Prevalence and Predictive Clinical-Laboratory Parameters of Latent Tuberculosis in Rheumatoid Arthritis - A Retrospective Clinicopathologic Study of 161 Autopsy Patients

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Abstract

**Introduction:** The risk of latent, clinically not diagnosed tuberculosis is high in rheumatoid arthritis. Recognition of indolent tuberculosis is of great importance especially before starting immunosuppressive or biological therapy for rheumatoid arthritis.

**Aim:** The aim of this study was to determine the classic clinical-laboratory parameters associated with post-primary inactive fibrous or fibrocaseous tuberculosis, with or without active miliary dissemination of tuberculosis in rheumatoid arthritis.

**Patients and Methods:** A non-selected autopsy population of 161 in-patients with rheumatoid arthritis was studied. Rheumatoid arthritis was confirmed clinically according to the criteria of the American College of Rheumatology.

The post-primary fibrous, fibrocaseous or miliary disseminated tuberculosis 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.

Clinical-laboratory parameters of different patient cohorts were compared with the Student (Welch) t-probe.

**Results:** Post-primary tuberculosis was associated with rheumatoid arthritis in 21 (13.04%) of 161 patients.

Post-primary tuberculosis was localized to the lungs.

Twelve (57.14%) of 21 tuberculosis were histologically only fibrous, antracothic tuberculotic scars and 9 (42.86%) of 21 revealed a fibrocaseous tubercle.

One of 12 fibrous and 5 of 9 fibrocaseous tuberculosis were complicated by miliary dissemination in 6 (3.72% of 161; 28.57% of 21) rheumatoid arthritis patients.

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Eleven of 12 fibrous and 4 of 9 fibrocaseous tuberculosis were inactive (not complicated by miliary dissemination) in 15 (9.31% of 161; 71.43% of 21) patients.

There was no significant difference in most of the clinical laboratory parameters between patient cohorts with fibrous, fibrocaseous or miliary tuberculosis and without tuberculosis.

In fibrocaseous or miliary tuberculosis the total albumin and globulin levels of the blood decreased significantly; the albumin/globulin ratio was less than “1” (in contrast to the normal value which is more than “1”).

The proportion of α 1 and α 2 globulin % was significantly higher in rheumatoid arthritis patients with fibrocaseous or miliary tuberculosis in comparison without tuberculosis.

Discussion and Conclusions: Men and women could be affected by fibrous, fibrocaseous or miliary tuberculosis at any time during rheumatoid arthritis.

The onset and duration of rheumatoid arthritis in patient cohorts did not influence the prevalence and features of coexistent fibrous, fibrocaseous or miliary tuberculosis.

The significant and consequent decrease of albumin/ globulin quotient and elevated α 1 and α 2 globulin % in elderly patients with moderate clinical activity of rheumatoid arthritis 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.).

This tendency of the aforementioned laboratory parameters in patient cohorts with fibrocaseous or miliary tuberculosis, especially elderly women with moderate clinical activity of rheumatoid arthritis should warn the physicians of indolent tuberculosis, excluding other reasons of increased inflammatory activity.

Keywords: Rheumatoid Arthritis; Latent Inactive and Active Tuberculosis; Clinical-Laboratory Parameters

Abbreviations

RA: Rheumatoid Arthritis; TB: Tuberculosis; ESR: Erythrocyte Sedimentation Rate; CRP: C Reactive Protein; BUN: Blood Urea Nitrogen; RBC: Red Blood Cells; WBC: White Blood Cells; GOT: Glutamate-Oxalacetate-Transaminase (= AST - Aspartate Transaminase); GPT: Glutamate-Piruvate Transaminase (= ALT - Alanine Transaminase); GGT (gamma GT): Gamma-Glutamyl Transpeptidase; LDH: Lactate Dehydrogenase; SD: Standard Deviation; ND: No Data; NS: Not Significant; 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; *: Asterisk indicates negative value of association's coefficient (inverse relationship); DMARD: Disease Modifying Antirheumatic Drugs; CDAI: Clinical Disease Activity Index for Rheumatoid Arthritis (Aletaha D); SDAI: Simple Disease Activity Index for Rheumatoid Arthritis (Aletaha D); DAS28-CRP: Disease Activity Score-28 for Rheumatoid Arthritis with CRP (Fransen J)

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Introduction

The risk of latent, clinically not diagnosed tuberculosis (TB) is high in rheumatoid arthritis (RA) [1-4]. Recognition of indolent TB is of great importance especially before starting immunosuppressive or biological therapy for RA.

Aim of the Study

The aim of this study was to determine the classic clinical-laboratory parameters associated with post-primary inactive fibrous or fibrocaseous TB and active disseminated miliary TB in RA.

Patients (Autopsy Population) and Methods

A non-selected autopsy population of 161 in-patients with RA was studied. The patients died at the National Institute of Rheumatology between 1969 and 1992 [5].

RA was confirmed clinically according to the criteria of the American College of Rheumatology [6].

The fibrous, fibrocaseous or miliary TB was diagnosed at autopsy, confirmed microscopically by a detailed review of extensive histological material, reviewing retrospectively all available clinical and pathological reports.

The correlations were determined by the Student (Welch) t-probe [7], comparing the age, sex, onset of RA, duration of disease and classic laboratory parameters (Latex, Waaler-Roose values, ESR, CRP, serum albumin/globulin ratio, serum electrophoresis (albumin, α 1-globulin, α 2-globulin, beta-globulin, gamma-globulin), RBC, hemoglobin, WBC, blood urea nitrogen (BUN), serum creatinin, serum potassium and sodium values, urine specific gravity, proteinuria, urine sediment (RBC, WBC), serum bilirubin, LDH, GPT, GGT; blood sugar and diastase values, systolic and diastolic blood pressure at the last hospitalization.

Results

Prevalence of post-primary TB in RA

Post-primary fibrous TB (n = 12) or fibrocaseous TB (n = 9) localized to the lungs accompanied RA in 21 (13.04% of 161) patients.

One of 12 fibrous TB and 5 of 9 fibrocaseous TB were complicated by active miliary dissemination of tuberculosis in 6 (3.73% of 161; 28.57% of 21) RA patients. Miliary epithelioid granulomatous inflammation was not observed without post-primary fibrous or fibrocaseous TB.

Eleven of 12 fibrous and 4 of 9 fibrocaseous TB were inactive (not complicated by miliary TB) in 15 (9.31% of 161; 71.43% of 21) RA patients.

Demographics, onset and duration of RA in patients with and without TB

Table 1 and figure 1 summarize the demographics, onset and disease duration of RA in patients with TB (n = 21), fibrous TB (n = 12), fibrocaseous TB (n = 9), miliary TB (n = 6), or inactive TB (n = 15: fibrous n = 11 or fibrocaseous TB n = 4) and without TB (n = 140).
Table 1: Sex, mean age with SD, range, onset and disease duration (in years) of 161 RA patients with fibrous, fibrocaseous or miliary TB, with inactive fibrous or fibrocaseous TB and without TB.

Glossary to table 1
RA: Rheumatoid Arthritis; TB: tuberculosis; SD: Standard Deviation.

The mean age of RA patients was higher with TB (n = 21), fibrous TB (n = 12), fibrocaseous TB (n = 9), miliary TB (n = 6), or inactive fibrous and fibrocaseous TB (n = 15) in comparison to the total population (n = 161) or to patients without TB (n = 140), but this difference was significant only between patient cohorts with fibrous TB and without TB (70.92 years versus 64.77, p < 0.043).

Elderly RA patients with miliary TB (n = 6) died earlier than patients without TB (n = 140), but this difference was not significant (9.67 years versus 14.36, p < 0.087 - NS).

The mean age of female RA patients with TB (70.20 ys), fibrous TB (73.00 ys) fibrocaseous TB (67.75 ys), miliary TB (68.33 ys) and inactive fibrous or fibrocaseous TB (71.44 ys) was also higher, than the mean age of females without TB (64.17 ys), but these differences were not significant.

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Elderly females with miliary TB (n = 6) died earlier than females without TB (n = 101), but this difference was not significant (9.67 years versus 14.64, p < 0.076 - NS).

There was no significant difference in the onset and disease duration of RA between patient cohorts with TB (n = 21), fibrous TB (n = 12), fibrocaseous TB (n = 9), miliary TB (n = 6), or inactive fibrous and fibrocaseous TB (n = 15) in comparison to total population (n = 161) or to the patients without TB (n = 140). The onset and duration of RA in patient cohorts did not influence the prevalence and features of coexistent TB (fibrous, fibrocaseous or miliary TB).

Men and women could be affected by TB (fibrous, fibrocaseous or miliary TB) at any time during RA (Table 1). The risk of active miliary dissemination was particularly high in women; women with miliary TB died earlier then women without TB.

Figure 1 demonstrates the mean age, onset and duration of RA in patients with TB (n = 21), fibrous TB (n = 12), fibrocaseous TB (n = 9), active miliary TB (n = 6) or inactive TB (n = 15, fibrous TB n = 11 of 15 and fibrocaseous TB n = 4 of 15) and without TB (n = 140) at death.

Table 2 summarizes the statistical correlations ("p" values) between female and male RA patients with TB, fibrous TB, fibrocaseous TB, miliary TB or inactive TB and without TB.
### Table 2: Relationship between patient cohorts with TB, fibrous TB, fibrocaseous TB, miliary TB or inactive TB and without TB.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>RA patients n = 161 versus pts. with fibrocaseous TB n = 9 of 21</th>
<th>p &lt; 0.779</th>
<th>p &lt; 0.359</th>
<th>p &lt; 0.230</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female n = 116 of 161 versus n = 8 of 9</td>
<td>p &lt; 0.516</td>
<td>p &lt; 0.352</td>
<td>p &lt; 0.332</td>
</tr>
<tr>
<td></td>
<td>Male n = 45 of 161 versus n = 1 of 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA patients n = 161 versus pts. with miliary TB n = 6 of 21</td>
<td>p &lt; 0.576</td>
<td>p &lt; 0.090</td>
<td>p &lt; 0.083</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female n = 116 of 161 versus n = 6 of 6</td>
<td>p &lt; 0.532</td>
<td>p &lt; 0.072</td>
<td>p &lt; 0.068</td>
</tr>
<tr>
<td></td>
<td>Male n = 45 of 161 versus n = 0 of 6</td>
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<td></td>
</tr>
<tr>
<td>With TB n = 21 of 161 pts. versus without TB n = 140</td>
<td>p &lt; 0.093</td>
<td>p &lt; 0.329</td>
<td>p &lt; 0.880</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female n = 15 of 21 versus n = 101 of 140</td>
<td>p &lt; 0.956</td>
<td>p &lt; 0.326</td>
<td>p &lt; 0.792</td>
</tr>
<tr>
<td></td>
<td>Male n = 6 of 21 versus n = 39 of 140</td>
<td>p &lt; 0.944</td>
<td>p &lt; 0.891</td>
<td>p &lt; 0.811</td>
</tr>
<tr>
<td>With fibrous TB n = 12 of 161 pts. versus without TB n = 140</td>
<td>p &lt; 0.043</td>
<td>p &lt; 0.685</td>
<td>p &lt; 0.0307</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female n = 7 of 12 versus n = 101 of 140</td>
<td>p &lt; 0.057</td>
<td>p &lt; 0.825</td>
<td>p &lt; 0.276</td>
</tr>
<tr>
<td></td>
<td>Male n = 5 of 12 versus n = 39 of 140</td>
<td>p &lt; 0.701</td>
<td>p &lt; 0.838</td>
<td>p &lt; 0.929</td>
</tr>
<tr>
<td>With fibrocaseous TB n = 9 of 161 pts. versus without TB n = 140</td>
<td>p &lt; 0.678</td>
<td>p &lt; 0.315</td>
<td>p &lt; 0.237</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female n = 8 of 9 versus n = 101 of 140</td>
<td>p &lt; 0.413</td>
<td>p &lt; 0.268</td>
<td>p &lt; 0.314</td>
</tr>
<tr>
<td></td>
<td>Male n = 1 of 9 versus n = 39 of 140</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With miliary TB n = 6 of 161 pts. versus without TB n = 140</td>
<td>p &lt; 0.512</td>
<td>p &lt; 0.073</td>
<td>p &lt; 0.087</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female n = 6 of 6 versus n = 101 of 140</td>
<td>p &lt; 0.447</td>
<td>p &lt; 0.055</td>
<td>p &lt; 0.076</td>
</tr>
<tr>
<td></td>
<td>Male n = 0 of 6 versus n = 39 of 140</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With inactive fibrous or fibrocaseous TB n = 15 of 21 vs without TB n = 140</td>
<td>p &lt; 0.108</td>
<td>p &lt; 0.679</td>
<td>p &lt; 0.521</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female n = 9 of 15 versus n = 101 of 140</td>
<td>p &lt; 0.064</td>
<td>p &lt; 0.771</td>
<td>p &lt; 0.412</td>
</tr>
<tr>
<td></td>
<td>Male n = 6 of 15 versus n = 39 of 140</td>
<td>p &lt; 0.944</td>
<td>p &lt; 0.891</td>
<td>p &lt; 0.811</td>
</tr>
<tr>
<td>With inactive fibrous or fibrocaseous TB n = 15 of 21 vs active miliary TB n = 6 of 21</td>
<td>p &lt; 0.870</td>
<td>p &lt; 0.321</td>
<td>p &lt; 0.109</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female n = 9 of 15 versus n = 6 of 21</td>
<td>p &lt; 0.614</td>
<td>p &lt; 0.434</td>
<td>p &lt; 0.133</td>
</tr>
<tr>
<td></td>
<td>Male n = 6 of 15 versus n = 0 of 21</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legends to table 2**

There was no significant difference in mean age, onset and duration of RA between patient cohorts with TB, fibrocaseous TB, or miliary TB and without TB; the mean age of patients with fibrous TB was significantly higher, than the mean age of RA patients without TB (70.92 years versus 64.77, \( p < 0.043 \)).

There was no significant difference between RA patients with inactive \((n = 15)\) and active miliary TB \((n = 6)\) in mean age, onset or duration of RA.

The onset and duration of RA did not influence basically the prevalence and features of coexistent TB (fibrous, fibrocaseous or miliary TB) in patients and the “\( p \)” values in women were also higher, than 0.05.

**Glossary to table 2**

RA: Rheumatoid Arthritis; TB: Tuberculosis.
Comparing the age, onset and duration of RA at the time of death there was no significant difference in survival time (p < 0.870 - NS), onset (p < 0.321 - NS) or duration of RA (p < 0.109 - NS) between patient cohorts with inactive (fibrous or fibrocaseous TB: n = 15) and active (n = 6) miliary TB; active miliary dissemination developed at any time in the course of RA accompanying with TB.

We found that miliary dissemination could have developed at any time in the course of RA accompanying with TB.

In our autopsy population only female patients were involved with miliary TB.

Comparing the age, onset of RA and duration of disease in women at death, there was no significant difference in survival time (p < 0.614 - NS), onset (p < 0.434 - NS), or duration of RA (p < 0.133 - NS) between women with inactive (fibrous or fibrocaseous TB n = 9) and active miliary TB (n = 6); miliary TB developed in women at any time in the course of RA accompanying with TB.

Significantly different clinical laboratory parameters of RA patients with and without TB

There was no significant difference in clinical laboratory parameters between patient cohorts with (n = 21) and without TB (n = 140), except total globulin level of the blood; the amount of globulin decreased significantly in RA patients with TB (32.50 g/L; p < 0.024), fibrocaseous TB (31.83 g/L; p < 0.022) or miliary TB (32.50 g/L; p < 0.054 - NS) compared to the patients without TB (35.89 g/L).

In RA patients with TB, fibrocaseous TB and miliary TB the total albumin levels decreased to a greater, the globulin levels to a relatively lesser extent (g/L) compared to the normal values; the albumin/globulin ratio was in all of these patient cohorts less than 1 (in contrast to the normal value which is more than 1).

The proportion of α 1 and α 2 globulin % was significantly higher in RA patients with fibrocaseous TB (6.45% and 14.89%) in comparison without TB (5.40% and 13.50%; p < 0.029 and p < 0.035).

In RA patients with miliary TB the proportion of α 1 and α 2 globulin % showed a further increment (6.66% and 15.30%), but only the rise of α 2 globulin % was significantly higher (p < 0.030) compared to the patients without TB.

In our patient population the miliary dissemination of TB occurred with a significantly higher level of serum sodium (142.4 mmol/L; p < 0.011) and lower level of GGT (24.24 U/L; p < 0.004) or blood sugar concentration (4.58 mmol/L; p < 0.006); but these values remained in the normal range.

Table 3.1-3.2 and figure 2.1-2.2 summarize the significantly different clinical laboratory parameters of RA patients with TB (n = 21), fibrous TB (n = 12), fibrocaseous TB (n = 9), active miliary TB (n = 6) or inactive TB (n = 15: fibrous TB 11 or fibrocaseous TB 4 of 15) and without TB (n = 140) at death.

<table>
<thead>
<tr>
<th>Parameters ± SD</th>
<th>Normal range</th>
<th>With TB n = 21</th>
<th>Without TB n = 140</th>
<th>With fibrous TB n = 12</th>
<th>With fibrocaseous TB n = 9</th>
<th>With miliary TB n = 6</th>
<th>With inactive fibrous or fibrocaseous TB n = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin - g/L</td>
<td>35 - 50 g/L</td>
<td>28.80 ± 3.66</td>
<td>30.84 ± 6.96</td>
<td>28.00 ± 5.15</td>
<td>29.33 ± 1.97</td>
<td>29.75 ± 1.92</td>
<td>28.17 ± 4.34</td>
</tr>
<tr>
<td>Globulin - g/L</td>
<td>25 - 35 g/L</td>
<td>32.50 ± 3.35</td>
<td>35.89 ± 6.61</td>
<td>33.50 ± 3.84</td>
<td>31.83 ± 2.79</td>
<td>32.50 ± 2.06</td>
<td>32.50 ± 3.99</td>
</tr>
<tr>
<td>Albumin/Globulin ratio</td>
<td>1 &lt;</td>
<td>0,8861</td>
<td>0,8592</td>
<td>0,8358</td>
<td>0,9214</td>
<td>0,9153</td>
<td>0,8667</td>
</tr>
<tr>
<td>α 1 globulin %</td>
<td>1.0 - 3.2%</td>
<td>5.84 ± 1.02</td>
<td>5.40 ± 1.68</td>
<td>5.29 ± 0.67</td>
<td>6.45 ± 0.99</td>
<td>6.66 ± 1.12</td>
<td>5.49 ± 0.74</td>
</tr>
<tr>
<td>α 2 globulin %</td>
<td>7.4 - 12.6%</td>
<td>13.63 ± 2.46</td>
<td>13.50 ± 3.49</td>
<td>12.37 ± 2.64</td>
<td>14.89 ± 1.39</td>
<td>15.30 ± 1.35</td>
<td>12.79 ± 2.46</td>
</tr>
<tr>
<td>Serum sodium - mmol/L</td>
<td>135 - 145</td>
<td>140.67 ± 3.14</td>
<td>139.60 ± 4.88</td>
<td>140.36 ± 3.26</td>
<td>141.14 ± 2.90</td>
<td>142.50 ± 1.12</td>
<td>140.14 ± 3.34</td>
</tr>
<tr>
<td>gamma GT - U/L</td>
<td>11 - 50 U/L</td>
<td>60.08 ± 75.79</td>
<td>64.18 ± 58.02</td>
<td>33.71 ± 35.39</td>
<td>90.83 ± 96.05</td>
<td>24.25 ± 13.24</td>
<td>76.00 ± 85.99</td>
</tr>
<tr>
<td>Blood sugar - mmol/L</td>
<td>4.10 - 6.00</td>
<td>9.16 ± 10.29</td>
<td>6.60 ± 3.52</td>
<td>11.06 ± 10.29</td>
<td>5.90 ± 2.06</td>
<td>4.58 ± 0.93</td>
<td>10.79 ± 11.54</td>
</tr>
</tbody>
</table>

Table 3.1: Significantly different or characteristic clinical laboratory parameters of RA patients with TB, fibrous TB, fibrocaseous TB, miliary TB or inactive TB and without TB.

Glossary to table 3.1
RA: Rheumatoid Arthritis; TB: Tuberculosis; SD: Standard Deviation.

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<table>
<thead>
<tr>
<th>Parameters - p &lt; 0.05</th>
<th>TB n = 21 vs without TB n = 140</th>
<th>Fibrous TB n = 12 vs without TB n = 140</th>
<th>Fibrocaseous TB n = 9 vs without TB n = 140</th>
<th>Miliary TB n = 6 vs without TB n = 140</th>
<th>Miliary TB n = 6 vs inactive TB n = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin - g/L</td>
<td>p &lt; 0.197</td>
<td>p &lt; 0.423</td>
<td>p &lt; 0.423</td>
<td>p &lt; 0.478</td>
<td>p &lt; 0.479</td>
</tr>
<tr>
<td>Globulin - g/L</td>
<td>p &lt; 0.024</td>
<td>p &lt; 0.371</td>
<td>p &lt; 0.022</td>
<td>p &lt; 0.054</td>
<td>p &lt; 0.914</td>
</tr>
<tr>
<td>Albumin/Globulin ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α1 globulin - %</td>
<td>p &lt; 0.172</td>
<td>p &lt; 0.704</td>
<td>p &lt; 0.029</td>
<td>p &lt; 0.087</td>
<td>p &lt; 0.162</td>
</tr>
<tr>
<td>α2 globulin - %</td>
<td>p &lt; 0.853</td>
<td>p &lt; 0.284</td>
<td>p &lt; 0.035</td>
<td>p &lt; 0.030</td>
<td>p &lt; 0.020</td>
</tr>
<tr>
<td>Serum sodium - mmol/L</td>
<td>p &lt; 0.325</td>
<td>p &lt; 0.602</td>
<td>p &lt; 0.310</td>
<td>p &lt; 0.011</td>
<td>p &lt; 0.055</td>
</tr>
<tr>
<td>Gamma GT - U/L</td>
<td>p &lt; 0.863</td>
<td>p &lt; 0.096</td>
<td>p &lt; 0.567</td>
<td>p &lt; 0.004</td>
<td>p &lt; 0.108</td>
</tr>
<tr>
<td>Blood sugar - mmol/L</td>
<td>p &lt; 0.309</td>
<td>p &lt; 0.262</td>
<td>p &lt; 0.470</td>
<td>p &lt; 0.006</td>
<td>p &lt; 0.098</td>
</tr>
</tbody>
</table>

Table 3.2: Statistical correlations ("p" values) between RA patients with TB, fibrous TB, fibrocaseous TB, miliary TB or inactive TB and without TB.

Glossary to table 3.2
RA: Rheumatoid Arthritis; TB: Tuberculosis; SD: Standard Deviation.

Figure 2.1: Significantly different or characteristic clinical laboratory parameters of RA patients with TB, fibrocaseous TB or miliary TB and without TB.

Legends to figure 2.1
There was a significant difference between RA patients with TB or miliary TB and without TB. The total albumin and globulin content of the blood decreased significantly in RA patients with TB (32.50 g/L; p < 0.024), fibrocaseous TB (31.83 g/L; p < 0.022) or miliary TB (32.50 g/L; p < 0.054 - NS) compared to the patients without TB (35.89 g/L).

The proportion of α1 (6.45% vs. 5.40%; p < 0.029) and α2 globulin % (14.89% vs. 13.50%; p < 0.035) was significantly higher in RA patients with fibrocaseous TB compared to the patients without TB.

In RA patients with miliary TB the proportion of α1 (6.66%) and α2 globulin % (15.30%) showed a further increment, but only the rise of α2 globulin % was significantly higher (p < 0.030) compared to the patients without TB.

Figure 2.2: Significantly different or characteristic clinical laboratory parameters of RA patients with TB, fibrocaseous TB or miliary TB and without TB.

Legend to figure 2.2

In RA patients with miliary TB the level of serum sodium (142.4 vs. 139.60 mmol/L; p < 0.011) was significantly higher and the level of GGT (24.24 vs. 64.18 U/L; p < 0.004) or blood sugar concentration (4.58 vs. 6.60 mmol/L; p < 0.006) significantly lower compared to the patients without TB, but these values remained in the normal range.

Figure 3-6 demonstrate fibrous, fibrocaseous or miliary TB with traditional HE staining, viewed by light microscopy.
**Figure 3a-3d:** Post-primary fibrocaseous tuberculous foci (yellow arrows) in the lung with concomitant occlusive arteritis of a small artery (red star).

Massive internal bleeding caused by erosion of a pulmonary blood vessel is one of the main causes of death in tuberculosis.

(a) HE, x 20, (b) same as (a) x40, (c) same as (a) HE, x 100, (d) same as (a) x100.

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**Figure 4a and 4b:** Miliary granulomas (yellow arrows) with giant cell of Langhans (red point) accompanied with lymphoid cellular infiltration in the pituitary gland.

Miliary dissemination involving the endocrine regulatory system (pituitary gland) may lead to death in tuberculosis.

(a) HE, x 40, (b) same as (a) HE, x 100.
Figure 5a and 5b: Exudative miliary granuloma (yellow arrows) surrounded by pronounced lymphoid cellular infiltration in the pituitary gland.
(a) HE, x 40, (b) same as (a) HE, x 100.

Figure 6a and 6b: Cellular miliary granuloma (yellow arrows) accompanied with lymphoid cellular infiltration in the pituitary gland.
(a) HE, x 40, (b) same as (a) HE, x 100.

Original magnifications correspond to the 24 x 36 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

RA is a chronic progressive systemic autoimmune disease characterized by repeated acute exacerbations of inflammation of different joints and various organs (heart, lungs, kidneys, serous membranes: peritoneum, pleura, pericardium, etc).

RA may modify the clinical course and symptoms of associated diseases, leading to missed diagnosis or late recognition of associated diseases [5].

TB is one of the most important diseases accompanying RA [5].

Inactive clinically latent tuberculosis may be aggravated by the limited immune reactivity of elderly patients, the autoimmune character of RA, the steroid and/or immunosuppressive drugs and nowadays by the disease modifying antirheumatic drugs (DMARD), leading to missing the diagnosis of TB, including lethal cases [8].

Recognition of indolent TB is of great importance; the age and sex (gender) of RA patients should alert the physicians to the possibility of reactivation of inactive dormant tuberculosis [9].

The mean age of RA patients was higher with TB, fibrous TB, fibrocaseous TB or miliary TB in comparison to total population or to the patients without TB and these differences were especially high in women, but the differences in mean age between patient cohorts were not significant (except fibrous TB and without TB (70.92 years versus 64.77, p < 0.043).

In senescent people with RA the morbidity of tuberculosis was higher than in younger ones, especially aged women had higher inclination (susceptibility) for TB [Present study and 9].

Inactive TB was complicated by active miliary dissemination at any time in the course of RA, but in our autopsy population only women were involved by miliary TB. The risk of miliary dissemination was particularly high in elderly women with fibrocaseous TB who died earlier than women without miliary TB (9.67 vs. 14.64 years p < 0.076 - NS).

In agreement with Ponce de León and coworkers (2005) [10] the onset and disease duration of RA did not influence basically the prevalence and features of coexistent fibrous, fibrocaseous or miliary TB [Present study and 9].

Most of the classic clinical laboratory parameters displayed no significant difference between patient cohorts with fibrous, fibrocaseous or miliary TB and without TB except the total albumin and globulin content of the blood, albumin/globulin ratio, α 1 and α 2 globulin %, which showed significant differences.

In RA patients with fibrocaseous or miliary TB the total albumin and globulin levels of the blood decreased significantly; the albumin/globulin ratio was less than “1” (in contrast to the normal value, which is more than “1”).

The proportion of α 1 and α 2 globulin % was significantly higher in RA patients with fibrocaseous or miliary TB in comparison without TB.

The significant and consequent reduction of albumin/globulin quotient and elevated α 1 and α 2 globulin% of RA patients may indicate the reactivation of dormant clinically latent TB excluding other reasons (for example attenuated or subclinical septic infection, rheumatoid vasculitis [11], inflammatory AA amyloidosis [12], etc).

The significantly lower levels of GGT and blood sugar remained within the normal range and this may be due the fact that our female patients with miliary TB had a relatively good liver function and were not alcoholics or diabetics.
The value of discussed inflammatory clinical-laboratory parameters is limited, alludes to the actual inflammatory activity of the patients and refers (more or less) only indirectly to tuberculosis. None of them is specific or unique to tuberculosis and indicates only actual inflammatory activity [13,14].

The clinical activity of RA (measured by CDAI, SDAI [15], DAS28-CRP [16], etc.) is usually moderate in elderly patients.

The significant, consequent and tendentious changes of inflammatory parameters especial in elderly patients with moderate clinical activity of RA should alert physicians to reactivation of dormant TB, excluding other causes of actual inflammatory activity.

Conclusion

In senescent people with RA the morbidity of tuberculosis was higher than in younger ones, especially aged women had higher inclination (susceptibility) for TB.

Post-primary fibrocaseous tuberculotic foci of the lungs represented the highest risk of reactivation of dormant TB and the main hazard of miliary dissemination, especially in elderly women.

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

The discussed clinical-laboratory parameters allude to inflammation and only more or less refer to tuberculosis. None of them is specific or unique to tuberculosis itself.

Despite these limitations the decreased albumin/globulin quotient and elevated α 1 and α 2 globulin % of patients with moderate clinical activity of RA may indicate the reactivation of dormant inactive tuberculotic processes, excluding other causes of inflammatory activity.

Constant and tendentious changes of mentioned laboratory parameters in patient cohorts with fibrocaseous or miliary TB, especial in elderly women with moderate clinical activity of RA may alert or should warn the physicians for recognition of indolent TB.

Disclosure

Article has not been published elsewhere or communicated for the purpose of any other publication. There is no conflict of interest.

Bibliography


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