71% of 28; 10.26% of 234) patients.

Relationships (statistical links) between mortality and clinical diagnosis of TB, fTB, fcTB or mTB

The links between mortality and clinical diagnosis of TB (c = 0.5714, χ^2 = 0.0156, p < 0.9007 - NS), fTB (c = 0.4348, χ^2 = 0.0547, p < 0.8150 - NS), fcTB (c = -0.4348*, χ^2 = 0.0547, p < 0.8150 - NS) or mTB (c = -0.2000*, χ^2 = 0.0611, p < 0.6042 - NS) were not significant (based on 28 tuberculotic patients); the histological appearance or characteristics of fTB, fcTB or mTB did not influence statistically the clinical recognition of TB (the positive clinical diagnosis was independent of mortality).

Prevalence, mortality and clinical diagnosis of TB, fTB, fcTB with or without mTB are summarized in table 4.

RA population n = 234	inactive fTB or fcTB without mTB	fTB or fcTB with active mTB	Lethal outcome	Clinically diagnosed
TB n = 28 (11.96%) of 234	n = 19 of 28 (8.12%) of 234 (67.86%) of 28	n = 9 of 28 (3.84%) of 234 (32.14%) of 28	n = 3 of 28 (1.28%) of 234 (10.71%) of 28	n = 4 of 28 (1.71%) of 234 (14.28%) of 28
fTB n = 16 (6.83%) of 234 (57.14%) of 28	n = 14 of 16 (5.98%) of 234 (50.00%) of 28	fTB with mTB n = 2 of 16 (0.62%) of 234 (4.76%) of 28	n = 0 of 16	n = 3 of 16
fcTB n = 12 (5.12%) of 234 (42.86%) of 28	n = 5 of 12 (2.48%) of 234 (19.05%) of 28	fcTB with mTB n = 7 of 12 (3.11%) of 234 (23.81%) of 28	n = 3 of 12	n = 1 of 12

Table 4: *Prevalence, mortality and clinical recognition of TB, fTB, fcTB with or without mTB in 28 of 234 RA patients.*

Glossary to table 4: RA: Rheumatoid Arthritis; TB: Tuberculosis; fTB: Fibrous Tuberculosis; fcTB: Fibro-Caseous Tuberculosis; mTB: Miliary Tuberculosis (Active Tuberculosis with Miliary Dissemination); Inactive TB: Inactive Tuberculosis.

Complications and comorbidities of RA in patients with TB

The most important complications and associated diseases of RA patients with fTB, fcTB or mTB are summarized in table 5.

	f/m	Basic disease	Complication(s)	Cause of death	Associated disease	Cl+ Cl-	Pr. n /Year
1	f	fcTB	mTB	Circulatory failure	RA-DM	Cl-	61/70
2	f	fcTB	mTB	Circulatory failure	RA	Cl-	140/70
3	f	fcTB	mTB	Erosion bronchial artery	RA-DM	Cl+	287/71

4	f	RA	AV -AAa	Myocardiocy-tolysis	fcTB-mTB	Cl-	395/76
5	f	RA	AV -AAa	Myocardiocy-tolysis	fTB-mTB	Cl-	240/88
6	f	RA	AV -AAa	Myocardiocy-tolysis	fcTB-mTB-HT	Cl-	227/89
7	f	RA	AV -Pan-carditis	Circulatory failure	fcTB-mTB-Ath	Cl-	87/90
8	f	RA	AV	Multiple brain necro-sis	fTB-CAA-DM	Cl-	279/87
9	m	RA	AV	Circulatory failure	fTB	Cl+	174/72
10	m	RA	AV	Circulatory failure	fTB-Ath	Cl-	36/86
11	f	RA	AV-Pan-carditis	Circulatory failure	fcTB-DM-Ath	Cl-	41/90
12	f	RA	AV-Coronary thrombosis	Myocardial necrosis	fcTB-Ca-Ath	Cl-	65/90
13	f	RA	Purulent arthritis	Septic infec-tion	fcTB	Cl-	287/75
14	m	RA	Purulent arthritis	Septic infec-tion	fcTB-Ath	Cl-	169/89
15	f	RA	Phlegmonous colitis	Septic infec-tion	fcTB-Ath	Cl-	163/93
16	m	RA	Duodenal ulcer	Septic infec-tion - SV	fcTB-mTB	Cl-	375/95
17	f	RA	Myocarditis	Septic infec-tion	fTB-mTB-DM-Ca	Cl+	155/97
18	m	RA	Fibrinous pericar-ditis	Circulatory failure	fTB-Ath	Cl-	30/75
19	f	RA	Interstitial pneu-monitis-ILyH	Multifocal pneumonia	fTB-DM-Ath-HT	Cl-	115/84
20	f	RA	Bronchoalveolar Ca****-AAa	Broncho-pneumonia	fTB-Ath		226/85
21	f	Ath	Myocardial fibrosis	Broncho-pneumonia	RA-fTB	Cl-	318/76
22	f	Ath	Myocardial fibrosis	Circulatory failure	RA-fTB	Cl+	208/77
23	f	Ath	Myocardial fibrosis	Circulatory failure	RA-fTB	Cl-	257/80
24	m	Ath	Coronary throm-bosis	Myocardial necrosis	RA-fTB-DM-G	Cl-	283/80

25	m	Ath	Cerebral artery sclerosis	Multiple brain necrosis	RA-fTB-DM-G	Cl-	62/83
26	f	Ath	Coronary thrombosis	Myocardial necrosis	RA-fTB -DM	Cl-	121/87
27	f	Ath	Femoral artery thrombosis	Broncho-pneumonia	RA-fTB -DM	Cl-	190/95
28	f	Ath	Cerebral artery thrombosis	Brain necrosis	RA-fTB -DM-HT	Cl-	309/96

Table 5: *The prevalence (28 of 234) and mortality (3 of 234) of tuberculosis in RA with the most important complications and concomitant diseases listed according to the basic disease.*

Remarks to table 5: Basic disease (underlying disease related to death): fcTB complicated by mTB led to death in 3, RA in 17, and Ath in 8 of 28 patients.

Complications of RA (consequence of basic disease leading directly to death or contributed to the fatal outcome): AV in 5 of 9, AAa in none of 4, SI in 5 (including 2 complicated by PA) patients etc. led directly to death.

Associated (accompanying) diseases (important disorder without direct causal role in death): Ath in 9, DM in 7, HT in 3 of 28 cases etc. accompanied to TB.

Cl+: Clinically diagnosed Cl-: Clinically not recognized fTB, fcTB or mTB.

Pr. n^0/y - Autopsy protocol number/year.

Abbreviations: RA: Rheumatoid Arthritis; TB: Tuberculosis; fTB: Fibrous Tuberculosis; fcTB: Fibro-Caseous Tuberculosis; mTB: Miliary Tuberculosis; AV: Autoimmune Vasculitis; AAa: AA Amyloidosis; AbSI: Acute Bacterial Lethal Septic Infection; PA: Purulent Arthritis; Ath: Atherosclerosis; HT**: Hypertension; DM***: Diabetes Mellitus Adult Type 2; CAA: Cerebral Amyloid Angiopathy; Ca: Bronchoalveolar Carcinoma****; G: Gout; ILyH: Pulmonary Interstitial Lymphoid Hyperplasia.*

Ath was diagnosed in RA patients only when it was present macroscopically as a "severe" atherosclerotic process or when it was the basic disease leading to death.*

*HT** Only atherosclerosis related hypertension was listed; RA related hypertension caused by glomerulonephritis or renal AAa, AV, Cushing syndrome etc. we're not considered.*

ILyH - Interstitial nodular Lymphoid Hyperplasia [9].

*The diagnosis of HT** and DM*** was based on clinical data.*

*Bronchoalveolar Ca**** - Bronchoalveolar Ca of apical scar perhaps arising from a tuberculotic apical scar.*

Possible influence of TB (fTB, fcTB or mTB) on complications (AV, AAa, SI or PA) of RA with and without fatal outcome

Autoimmune vasculitis (AV), AA amyloidosis (AAa), and septic infection (SI) with or without purulent arthritis (PA) were the most important complications of RA in association with TB (Table 5).

Autoimmune vasculitis

Systemic autoimmune vasculitis (AV) complicated RA in 43 (18.38%) of 234 patients and led directly to death in 24 (10.25% of 234 and 55.81% of 43) cases; AV existed in 19 (8.12% of 234 and 44.18% of 43) patients without direct causal role in death.

Three types of vasculitis were found in patients with AV: nonspecific (Ns), fibrinoid necrotic (Fn), and granulomatous (Gr).

Various types of AV were detected side by side in the same histologic section, indeed in distinct segments or sectors of the same blood vessels; arteries and veins of different sizes were involved at the same time.

Nonspecific vasculitis has existed in all 43 patients, in combination with fibrinoid necrotic vasculitis in 20 (46.51% of 43) and combined with granulomatous vasculitis in 12 (27.91% of 43) patients.

Ns vasculitis alone or combined contributed to the mortality in 24 of 43, Fn vasculitis in 11 of 20, and the Gr vasculitis in 11 of 12 cases.

Influence of tuberculosis on coexistent autoimmune vasculitis

TB (n = 28) was associated with nonspecific AV in 9, with fibrinoid necrotic AV in 3, with granulomatous AV in 4 of 28 patients.

Fibrous TB (n = 16) was associated with nonspecific AV in 4, with fibrinoid necrotic AV in 2, with granulomatous AV in 1 of 16 patients.

Fibro-caseous TB (n = 12) was associated with nonspecific AV in 5, with fibrinoid necrotic AV in 1, with granulomatous AV in 3 of 12 patients.

Active miliary TB (n = 9) was associated with nonspecific AV in 4, with fibrinoid necrotic AV in 2, with granulomatous AV in 4 of 9 patients.

Inactive TB (n = 19) was associated with nonspecific AV in 5, with fibrinoid necrotic AV in 1, with granulomatous AV in none of 19 patients.

There was a significant and positive correlation

- Between TB and prevalence of NsAV ($c^2 = 4.0189$, $p < 0.0449$),
- Between TB and prevalence of GrAV ($c^2 = 5.4823$, $p < 0.0192$),
- Between fcTB and prevalence of NsAV ($c^2 = 4.5747$, $p < 0.0324$),
- Between fcTB and prevalence of GrAV ($c^2 = 10.2663$, $p < 0.0113$),
- Between mTB and NsAV ($c^2 = 5.3406$, $p < 0.00394$) or
- Between mTB and GrAV ($c^2 = 17.7744$, $p < 0.0000001$).

TB was associated with AV in 9 of 28 patients; AV in 5 of 9 patients led directly to death, and in 4 of 9 cases contributed to circulatory failure with lethal outcome (Table 5).

There was no relation between TB, fTB, fcTB, mTB or inactive TB and mortality of AV; the TB, fTB, fcTB, mTB or inactive TB did not influence statistically the mortality of AV, indeed in some cases the relationship was inverse.

AA amyloidosis

Systemic AA amyloidosis (AAa) complicated RA in 49 (20.94%) of 234 patients and led directly to death in 20 (8.55% of 234 and 40.82% of 49) cases; AAa existed in 29 (12.39% of 234 and 59.18% of 49) patients without direct causal role in death.

Influence of tuberculosis on coexistent AA amyloidosis

TB (n = 28) associated with AAa in 4 cases: fTB in 2 (one of them complicated by mTB), and fcTB in 2 (both complicated by mTB.

Inactive TB (n = 19) associated with AAa in 1 patient.

TB was not associated with fatal AAa.

TB, fTB, fcTB, mTB or inactive TB did not influence statistically the prevalence or mortality of AAa, indeed the relationships were in most of the cases negative (inverse).

Acute bacterial (lethal) septic infection

Acute bacterial (lethal) septic infection (AbSI) complicated RA in 33 (20.94%) of 234 patients, with purulent arthritis in 15 (6.41% of 234 and 45.45% of 33) cases.

Influence of tuberculosis on coexistent lethal septic infection and purulent arthritis

TB (n = 28) was associated with AbSI in 5 cases: fTB in 1 (one of them complicated by mTB), and fcTB in 4 (one of them complicated by mTB.

Inactive TB (n = 19) associated with AAa in 3 patients.

TB (n = 28) associated with PA in 2 patients:0 fTB in none, fcTB in 2, and mTB in none.

TB, fTB, fcTB, mTB or inactive TB did not influence statistically the prevalence of AbSI or PA, indeed the relationships were in some cases negative (inverse).

The statistical links between TB (fTB, fcTB or mTB) and complications (AV, AAa, SI, or PA) of RA are summarized in table 6.

AV, AAa, SI or PA vs. TB, fTB, fcTB or mTB	**Prevalence of NsAV n = 43 of 234**	**Prevalence of FnAV n = 20 of 43**	**Prevalence of GrAV n = 12 of 43**	**Prevalence of AAa n = 49 of 234**	**Prevalence of AbSI n = 33 of 234**	**Prevalence of PA n = 15 of 33**
TB n = 28 of 234	**c = 0.41, χ^2 = 4.0189, p < 0.0449**	c = 0.14, χ^2 = 0.0059, p < 0.9386	**c = 0.61, χ^2 = 5.4823, p < 0.0192**	c = -0.25*, χ^2 = 0.8507, p < 0.3563	c = 0.0085, χ^2 = 0.0009, p < 0.9763	c = 0.0241, χ^2 = 0.1141, p < 0.7355
fTB n = 16 of 28	c = 0.21, χ^2 = 05024, p < 0.47842	c = 0.23, χ^2 = 0.0151, p < 0.9023	c = 0.11, χ^2 = 0.1417, p < 0.7066	c = -0.31*, χ^2 = 0.2931, p < 0.5825	c = -0.7428*, χ^2 = 0.0329, p < 0.8561	c = -1.0*, χ^2 = 0.3090, p < 0.5783
fcTB n = 12 of 28	**c = -0.55, χ^2 = 4.5744, p < 0.0324**	c = -.0.01*, χ^2 = 0.2529, p < 0.6150	**c = 0.78, χ^2 = 10.2663, p < 0.0113**	c = -0.15*, χ^2 = 0.0001, p < 0.9925	c = 0.1040, χ^2 = 0.0268, p < 0.8699	c = 0.4526, χ^2 = 0.4598, p < 0.4971

mTB (active) n = 9 of 228	**c = -0.58, χ^2 = 4.2404, p < 0.00394**	c = 0.09, χ^2 = 0.0307, p < 0.8609	**c = 091, χ^2 = 29.7384, p < 0.0000001**	c = 0.32, χ^2 = 0.2643, p < 0.6071	c = 0.28, χ^2 = 0.0508, p < 0.8216	c = -1.0*, χ^2 = 0.0114, p < 0.9149
mTB (fatal) n = 3 of 9	c = -1.0*, χ^2 = 0.0059, p < 0.9386	c = -1.0*, χ^2 = 0.0335, p < 0.8547	c = -1.0*, χ^2 = 0.0004, p < 0.9838	c = -1.0*, χ^2 = 0.0335, p < 0.8547	**	**
TB (inactive) n = 19 of 28	c = 0.25, χ^2 = 08691, p < 0.3512	c = -0.2713*, χ^2 = 0.0113, p < 0.9155	c = -1.0*, χ^2 = 0.2649, p < 0.6067	c = -0.67*, χ^2 = 2.1257, p < 0.1448	c = 0.0724, χ^2 = 0.0152, p < 0.9017	c = -0.1224, χ^2 = 0.0640, p < 0.8002

Table 6: *Relationships between coexistent (fTB, fcTB, mTB) or inactive TB and complications (AV, AAa, SI or PA) in 234 RA patients.*

Remarks to table 6: There was a significant and positive correlation:

Between TB (χ^2 = 4.0189, p < 0.0449), fcTB (χ^2 = 4.5744, p < 0.0324) or mTB (χ^2 = 4.2404, p < 0.0039) and prevalence of NsAV, furthermore.

Between TB (χ^2 = 5.4823, p < 0.0192), fcTB (χ^2 = 10.2663, p < 0.0113) or mTB (χ^2 = 29.7384, p < 0.0000001) and prevalence of GrAV.

Inactive fTB or fcTB (without miliary dissemination) not influenced the histological character of AV.

*Glossary to table 6: c: Coefficient of colligation or 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. Bold indicates significant values of association (the difference was regarded significant between two samples at an alpha level of 0.05). *Asterisk indicates a negative value of association's coefficient, and refers to an inverse relationship. Association's coefficient was positive in all of the cases except fcTB and FnAV, mTB and FnAV, inactive TB and FnAV or GrAV. The correlations were negative (invers) between TB, fTB, fcTB or mTB and prevalence of AAa. **One patient can have only one cause of death.*

Abbreviations: TB: Tuberculosis; fTB: Fibrous Tuberculosis; fcTB: Fibro-Caseous Tuberculosis; mTB: Miliary Tuberculosis; AbSI: Acute Bacterial Septic Infection of Lethal Outcome (Only Lethal Septic Infections with Clinically Identified Pathogenic Agents were Considered); PA: Purulent Arthritis.

Possible influence of TB (fTB, fcTB or mTB) on comorbidities (Ath, HT or DM) of RA with and without fatal outcome

Atherosclerosis (Ath), hypertension (HT) and adult type 2 diabetes mellitus (DM) were the most important comorbidities of RA in association with TB (Table 5).

Atherosclerosis

Ath accompanied RA in 87 (37.18%) of 234 patients, and led directly to death in 49 (20.94% of 234 and 56.32% of 87) cases; Ath in 38 (16.24% of 234 and 43.68% of 87) cases was only concomitant (associated disease) without direct causal role in death.

TB was associated with Ath in 17 of 87 patients: fTB in 12, fcTB in 5 (one of them complicated by mTB) cases.

TB was associated with fatal Ath in 8 of 49 patients; fTB in 8, fcTB or mTB in none of 49 patients.

TB was associated with concomitant Ath in 9 of 38 patients, fTB in 4, fcTB in 5 (one complicated by mTB) cases (Table 5).

Fatal mTB (n = 3) was not associated with Ath; the correlation was not significant, indeed negative.

The correlations were not significant between

- fcTB or mTB and prevalence of Ath (n = 87),
- TB (fcTB or mTB) and mortality of Ath (n = 49) or
- TB (fTB or mTB) and concomitant Ath (n = 38).

There was a positive and significant correlation between

- TB and prevalence of Ath (c = 0.50, χ^2 = 7.5426, p < 0.0060).
- fTB and prevalence of Ath (c = 0.70, χ^2 = 10.5179, p < 0.0012).
- fTB and mortality of Ath (c = 0.62, χ^2 = 8.7605, p < 0.0031).
- Inactive TB and prevalence of Ath (c = 0.76, χ^2 = 15.4458, p < 0.00008).
- Inactive TB and mortality of Ath (c = 0.55, χ^2 = 6.4552, p < 0.0110).
- Inactive TB and concomitant Ath (c = 0.51, χ^2 = 55955, p < 0.0180).

Hypertension

Hypertension (HT) was observed in 35 (14.96%) of 234 RA patients; the HT was controlled in all cases and did not lead to death.

TB was associated with HT in 3 of 35 patients: fTB in 2, fcTB in 1 case (complicated by mTB).

The correlations were not significant between TB (fTB, fcTB or mTB) or inactive TB and HT.

Fatal mTB (n = 3) was not associated with HT; the mortality of TB did not influence the prevalence of HT due to atherosclerosis.

Adult type 2 diabetes mellitus

Adult type 2 diabetes mellitus (DM) was found in 37 (15.81%) of 234 RA patients; the DM was controlled in all cases and did not lead to death.

TB was associated with DM in 11 of 37 patients: fTB in 8, fcTB in 3 (in one case complicated by mTB).

The correlations were significant between TB, fTB or inactive TB and DM, and were not between fcTB or mTB and DM.

Fatal mTB (n = 3) was associated with DM in one of three patients; the correlation was not significant.

The statistical links between TB (fTB, fcTB or mTB) and comorbidities (Ath, Hy or DM) are summarized in table 7.

Ath, HT or DM vs TB, fTB, fcTB or mTB	**Prevalence of Ath n = 87 of 234**	**Mortality of Ath n = 49 of 87**	**Concomitant Ath n = 38 of 87**	**Prevalence of HT n = 35 of 234**	**Prevalence of DM n = 37 of 234**
TB n = 28 of 234	**c = 0.50, χ^2 = 7.5426, p < 0.0060**	c = 0.23, χ^2 = 1.1188, p < 0.2902	**c = 0.49, χ^2 = 5.9141, p < 0.0150**	c = -0.21*, χ^2 = 0.1510, p < 0.6975	**c = 0.63, χ^2 = 13.1654, p < 0.00028**

fTB n = 16 of 28	**c = 0.70, χ^2 = 10.5179, p < 0.0012**	**c = 0.62, χ^2 = 8.7605, p < 0.0030**	c = 0.29, χ^2 = 0.9691, p < 0.3249	c = -0.11*, χ^2 = 0.0592, p < 0.8077	**c = 0.73, χ^2 = 15.0797, p < 0.0001**
fcTB n = 12 of 28	c = -0.13, χ^2 = 0.1988, p < 0.6557	c = -1.00*, χ^2 = 2.1496, p < 0.1426	**c = 0.61, χ^2 = 6.0123, p < 0.0142**	c = -0.33*, χ^2 = 0.0600, p < 0.8064	c = 0.29, χ^2 = 0.2396, p < 0.6245
mTB (active) n = 9 of 228	c = -0.87*, χ^2 = 8.1495, p < 0.0043	c = -1.0*, χ^2 = 1.3382, p < 0.2473	c = -0.22*, χ^2 = 0.0013, p < 0.9717	c = 0.17*, χ^2 = 0.0215, p < 0.8834	c = -0.21*, χ^2 = 0.0043, p < 0.9474
mTB (fatal) n = 3 of 9	c = -1.0*, χ^2 = 0.5475, p < 0.4593	-**	c = -1.0*, χ^2 = 0.0004, p < 0.9838	c = -1.0*, χ^2 = 0.0070, p < 0.8064	c = -0.46, χ^2 = 0.0017, p < 0.9674
TB (inactive) n = 19 of 28	**c = 0.76, χ^2 = 15.4458, p < 0.00008**	**c = 0.55, χ^2 = 6.4552, p < 0.0110**	**c = 0.51, χ^2 = 5.5955, p < 0.0180**	c = -0.21*, χ^2 = 0.0526, p < 0.81857	**c = 0.64, χ^2 = 10.7395, p < 0.0010**

Table 7: *Relationships between coexistent TB (fTB, fcTB, mTB) or inactive TB and comorbidities (Ath, HT or DM) in 234 RA patients.*

Remarks to table 7: There was a significant and positive correlation:

Between TB (χ^2 = 4.0189, p < 0.0449), fTB (χ^2 = 4.5744, p < 0.0324) or inactive TB (χ^2 = 4.2404, p < 0.0039) and prevalence of Ath, furthermore.

Between TB (χ^2 = 5.4823, p < 0.0192), fTB (χ^2 = 10.2663, p < 0.0113) or inactive TB (χ^2 = 29.7384, p < 0.0000001) and prevalence of DM.

fcTB or mTB did not influence the prevalence or mortality of Ath, and prevalence of HT or DM, indeed the correlations were negative (invers).

*Glossary to table 7: Bold indicates significant values of association (the difference was regarded significant between two samples at an alpha level of 0.05). *Asterisk indicates a negative value of association's coefficient. The negative association coefficient refers to an inverse link, and the positive association coefficient shows a parallel correlation. Controlled HT and adult type 2 DM were not fatal in our autopsy population. **One patient can have only one cause of death.*

Abbreviations: Ath: Atherosclerosis; HT: Hypertension; DM: Diabetes Mellitus Adult Type 2; TB: Tuberculosis; fTB: Fibrous Tuberculosis; fcTB: Fibro-Caseous Tuberculosis; mTB: Miliary Tuberculosis.

Figure 1-4 and 6 demonstrate TB with miliary hematogenous dissemination, and miliary granulomas (mTB), figure 5 and 7 demonstrate GrAV and rheumatoid nodule with traditional staining.

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

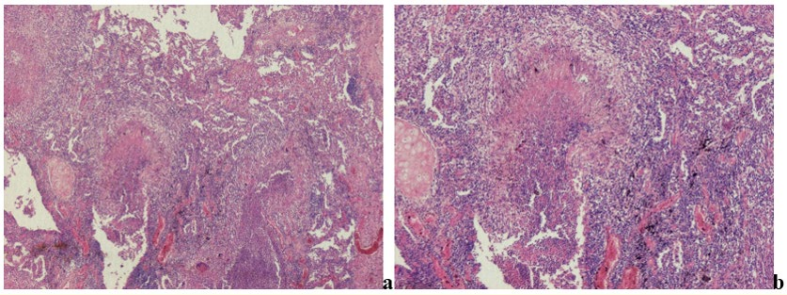


Figure 1: *Legend to figure 1a and 1b: RA, post-primary caseous tuberculosis in the lung. Coalescent caseous cores of tuberculotic foci are surrounded by a moderately cellular zone of histiocytes not respecting the borders of lobular-sub lobular units of the lung. (a) HE, x20, (b) same as (a) x40.*

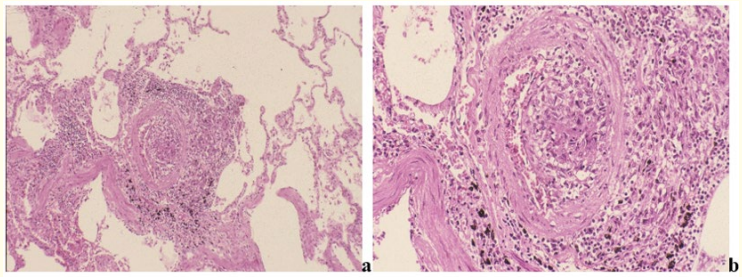


Figure 2: *Legend to figure 2a and 2b: RA, TB complicated by miliary dissemination, lung. Subintimal miliary granuloma in the wall of a small artery is the sign of hematogenic dissemination (distinct of tuberculosis granulomatous autoimmune vasculitis - see figure 5a-b). (a) HE, x 50, (b) same as (a) x125.*

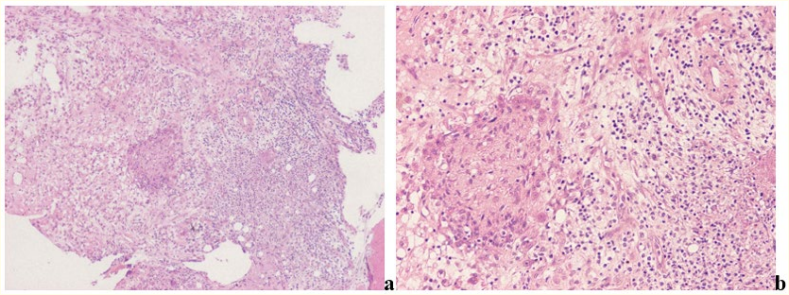


Figure 3: *Legend to figure 3a and 3b: A more cellular epithelioid miliary granuloma in bone marrow indicates a relatively good cellular response. (a) HE, x 50, (b) same as (a) x125.*

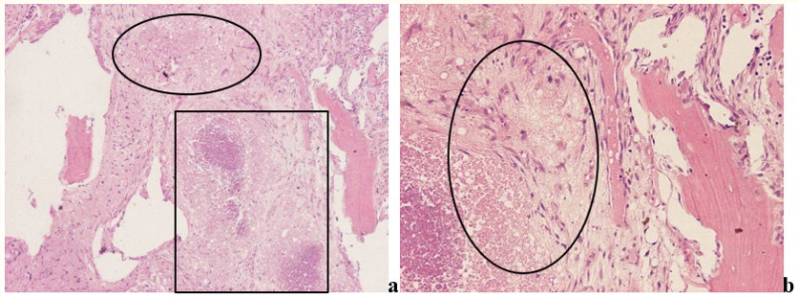


Figure 4: *Legend to figure 4a and 4b: Exudative (ellipse), and coalescent (rectangle) miliary granulomas in bone indicate a reduced cellular response of the patients. (a) HE, x 50, (b) same as (a) x125.*

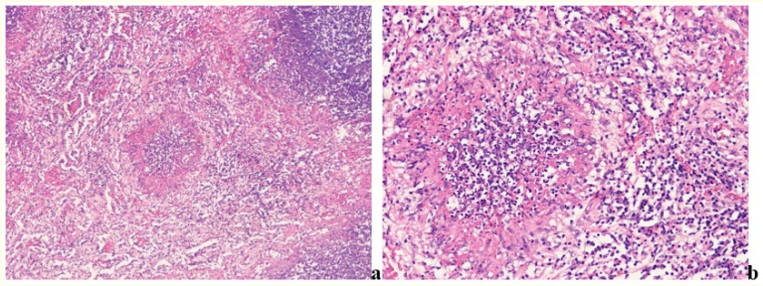
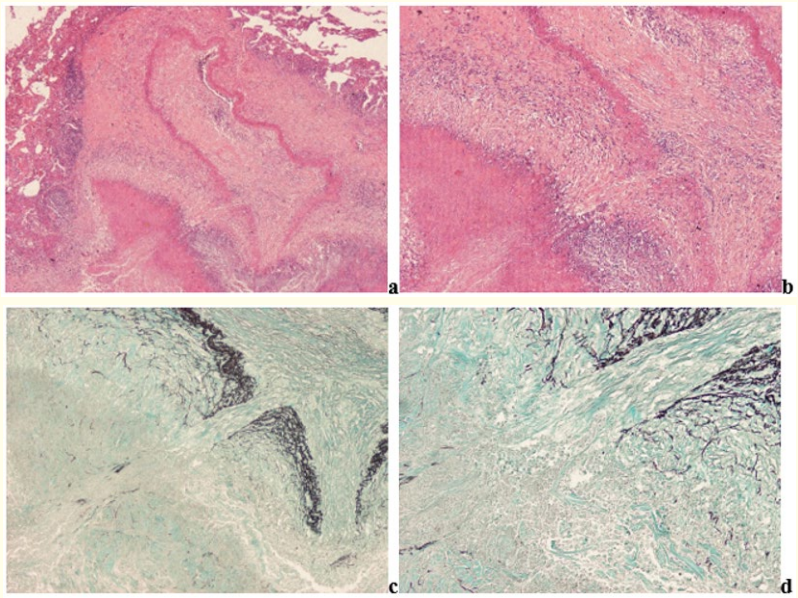


Figure 5: *Legend to figure 5a and 5b: RA in association with co-existent TB complicated by mTB. RA, lung, small artery, granulomatous autoimmune arteritis (granulomatous transformation of the vessel wall due to the modified reactivity). (a) HE, x 20, (b) same as (a) x50.*



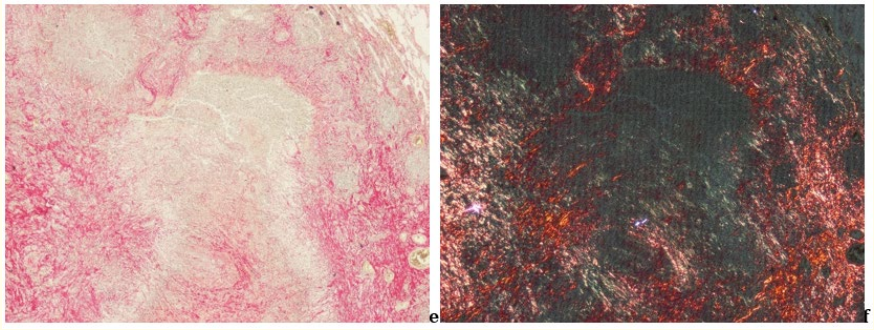


Figure 6: *Legend to figure 6a-6f: RA in association with co-existent TB complicated by mTB. RA, lung, erosive fibro-caseous tubercle with adjacent medium size obliterated pulmonal artery (the caseous necrosis does not respect the anatomical borders). Interstitial cellular infiltration (reminiscent of interstitial pneumonitis) is found only close to tuberculotic foci. (a) HE, x 20, (b) same as (a) x40, (c) Light-green-Orcein, same as (b) [32], x 40, (d) same as (c) x100, (e) Picrosirius red F3BA [33, 34], x 20, (f) same as (e) viewed under polarized light x40.*

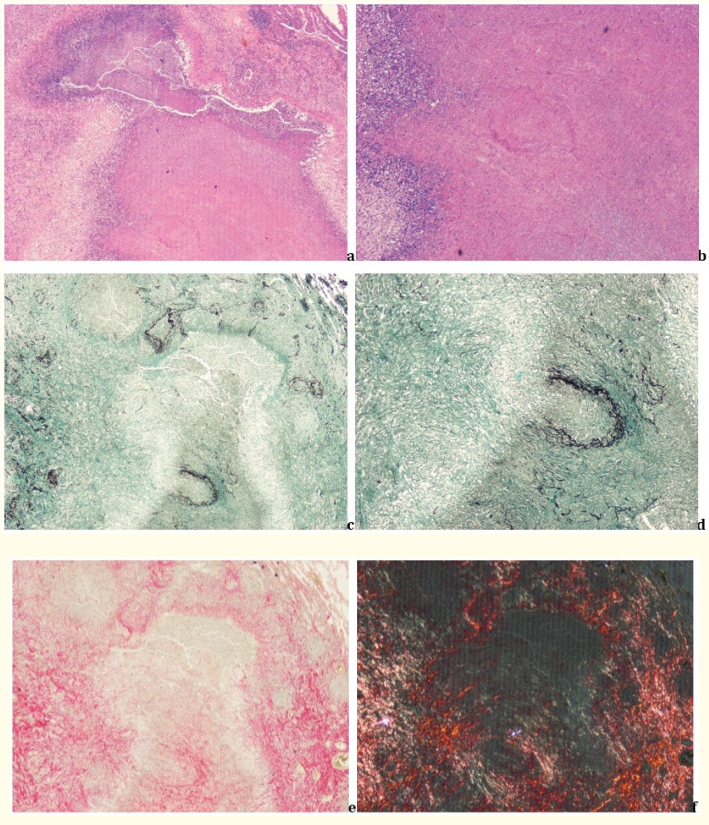


Figure 6: *Legend to figure 6a-6f: RA in association with co-existent TB complicated by mTB. RA, lung, erosive fibro-caseous tubercle with adjacent medium size obliterated pulmonal artery (the caseous necrosis does not respect the anatomical borders). Interstitial cellular infiltration (reminiscent of interstitial pneumonitis) is found only close to tuberculotic foci. (a) HE, x 20, (b) same as (a) x40, (c) Light-green-Orcein, same as (b) [32], x 40, (d) same as (c) x100, (e) Picrosirius red F3BA [33, 34], x 20, (f) same as (e) viewed under polarized light x40.*

Discussion

Ad 1.

Post-primary TB especially fcTB represents a high risk of miliary dissemination in RA. The strong positive correlations between TB, fTB, fcTB or mTB indicates that miliary dissemination was caused by endogenous exacerbation (reactivation) of post-primary inactive TB and not due to exogenous reinfection.

Miliary dissemination of tuberculosis (mTB) may be considered as a terminal phenomenon, because of the limited numbers of granulomas involving only a few organs (Table 1).

The exudative (more serious, clear, less cellular), and proliferative (more or less cellular) miliary foci without caseous necrosis or fibrous transformation and calcification also support the assumption that hematogenous dissemination was terminal i.e., premortem. The exudative character, beside proliferative epithelioid granulomas may be regarded as histological evidence of impaired and gradually decreasing immune reactivity, an unfavorable prognostic sign in elderly patients (Figure 4). The coalescent central foci of epithelioid granulomas without caseous necrosis also indicate the poor reactivity of the patients.

Ad 2.

Inactive or active TB (fTB, fcTB, mTB) involved both genders, and developed at any time in the course of the disease.

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, but these differences were not significant.

The risk of miliary dissemination (mTB) was particularly high in elderly women; females with mTB died earlier than females without mTB.

The onset, and duration of RA did not influence the prevalence, histological features, and mortality of TB; inactive or active TB (fTB, fcTB or mTB) with or without fatal outcome developed at any time in the course of RA (Table 2 and 3).

Ad 3.

RA itself or its treatment modify the clinical symptoms of associated diseases and present atypical clinical manifestations leading to late recognition or missed diagnosis. The limited immune reactivity of elderly patients, the autoimmune character of RA, steroid and/or immunosuppressive drugs, and nowadays biological therapy may also play a role in missing the diagnosis of inactive or active TB, including lethal cases.

The diagnosis of inactive or active 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 a tuberculin skin test may be also limited due to poor response of the patients [20], as well the QuantiFERON blood test [21,22]. A positive Interferon-Gamma (γ) Release Assays (IGRA) result may not necessarily indicate TB infection with tuberculous mycobacteria [21]. A negative IGRA does not rule out active TB disease [22].

The value of inflammatory clinical-laboratory parameters is limited; none of them is specific for tuberculosis, and indicates only actual inflammatory activity [23,24].

The significant and consequent decrease of albumin/ globulin quotient and elevated α1 and α2 globulin % in elderly patients with moderate clinical activity of RA (measured by CDAI, SDAI [25], DAS28-CRP [26], etc.) may indicate the reactivation of dormant inactive

tuberculotic processes, excluding other causes of actual inflammatory activity (for example attenuated or subclinical septic infection, rheumatoid vasculitis, inflammatory AA amyloidosis, etc.) [24].

Microbiologic culture may be necessary, but takes time (may be critical) the results may be false negative, and in clinically latent TB may not appear indicated.

Detailed medical history and targeted X-ray examination, as well as the tuberculin skin test (despite its limitations) are key factors in diagnosing clinically latent TB with or without subclinical atypical miliary exacerbation [27]. "Histopathology remains one of the most important methods for diagnosing tuberculosis" [28,29].

Our results suggest that the link between clinical diagnosis and mortality of TB was not significant, indicating the incidental nature of diagnosis.

Ad 4.

In our autopsy population tuberculosis (TB) was often associated with important complications of RA: such as systemic autoimmune vasculitis (AV), systemic AA amyloidosis (AAa), and acute bacterial septic infection (AbSI) with or without purulent arthritis (PA), and was often accompanied by other associated diseases: atherosclerosis (Ath) with or without hypertension (HT), and with the adult type 2 diabetes mellitus (DM).

Ad 4.1.

The significant and positive correlation between TB, fcTB or mTB and AV means a positive influence of tuberculosis on prevalence of autoimmune vasculitis in RA.

Granulomatous type of vasculitis (GrAV) was associated with TB, fcTB or mTB and this correlation was statistically significant.

The close relationship between TB, fcTB or mTB and GrAV is related - according to our interpretation - to the disease modifying effect of TB, fcTB or mTB in the histologic appearance of autoimmune vasculitis [9,30]. We assume that the granulomatous transformation of blood vessels can be regarded as an indirect histological sign of dormant TB, which should alert the clinicians to exclude a possible co-existent TB [9,30].

Koizumi (1979) regarded the rheumatoid nodule (without TB) the most serious form of granulomatous necrotizing vasculitis [31].

Distinction between a rheumatoid nodule and fibro-caseous tubercle in the lung may present a difficult differential diagnostic problem.

The anthracotic pigmentation of fibrotic scars, the demarcating zone around the tubercle with dominant histiocytic cellular infiltration, the obliterative vasculitis, and the interstitial cellular infiltration (reminiscent of interstitial pneumonitis) close to tuberculotic foci, furthermore the colliquation or caseous necrosis not respecting anatomical borders are characteristics of tuberculotic origin (Figure 6). Immunohistochemically the dominant infiltration of T-lymphocytes (CD3, CD4, CD8, CD43) in surrounding areas beside B-cells (CD20, CD79α etc.) also support the tuberculotic origin of fibrous or fibro-caseous foci.

In contrast, rheumatoid nodules are characterized only in early stage by histiocytes, later fibroblasts and fibrocytes dominate the demarcating zone. Shadows of blood vessels within necrotic area (Figure 7), different stages of vasculitis NsAV, FnAV, and/or GrAV) with or without interstitial pneumonitis at widespread involvement of the lung are characteristics of RA. Immunohistochemically the moderate T-cell (CD3) and dominant B-cell (CD20) support the presence of rheumatoid nodules.

Ad 4.2.

The high values of association coefficient, the positive and significant correlation between fTB and prevalence ($c = 0.70$, $\chi^2 = 10.5179$, $p < 0.0012$) or mortality of Ath ($c = 0.62$, $\chi^2 = 8.7605$, $p < 0.0030$), furthermore between fTB and DM ($c = 0.73$, $\chi^2 = 15.0797$, $p < 0.0001$) refer to a very close connection, but this does not necessarily mean a causal relationship; coincidence of parallel phenomena seems more likely. The strong positive correlation may be due to the equally high prevalence of fTB, Ath or DM in aged RA patient cohorts. In our opinion fTB, Ath or DM are coincident comorbidities of elderly RA patients.

The correlations were not significant between fcTB, mTB or mortality of mTB and prevalence of Ath (n = 87), HT (35) or DM (n = 37).

The lack of correlation between fcTB or mTB and comorbidities (Ath, HT or DM) indicate that these are sovereign phenomena (associated diseases) in RA, which may be present at the same time, and can lead to death independently from each other. This assumption is supported by the not significant "p" values, moreover by the negative values of association coefficients between them.

Conclusion

In elderly people with RA the morbidity of tuberculosis is higher than in younger ones, especially aged women have a higher inclination (susceptibility) for TB.

Inactive or active TB (fTB, fcTB, mTB) can develop in both sexes, and at any time in the course of the disease.

The presence of fcTB or mTB increases the risk of mortality of RA patients, especial of women, while consolidated anthracotic scars (fTB) do not.

The risk of active miliary dissemination (mTB) and fatal outcome is particularly high in females; women with mTB die earlier then women without mTB.

The onset, and duration of RA does not influence the prevalence and mortality of inactive or active TB.

A decreased albumin/globulin quotient and elevated α1 and α2 globulin % of patients with moderate clinical activity of RA may indicate the reactivation of a dormant inactive tuberculotic process and exclude other causes of inflammatory activity.

Granulomatous autoimmune vasculitis can be regarded as an indirect histological sign of dormant TB with or without miliary dissemination, supported by the close relationship between epithelioid granulomas and granulomatous transformation of blood vessels, independently of the origin of the tissue samples.

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