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Research Article

Prevalence and Features of Tuberculosis Characterized by Demographics, Onset and Disease Duration of Rheumatoid Arthritis - A Retrospective Clinicopathologic Study of 161 Autopsy Patients

Miklós Bély[1]* and Ágnes Apáthy[2]

[1]*Department of Pathology, Hospital of the Order of the Brothers of Saint John of God in Budapest, Hungary*

[2]*Department of Rheumatology, St. Margaret Clinic Budapest, Hungary*

***Corresponding Author:** Miklós Bély, Department of Pathology, Hospital of the Order of the Brothers of Saint John of God in Budapest, Hungary.

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Abstract

Introduction: The risk of tuberculosis (TB) is higher in rheumatoid arthritis (RA) compared to the general population. TB is one of the most important associated diseases in RA.

Aim of the Study: To determine the prevalence of fibrous (fTB) or fibrocaseous tuberculosis (fcTB), with and without active miliary dissemination (mTB) in RA, to assess the relationship between TB and fTB, fcTB or mTB, in order to decide the origin of tuberculotic processes; are they consequence of endogenous exacerbation of dormant TB or caused by exogenous reinfection, and to ascertain the group of patients in our autopsy population in which the risk of latent TB is the highest, based on the age, sex of patients, onset and duration of RA.

Patients (Autopsy Population) and Methods: One hundred sixty-one (161) non-selected autopsy patients with RA were studied. RA was confirmed clinically according to the criteria of the American College of Rheumatology (ACR). The post-primary inactive fibrous or fibrocaseous TB with or without active miliary dissemination 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.

Results: Post-primary TB was associated with RA in 21 (13.04%) of 161 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 complicated by disseminated (miliary) tuberculosis (mTB) in 6 (3.7% of 161; 28.57% of 21) RA patients with fTB or fcTB.

Discussion and Conclusion: Post-primary TB especially fcTB represents a high risk of miliary dissemination in RA. In our autopsy material miliary dissemination of TB was the consequence of endogenous exacerbation of TB (and was not due to an exogenous reinfection), based on the high values of association coefficients between TB or fcTB and mTB.

Clinically latent TB (fTB, fcTB, mTB) may be present in both sexes, and at any time in the course of RA.

The onset and disease duration of RA do not influence basically the prevalence and features of coexistent TB (fTB, fcTB, mTB).

The risk of TB is higher in elderly RA patients than in younger ones, especially elderly females are more likely to be affected by TB.

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

Demographics may contribute to the recognition of clinically latent TB beside detailed medical history, targeted X-ray examination, the tuberculin skin, and the QuantiFERON blood test.

Keywords: *Rheumatoid Arthritis; Latent Tuberculosis; Demographics; Onset and Duration of RA*

Abbreviations

RA: Rheumatoid Arthritis; ACR: American College of Rheumatology; TB: Tuberculosis; fTB: Fibrous TB (Inactive Tuberculotic Scar); fcTB: Fibrocaseous TB (Inactive Fibrocaseous Tubercle Without Miliary Dissemination); mTB: Miliary TB (Active TB with Miliary Dissemination); csDMARDs: Conventional Synthetic Disease Modifying Antirheumatic Drugs (Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquine, Chloroquine); bDMARDs or boDMARDs: Biological (Original) Disease Modifying Antirheumatic Drugs (TNF Inhibitors: Adalimumab, Certolizumab Pegol, Etanercept, Golimumab, Infliximab and Others); SD: Standard Deviation; ND: No Data; HE: Hematoxylin-Eosin Staining; 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; IGRAs: Interferon-Gamma (γ) Release Assays (QuantiFERON Blood Test)

Introduction

Tuberculosis (TB) is one of the ten leading causes of death worldwide [1].

The risk of TB is higher in rheumatoid arthritis (RA) compared to the general population [2-4].

TB is one of the most important associated diseases in RA, beside atherosclerosis, hypertension or adult type 2 diabetes mellitus [5].

Introduction of biological disease-modifying anti-rheumatic drugs (bDMARDs) (TNF inhibitors, etc.) increase the risk of reactivation of dormant TB in RA [6-8].

Aim of the Study

To determine the prevalence of fibrous (fTB) or fibrocaseous tuberculosis (fcTB), with and without active miliary dissemination (mTB) in RA, to assess the relationship between TB and fTB, fcTB or mTB, in order to decide the origin of tuberculotic processes; are they consequence of endogenous exacerbation of dormant TB or caused by exogenous reinfection, and to ascertain the group of patients in our autopsy population in which the risk of latent TB is the highest, based on the age, sex of patients, onset and duration of RA.

Patients (Autopsy Population) and Methods

One hundred sixty-one (161) non-selected autopsy patients with RA were studied [5]. The patients were treated and died in the National Institute of Rheumatology, Budapest, Hungary, between 1969 and 1992 in an era of steroid and conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), before introduction of biological therapy (bDMARDs (TNF inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, etc.).

RA was confirmed clinically according to the criteria of the American College of Rheumatology (ACR) [9].

The post-primary inactive fibrous or fibrocaseous TB (fTB, fcTB) 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 [8].

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

Serial sections (5 microns) were stained with hematoxylin-eosin (HE) [10].

In case of fTB, fcTB or mTB additional histological sections were stained according to Ziehl-Neelsen [11] using positive control.

Demographics of different patient cohorts were compared with the Student (Welch) t-probe [12]. 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 inactive fTB or fcTB and active mTB [12].

Results

Post-primary TB was associated with RA in 21 (13.04%) of 161 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 disseminated (miliary) tuberculosis (mTB) in 6 (3.7% of 161; 28.57% of 21) RA patients with fTB or fcTB.

There was a strong positive correlation between: TB and fTB ($c = 1$, $\chi^2 = 78.3573$, $p < 0.00000001$), TB and fcTB ($c = 1$, $\chi^2 = 55.6914$, $p < 0.00000001$), TB and mTB ($c = 1$, $\chi^2 = 33.9665$, $p < 0.00000001$) or fcTB and mTB ($c = 0.9895$, $\chi^2 = 56.8924$, $p < 0.000001$). The link between fTB and mTB was not significant ($c = 0.4472$, $\chi^2 = 0.0070$, $p < 0.9333$ - NS).

Table 1 summarizes the demographics, onset and diseases duration of RA patients with and without TB, fTB, fcTB, or mTB.

Sex	Number of autopsies	Mean age in years at death ± SD	Range (in years)	Mean age at onset of disease ± SD	Disease duration (in years) mean ± SD
RA patients (total)	**161**	**65.32 ± 12.95**	**16 - 88**	**50.83 ± 16.96**	**14.43 ± 10.51**
Female	116	64.95 ± 11.79	16 - 87	50.19 ± 15.70	14.79 ± 10.65
Male	45	66.27 ± 15.50	19 - 88	52.57 ± 19.88	13.46 ± 10.08
With TB	**21 of 161**	**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	50 - 78	53.33 ± 11.80	12.67 ± 7.45
With fibrous TB	**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 fibrocaseous TB	**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 miliary TB	**6 of 21**	**68.33 ± 11.09**	**50 - 82**	**58.67 ± 8.24**	**9.67 ± 4.85**
Female	6	68.33 ± 11.09	50 - 82	58.67 ± 8.24	9.67 ± 4.85
Male	0	-	-	-	-
Without TB	**140 of 161**	**64.77 ± 13.28**	**16 - 88**	**50.22 ± 16.99**	**14.36 ± 10.13**
Female	101	64.17 ± 11.81	16 - 87	49.42 ± 15.15	14.64 ± 9.97
Male	39	66.31 ± 16.38	19 - 88	52.42 ± 21.08	13.61 ± 10.51
Without fibrous TB	**149 of 161**	**64.87 ± 13.14**	**16 - 88**	**50.69 ± 17.04**	**14.03 ± 10.18**
Female	109	64.43 ± 11.76	16 - 87	50.12 ± 15.52	14.26 ± 10.09
Male	40	66.05 ± 16.25	19 - 88	52.34 ± 20.76	13.38 ± 10.42
Without fibrocaseous TB	**152 of 161**	**65.26 ± 13.07**	**16 - 88**	**50.42 ± 16.91**	**14.76 ± 10.48**
Female	108	64.74 ± 11.85	16 - 87	49.55 ± 15.38	15.18 ± 10.57
Male	44	66.50 ± 15.59	19 - 88	52.64 ± 20.15	13.67 ± 10.14
Without miliary TB	**155 of 161**	**65.21 ± 13.00**	**16 - 88**	**50.47 ± 17.17**	**14.65 ± 10.65**
Female	110	64.76 ± 11.80	16 - 87	49.65 ± 15.90	15.12 ± 10.83
Male	45	66.27 ± 15.50	19 - 88	52.57 ± 19.88	13.46 ± 10.08
Without mTB	**15 of 21**	**69.27 ± 9.07**	**56 - 84**	**52.40 ± 18.37**	**16.87 ± 13.84**
Female	9	71.44 ± 9.32	57 - 84	51.78 ± 21.65	19.67 ± 16.20
Male	6	66.00 ± 7.59	56 - 78	53.33 ± 11.80	12.67 ± 7.45

Table 1: *Sex, mean age with SD, range, onset and disease duration (in years) of 161 RA patients with and without TB, fTB, fcTB, or mTB.*

Glossary to table 1

RA: Rheumatoid Arthritis; TB: Tuberculosis; fTB: Fibrous Tuberculosis (Inactive Tuberculosis); fcTB: Fibrocaseous Tuberculosis (Inactive Tuberculosis Without Miliary Dissemination); mTB: Miliary Tuberculosis (Active Tuberculosis With Miliary Dissemination); SD: Standard Deviation.

The mean age of RA patients was higher with TB (n = 21), fTB (n = 12), fcTB (n = 9) or mTB (n = 6) in comparison to total population (n = 161) or to the patients without TB (n = 140), fTB (n = 149), fcTB (n = 152) or mTB (n = 155), but this difference was significant only between patient cohorts with and without fTB (70.92 years versus 64.87, $p < 0.046$).

The mean age of female RA patients with TB was also higher than the mean age of females without TB (70.20 years versus 64.17, $p < 0.056$ - NS).

In our autopsy population only females had miliary dissemination of TB (all of 6 RA patients with mTB were women).

There was no significant difference in the onset and disease duration of RA between patient cohorts with TB (n = 21), fTB (n = 12), fcTB (n = 9) or mTB (n = 6) in comparison to total population (n = 161) or to the patients without TB (n = 140), fTB (n = 149), fcTB (n = 152) or mTB (n = 155), except in elderly females with mTB, who died earlier than females without mTB (9.67 years versus 15.12, $p < 0.056$ - NS).

TB (fTB, fcTB, mTB) developed in both sexes, and at any time in the course of the disease (Table 1 and 2).

Figure 1a-1f summarize the mean age of total population (n = 161) and of patient cohorts without TB (n = 140), with TB (n = 21), fTB (n = 12), fcTB (n = 9) or mTB (n = 6).

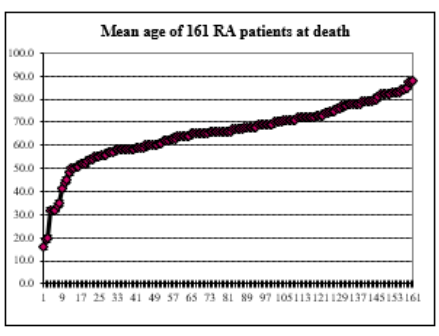

Figure 1a

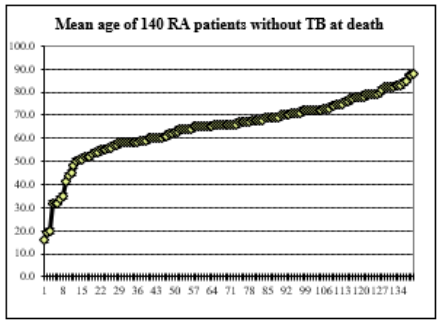

Figure 1b

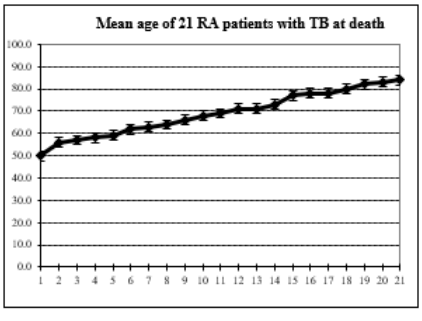

Figure 1c

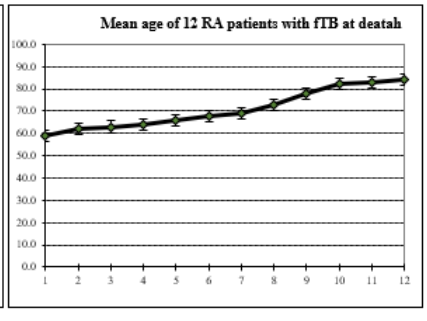

Figure 1d

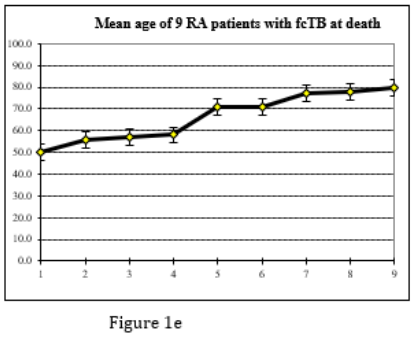

Figure 1e

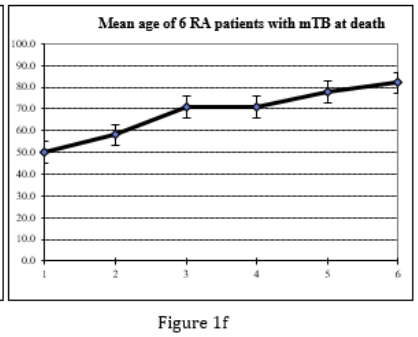

Figure 1f

Figure 1a-1f: *Mean age of total population (n = 161), and RA patients without TB (n = 140), with TB (n = 21), fTB (n = 12), fcTB (n = 9) or mTB (n = 6) at death with error bars. Legend to figure 1a-1f*

There was no significant difference in mean age of total population (n = 161) and RA patients without TB (n = 140).

The mean age of RA patients at death was higher with TB (n = 21), fTB (n = 12), fcTB (n = 9) or mTB (n = 6) compared to the total population (n = 161) or to the patient cohort without TB (n = 140); but these differences were not significant (Table 1 and 2).

Figure 2a-2f summarize the onset of RA in total population (n = 161) and in patient cohorts without TB (n = 140), with TB (n = 21), fTB (n = 12), fcTB (n = 9) or mTB (n = 6).

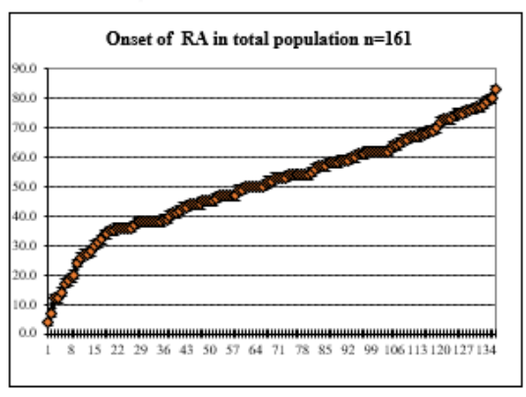

Figure 2a

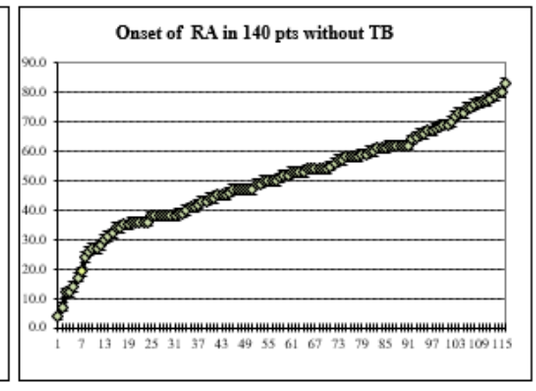

Figure 2b

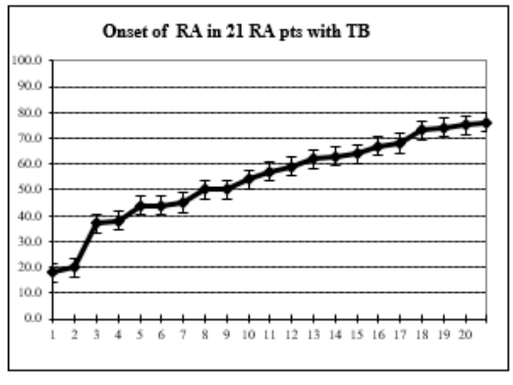

Figure 2c

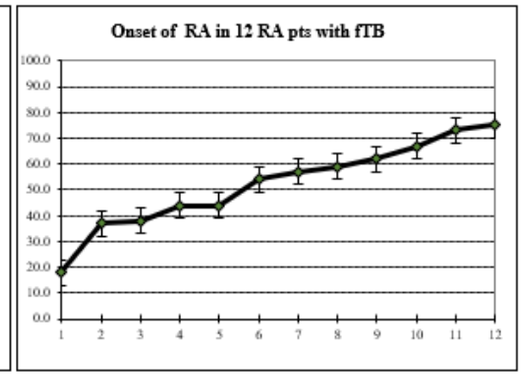

Figure 2d

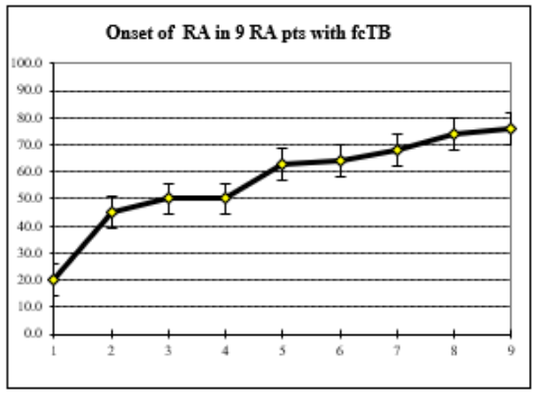

Figure 2e

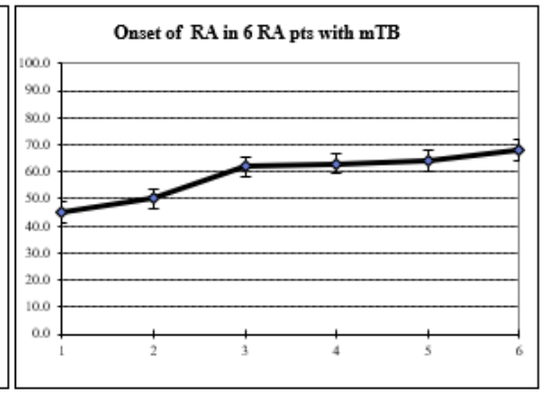

Figure 2f

Figure 2a-2f: *Onset of RA in total population (n = 161, and in patients without TB (n = 140), with TB (n = 21), fTB (n = 12), fcTB (n = 9) or mTB (n = 6) at death with error bars.*

Legend to figure 2a-2f RA started statistically at the same age in total population (n = 161) or in patient cohorts with or without TB, fTB, fcTB or mTB; differences in onset of RA were not significant (Table 1 and 2).

Duration of RA in total population (n = 161), and in patient cohorts, without TB (n = 140), with TB (n = 21), fTB (n = 12), fcTB (n = 9) or mTB (n = 6) are summarized in figure 3a-3f.

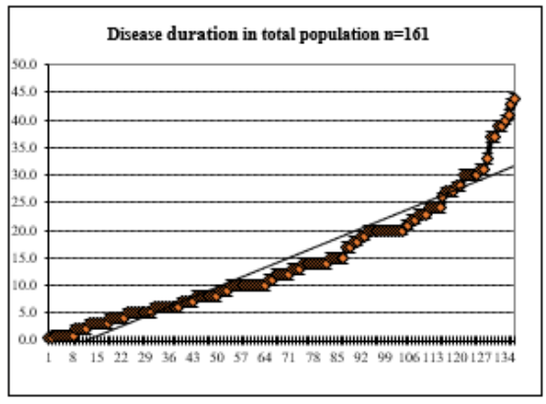

Figure 3a

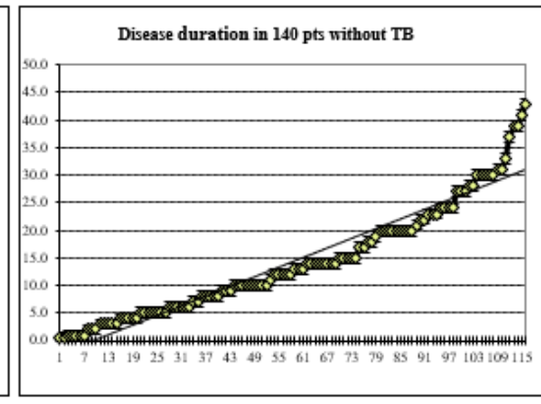

Figure 3b

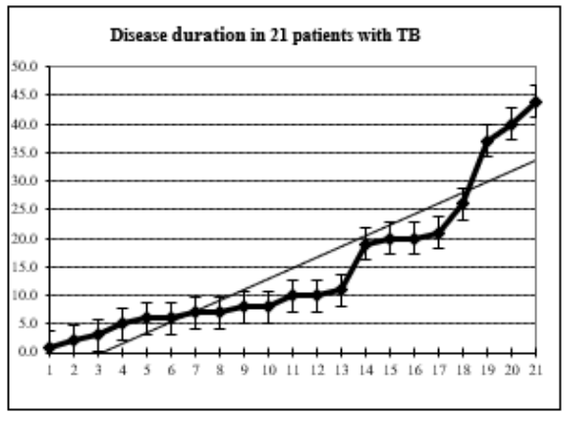

Figure 3c

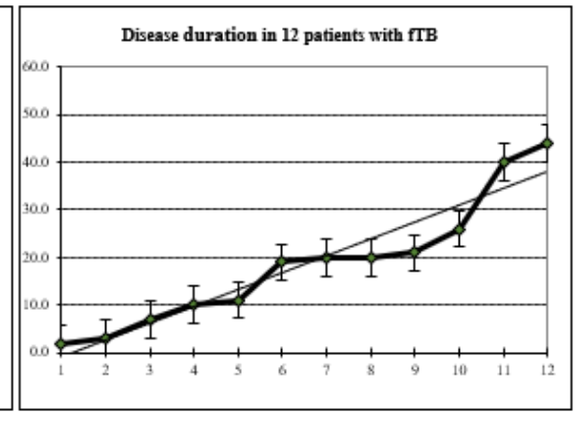

Figure 3d

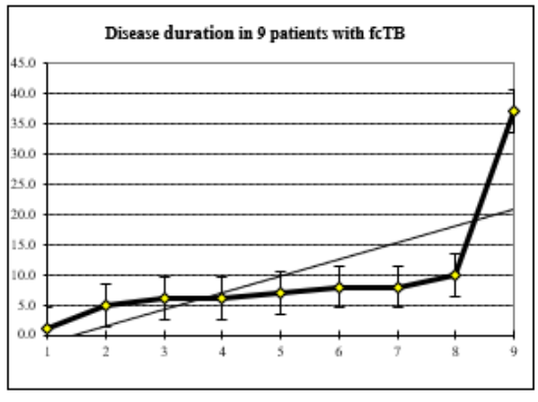

Figure 3e

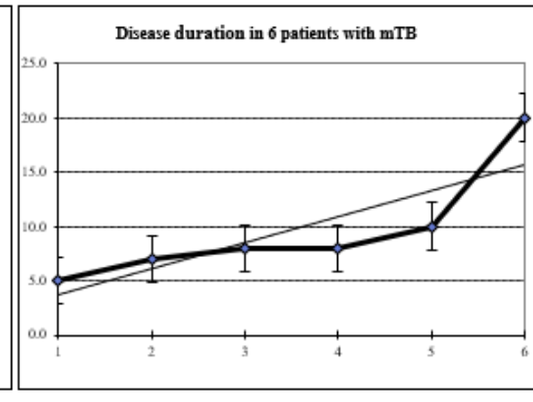

Figure 3f

Figure 3a-3f: *Duration of RA in total population (n = 161), and in patients without TB (n = 140), with TB (n = 21), fTB (n = 12), fcTB (n = 9) or mTB (n = 6) with error bars. Legend to figure 3a-3f*

Duration of RA was statistically not different in total population (n = 161) or in patient cohorts with or without TB, fTB, fcTB or mTB (Table 1 and 2).

Table 2 summarizes the statistical correlations ("p" values) between female and male RA patients with and without TB, fTB, fcTB, or mTB.

RA patients n = 161 (total)	Age	Onset of disease	Disease duration
RA patients n = 161 versus pts. with TB n = 21 of 161	p < 0.136	p < 0.402	p < 0.898
Female n = 116 of 161 versus n = 15 of 21	p < 0.090	p < 0.400	p < 0.822
Male n = 45 of 161 versus n = 6 of 21	p < 0.950	p < 0.905	p < 0.837
RA patients n = 161 versus pts. with fTB n = 12 of 21	p < 0.061	p < 0.771	p < 0.314
Female n = 116 of 161 versus n = 7 of 12	p < 0.073	p < 0.968	p < 0.262
Male n = 45 of 161 versus n = 5 of 12	p < 0.682	p < 0.653	p < 0.916
RA patients n = 161 versus pts. with fcTB n = 9 of 21	p < 0.779	p < 0.359	p < 0.230
Female n = 116 of 161 versus n = 8 of 9	p < 0.516	p < 0.352	p < 0.332
Male n = 45 of 161 versus n = 1 of 9	-	-	-
RA patients n = 161 versus pts. with mTB n = 6 of 21	p < 0.576	p < 0.090	p < 0.083
Female n = 116 of 161 versus n = 6 of 6	p < 0.532	p < 0.072	p < 0.068
Male n = 45 of 161 versus n = 0 of 6	-	-	-
with TB n = 21 of 161 pts. versus without TB n = 140	p < 0.093	p < 0.329	p < 0.880
Female n = 15 of 21 versus n = 101 of 140	p < 0.056	p < 0.326	p < 0.792
Male n = 6 of 21 versus n = 39 of 140	p < 0.944	p < 0.891	p < 0.811
with TB n = 21 of 161 pts. versus with fTB n = 12	p < 0.573	p < 0.762	p < 0.435
Female n = 15 of 21 versus n = 7 of 12	p < 0.550	p < 0.704	p < 0.397
Male n = 6 of 21 versus n = 5 of 12	p < 0.685	p < 0.938	p < 0.796
with TB n = 21 of 161 pts. versus with fcTB n = 9	p < 0.565	p < 0.725	p < 0.275
Female n = 15 of 21 versus n = 8 of 9	p < 0.620	p < 0.720	p < 0.329
Male n = 6 of 21 versus n = 1 of 9	-	-	-
with TB n = 21 of 161 pts. versus with mTB n = 6	p < 0.905	p < 0.402	p < 0.159
Female n = 15 of 21 versus n = 6 of 69	p < 0.750	p < 0.502	p < 0.177
Male n = 6 of 21 versus n = 0 of 6	-	-	-
with fTB n = 12 of 161 pts. versus with fcTB n = 9	p < 0.340	p < 0.575	p < 0.107
Female n = 7 of 12 versus n = 8 of 9	p < 0.350	p < 0.529	p < 0.133
Male n = 5 of 12 versus n = 1 of 9	-	-	-
with fTB n = 12 of 161 pts. versus with mTB n = 6	p < 0.656	p < 0.313	p < 0.061
Female n = 7 of 12 versus n = 6 of 6	p < 0.467	p < 0.382	p < 0.093
Male n = 5 of 12 versus n = 0 of 6	-	-	-
with fcTB n = 9 of 161 pts. versus with mTB n = 6	p < 0.767	p < 0.777	p < 0.979
Female n = 8 of 9 versus n = 6 of 6	p < 0.929	p < 0.880	p < 0.899
Male n = 1 of 9 versus n = 0 of 6	-	-	-
with fTB n = 12 of 161 pts. versus without fTB n = 149	p < 0.046	p < 0.750	p < 0.272
Female n = 7 of 12 versus n = 109 of 149	p < 0.060	p < 0.895	p < 0.253

Male n = 5 of 12 versus n = 40 of 149	p < 0.656	p < 0.830	p < 0.886
with fcTB n = 9 of 161 pts. versus without fcTB n = 152	p < 0.767	p < 0.328	p < 0.202
Female n = 8 of 9 versus n = 108 of 152	p < 0.488	p < 0.274	p < 0.261
Male n = 1 of 9 versus n = 44 of 152	-	-	-
with mTB n = 6 of 161 pts. vs. without mTB n = 15 of 21	p < 0.870	p < 0.321	p < 0.109
Female n = 6 of 6 versus n = 9 of 15	p < 0.614	p < 0.434	p < 0.133
Male n = 0 of 6 versus n = 6 of 15	-	-	-
with mTB n = 6 of 161 pts. versus without mTB n = 155	p < 0.562	p < 0.080	p < 0.073
Female n = 6 of 6 versus n = 110 of 155	p < 0.511	p < 0.060	p < 0.056
Male n = 0 of 6 versus n = 45 of 155	-	-	-

Table 2: *Relationship between patient cohorts with and without TB, fTB, fcTB or mTB.*

Legend to table 2 *The difference was not significant between most patient cohorts with and without TB, fTB, fcTB, or mTB; p values were higher than 0.05, except patient cohorts with and without fTB (70.92 years versus 64.87, p < 0.046). The mean age of female RA patients with TB was higher than the mean age of females without TB (70.20 years versus 64.17, p < 0.056 - NS). The females with mTB died earlier than females without mTB (9.67 years versus 15.12, p < 0.056 - NS).*

Glossary to table 2 *RA: Rheumatoid Arthritis; TB: Tuberculosis; fTB: Fibrous Tuberculosis (Inactive Tuberculosis); fcTB: Fibrocaseous Tuberculosis (Inactive Tuberculosis Without Miliary Dissemination); mTB: Miliary Tuberculosis (Active Tuberculosis With Miliary Dissemination).*

Figure 4 and 13 demonstrate the TB (fTB, fcTB, mTB) with traditional HE staining, viewed by light microscopy.

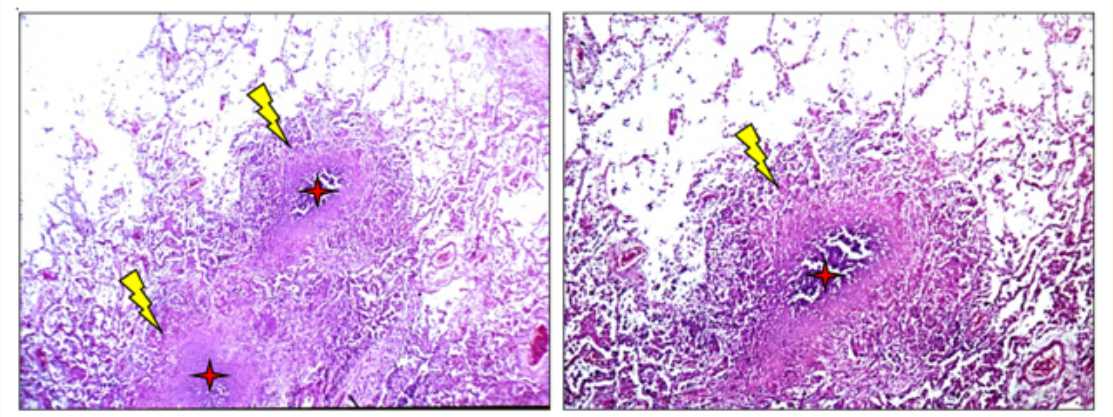

Figure 4a Figure 4b

Figure 4a-4b: *Post-primary caseous tuberculosis in the lung. Coalescent caseous cores (red stars) of tuberculotic foci (arrows) are surrounded by a moderately cellular zone of histiocytes not respecting the borders of lobular-sublobular units of the lung (stars indicate the center; arrow heads indicate the borders of granulomas). The coalescent character of miliary granulomas without true caseous necrosis or fibrous transformation indicate an impaired response. (a) HE, x 50, (b) same as (a) x125.*

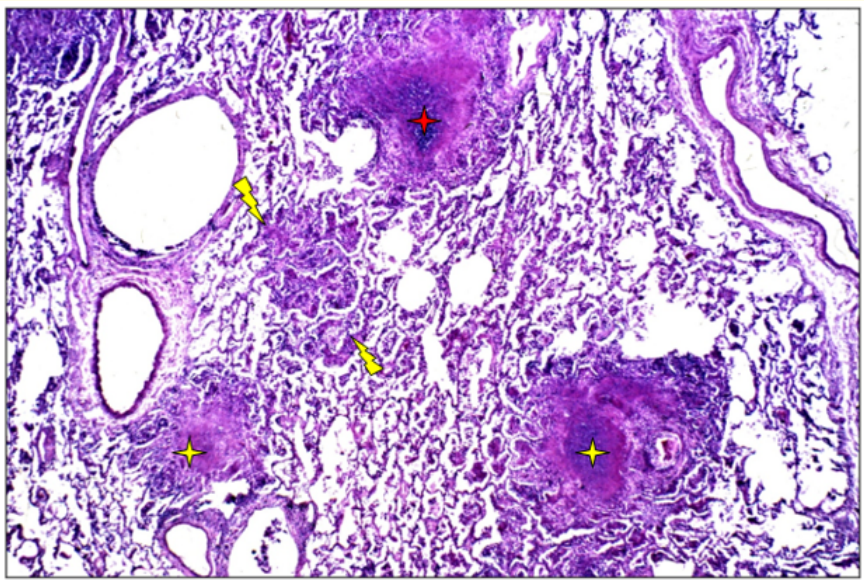

Figure 5: *Disseminated coalescent (red stars), moderately caseous (yellow star) and proliferative (arrow heads) miliary granulomas occurring simultaneously in the lung (stars indicate the center, arrow heads indicate the borders of granulomas). The tiny granulomas were distributed throughout the lung with decreasing prevalence from apex to basal regions of the lungs. HE, x 50.*

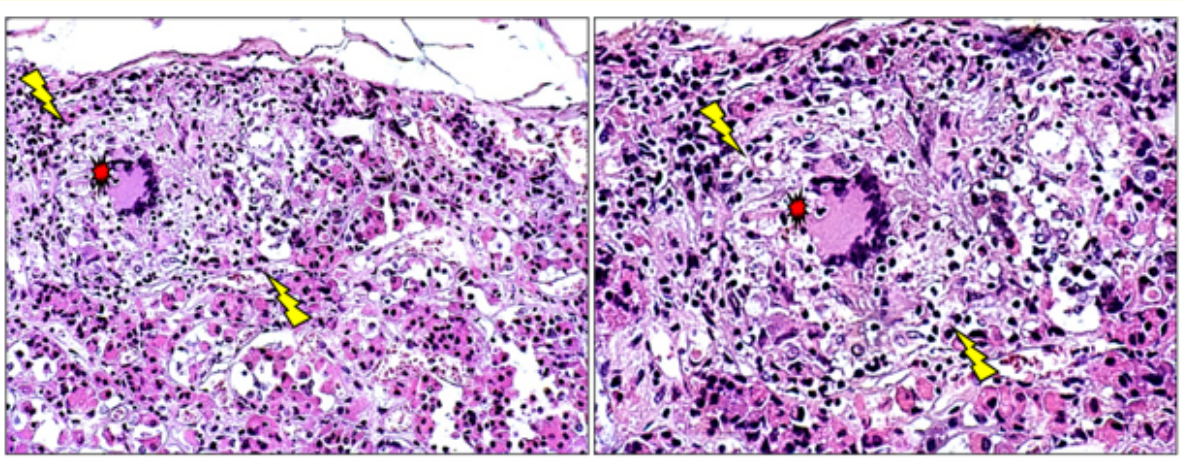

Figure 6a and 6b: *Moderatelly cellular proliferative miliary epithelioid granulomas (yellow arrow heads indicate the borders) with multinucleated giant cell of Langhans (red point) in the pituitary gland in terminal premortem stage of post-primary TB with hematogenous dissemination. (a) HE, x 50, (b) same as (a) x125.*

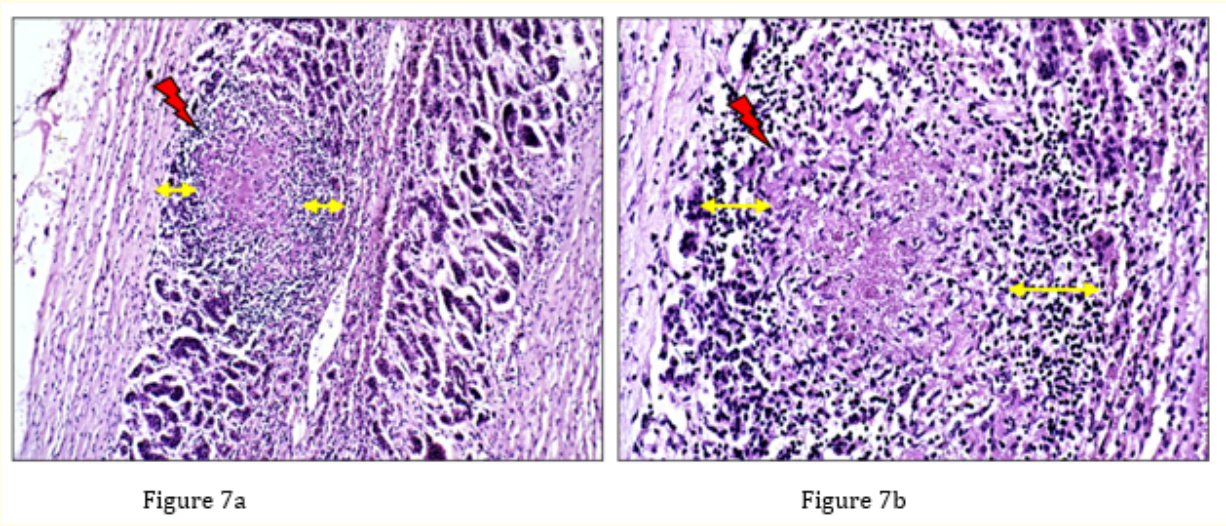

Figure 7a Figure 7b

Figure 7a and 7b: *Exudative miliary epithelioid granuloma (red arrow head) without epitheloid histiocytes and with zone of lymphoid cells at the periphery (yellow arrow) in the cortex of an atrophic adrenal gland caused by steroid treatment. The hematogenous dissemination may involve different organs in late (Ranke III) stage of TB. The exudative (serous) character of miliary granulomas without epitheloid histiocytes corresponds to the poor response (limited reactivity) of the patients. (a) HE, x 50, (b) same as (a) x125.*

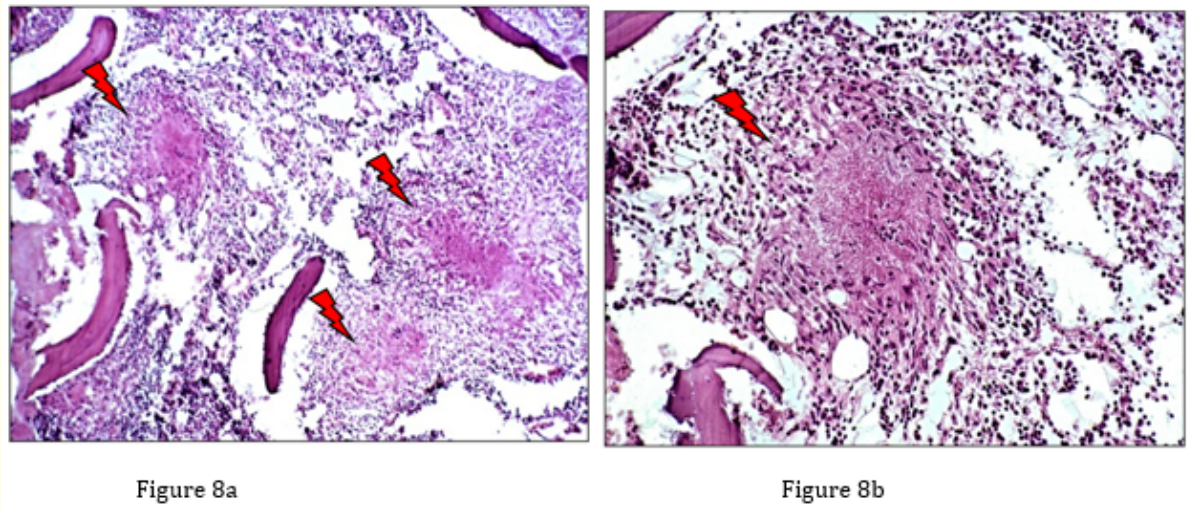

Figure 8a Figure 8b

Figure 8a and 8b: *Proliferative miliary epithelioid granulomas in atrophic bone (red arrows). Granulomas with more or less cellular reaction indicate the reactivity of the patients. (a) HE, x 50, (b) same as (a) x125.*

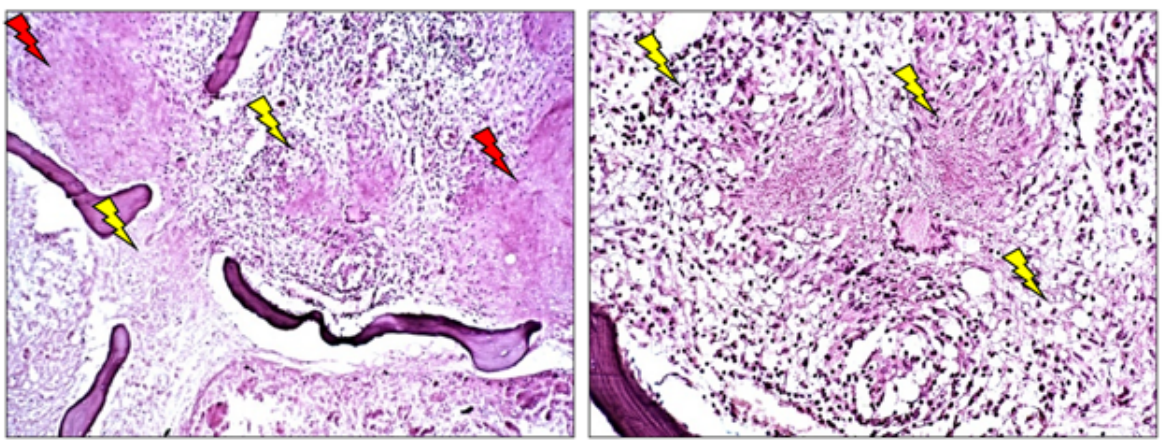

Figure 9a Figure 9b

Figure 9a and 9b: *Proliferative (red stars) and exudative (yellow stars) miliary epithelioid granulomas in bone indicate the gradually decreasing cellular response of the patients. (a) HE, x 50, (b) same as (a) x125.*

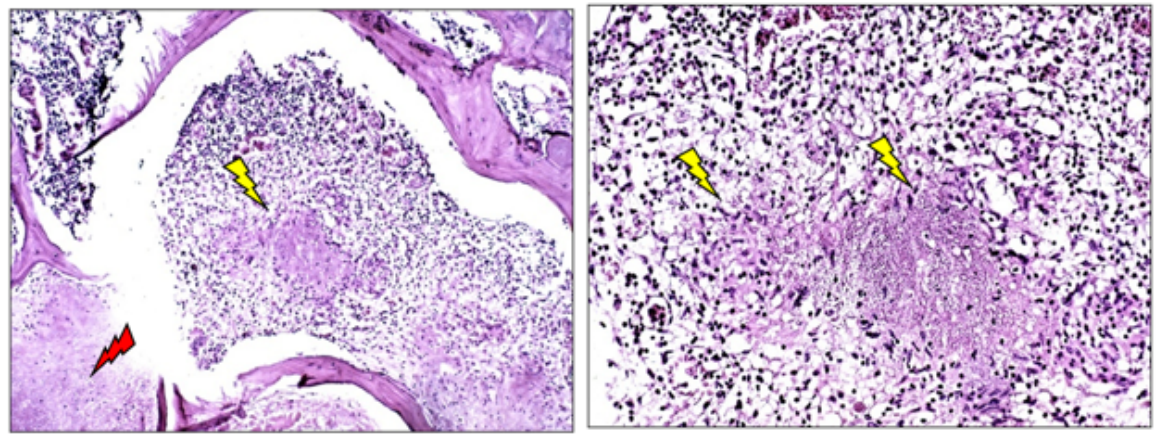

Figure 10a Figure 10b

Figure 10a and 10b: *Proliferative (red arrow) and more or less serous exudative (yellow arrow heads) miliary epithelioid granulomas in bone. The exudative involvement of the knee joints (hematogenous dissemination in bone and synovial membranes) may cause differential diagnostic problems for rheumatologists. (a) HE, x 50, (b) same as (a) x125.*

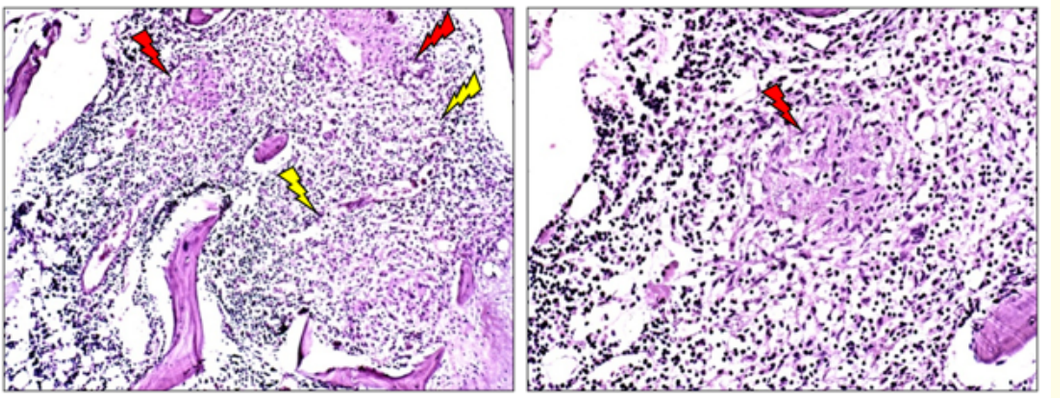

Figure 11a Figure 11b

Figure 11a and 11b: *Exudative (yellow arrow head) and moderately cellular (red arrow head) miliary epithelioid granulomas in bone. (a) HE, x 50, (b) same as (a) x125.*

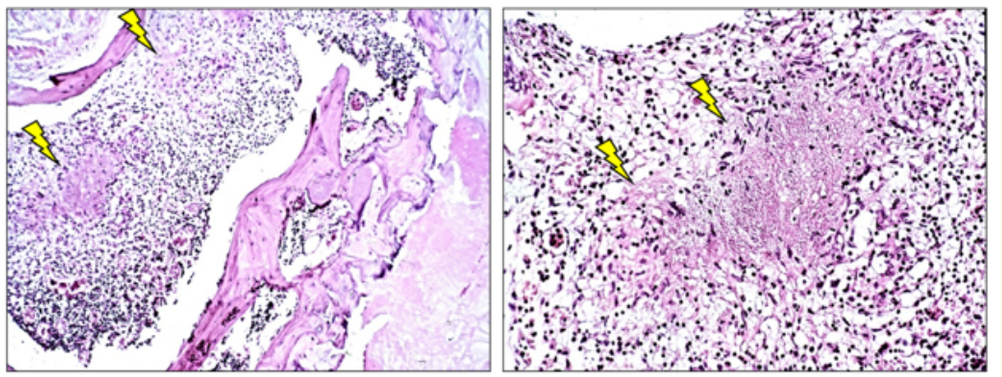

Figure 12a Figure 12b

Figure 12a and 12b: *More or less serous exudative miliary epithelioid granulomas (yellow arrow heads) in bone. (a) HE, x 50, (b) same as (a) x125.*

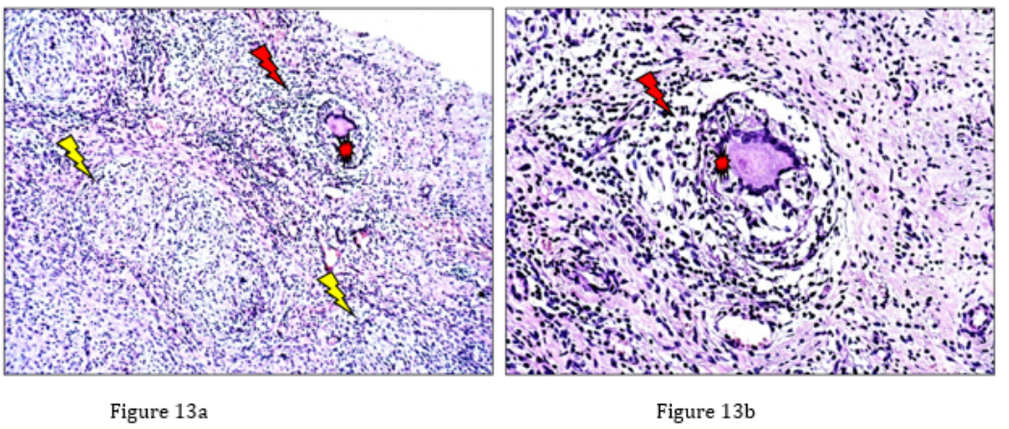

Figure 13a Figure 13b

Figure 13a and 13b: *Incipient exudative (yellow arrows) and proliferative (red arrows) miliary epithelioid granulomas with giant cell of Langhans (red point) in synovial membrane. (a) HE, x 50, (b) same as (a) x125.*

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

Discussion

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. The exudative (more serous, 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. The coalescent central foci of epithelioid granulomas without caseous necrosis also indicate the poor reactivity of the patients.

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 a tuberculin skin test may be also limited due to inadequate poor response of the patients [13], as well the QuantiFERON blood test. A positive Interferon-Gamma (γ) Release Assays (IGRA) result may not necessarily indicate TB infection with tuberculous mycobacteria. A negative IGRA does not rule out active TB disease.

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 [14].

Beside patient history or targeted X-ray "histopathology remains one of the most important methods for diagnosing tuberculosis" [15,16].

It is difficult to estimate the true prevalence of dormant TB even in autopsy population, because of the limited number of autopsies in recent years. In earlier studies [17-19] only some organs were evaluated with or without mentioning the histological characteristics of TB or their role in morbidity or mortality.

Table 3 summarizes the prevalence and mortality of TB in autopsied RA patients according to the pertinent literature [17-23].

Authors	Year of publication	Autopsy n =	Morbidity of TB	Mortality of TB
			n - %	n - % of Total
Baggenstoss and Rosenberg	1943 [17]	30	14 - 46.7% "heald" n = 11 "active" n = 3	0 of 14 - 0%
Young and Schwedel	1944 [18]	33	ND	1 of 33 - 3.03%
Gedda	1955 [19]	45	ND	1 of 45 - 2.22%
Püschel	1973 [20]	143	18 - 12.6%	5 of 18 - 3.49%
Bély and Apáthy	2012 [5]	161	21 - 13.04% fTB n = 12 fcTB n = 9 mTB n = 6	2 of 13 - 1.24% with mTB
Bély and Apáthy	2013 [21-23]	234	27 - 11.53% fTB n = 15 fcTB n = 12 mTB n = 8	3 of 27 - 1.28% with mTB

Table 3: *Literature on the morbidity and mortality of tuberculosis in RA.*

Glossary to table 3

RA: Rheumatoid Arthritis; TB: Tuberculosis; fTB: Fibrous Tuberculosis (Inactive Tuberculosis); fcTB: Fibrocaseous Tuberculosis (Inactive Tuberculosis Without Miliary Dissemination); mTB: Miliary Tuberculosis (Active Tuberculosis With Miliary Dissemination); ND: No Data.

In 1884 in Hungary the incidence of TB was 466/100.000 [24]. Since BCG vaccination (started in the 1960s) the morbidity and mortality of tuberculosis has decreased considerably in Hungary as well. The incidence of TB sunk below 100/100000 in the 70s, and it was 38/100.000 in 1990 [24]. In the 21st century (2000-2016) a further decline was observed; the incidence fell from 35 to 8.8, and the mortality rate from 4 to less than one per 100.000 populations per year [25].

Conclusion

The morbidity and mortality of TB was higher in our autopsy population in comparison to the general population of Hungary.

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 who die earlier than females without mTB.

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Volume 9 Issue 12 December 2020