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Research Article

Disease Modifying Effect of Tuberculosis on Coexistent Autoimmune Vasculitis in Rheumatoid Arthritis - A Retrospective Clinicopathologic Study of 161 Autopsy Patients

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Abstract

Introduction: The estimated global incidence and mortality of tuberculosis (TB) decreased between 2000-2021.

The risk of TB in rheumatoid arthritis (RA) is higher than in the general population, due to the impaired immune reactivity of elderly patients with autoimmune disease, steroid therapy, and the introduction of new disease modifying drugs.

Recognition of inactive tuberculosis and subclinical exacerbation of tuberculotic processes in RA or in other autoimmune diseases is a great challenge for physicians.

Aim of the Study: The aim of this study was to demonstrate the close connection between TB and granulomatous type of autoimmune vasculitis (gr AV) in RA, and demonstrate the value of the histological diagnosis of latent TB.

Patients and Methods: One hundred sixty-one (161) random autopsy patients with RA were studied.

Characteristics of TB and AV were analyzed histologically, and the relationship between TB and AV were evaluated statistically.

Results and Conclusion: RA can be associated with or complicated by autoimmune vasculitis at any age, in both sexes, and at any time in the course of the disease.

The risk of TB (without significance) and AV (at a significant level) is higher in elderly RA patients than in younger ones, especially elderly women are more likely to be affected by TB (without significance) or AV (at significant level).

Recognition of dormant TB without radiological evidence and diagnosis of AV without visible skin involvement is an implicit demand for proof.

Definitive diagnosis of vasculitis should be made upon biopsy of involved tissue.

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 involvement of blood vessels, independently of the biopsy sites.

Histological diagnosis of granulomatous vasculitis should alert clinicians to identify possible co-existent TB.

Keywords: *Tuberculosis; Autoimmune Vasculitis; Epithelioid Granuloma; Granulomatous Vasculitis*

Abbreviations

RA: Rheumatoid Arthritis; ACR: American College of Rheumatology; HE: Hematoxylin Eosin Staining; PAS: Periodic Acid Schiff Reaction; TB: Tuberculosis; fTB: Fibrous TB (Inactive Anthracotic Tuberculotic Scar without Miliary Dissemination); fcTB: Fibro-Caseous TB (Inactive Fibrous and Caseous Tuberculosis without Miliary Dissemination); mTB: Miliary TB (Active Tuberculosis with Miliary Dissemination); 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; Ns: Nonspecific; Fn: Fibrinoid Necrotic; Gr: Granulomatous

Glossary of AV (Definitions)

- 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 organs [14-16], excluding other causes of vasculitis, like hypertension, diabetes mellitus, tumors, septic infections etc.

Types of AV [14-16]: Ns - Nonspecific, Fn - Fibrinoid necrotic, Gr - Granulomatous.

Size of blood vessels [17]:

- Arteriole (a): No internal or external elastic membrane, < 500 micrometers in diameter.
- Small artery (A): Only internal elastic membrane present, vessels 500 - 1000 micrometers in diameter.
- Medium size artery (AA): Internal and external elastic membrane are present - vessel > 1000 micrometers in diameter.
- Venule (v), small vein (V), medium size vein (VV): Accompanying (a), (A) or (AA).

Introduction

The global trend in the estimated number of incidence and mortality of tuberculosis (TB) shows a decrease between 2000-2021 [1].

However, the increased number of TB deaths in 2020 and 2021 suggests that the number of people with undiagnosed and untreated TB has grown [1].

The risk of TB in rheumatoid arthritis (RA) is higher than in the general population [2-5].

The impaired immune reactivity of elderly patients (> 65 years) with autoimmune disease, and the daily use of glucocorticoid (≥ 5 mg) increase the risk of TB in RA patients [4].

Introduction of conventional or biological disease-modifying antirheumatic drugs (cDMARDs or bDMARDs) in rheumatic diseases presents a new challenge to recognize reactivated dormant tuberculosis [6,7].

All novel clinical or pathological information, which may help to recognize dormant (inactive) tuberculosis and subclinical (atypical) exacerbation of tuberculotic processes in RA or in other autoimmune diseases, should be kept in mind [8-11].

Aim of the Study

The aim of this study has been to demonstrate the close connection between TB and granulomatous autoimmune vasculitis in RA and to highlight its significance in the histological diagnosis of latent TB.

Patients (Autopsy Population) and Methods

At the National Institute of Rheumatology 9475 patients died between 1969 and 1992; among them 161 with RA, who were autopsied.

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

The post-primary inactive fibrous (fTB) or fibro-caseous tuberculosis (fcTB) with or without active miliary dissemination (mTB) was diagnosed at autopsy, confirmed and characterized microscopically. The extensive histological material and the available clinical and pathological reports were reviewed.

Systemic vasculitis was ascertained histologically in agreement with the recommendations of the Consensus Conference (2013) [13].

Autoimmune origin of systemic vasculitis (AV) was classified according to the type of vasculitis, the size of involved blood vessels and the stages of vasculitis [14-16], clinically excluding other causes of systemic vasculitis, such as other autoimmune diseases (lupus, progressive systemic sclerosis etc.), viral (hepatitis B and C) or bacterial septic infection, blood cancers, hypertension, endocrine diseases, reactions to certain drugs etc.

The "size" of arteries and veins was characterized according to the structure of the blood vessels (the "caliber" is fairly subjective and individual) [17].

Demographics of different patient cohorts were compared with the Student (Welch) t-probe [18].

The statistical correlations between tuberculosis and autoimmune vasculitis were confirmed by Pearson's chi-squared (χ^2) test [18].

Results

Prevalence of post-primary tuberculosis

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, anthracotic tuberculotic scars (fTB), and 9 (42.86%) of 21 revealed a fibro-caseous 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.

Active miliary epithelioid granulomatous inflammation was present in 6 (28.57%) of 21 patients with TB and was absent in 15 (71.43%) of 21 patients with TB (mTB was absent in 11 of 12 fTB and in 4 of 9 fcTB).

Miliary epithelioid granulomatous inflammation was not observed without post-primary fTB or fcTB.

TB led to death in 2 (9.52%) of 21 patients. Extensive miliary dissemination complicated the post-primary fibro-caseous tuberculosis in these two patients, who died of circulatory failure; the pituitary and adrenal glands were involved by epithelioid granulomas leading to circulatory insufficiency and a fatal outcome.

The 2 fatal cases of fcTB were clinically latent (not recognized and/or not mentioned in clinical reports).

Demographics, onset and duration of RA 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), fibro-caseous TB (n = 9), miliary TB (n = 6), and without TB (n = 140).

Sex	Number of autopsies	Mean age in years at death ± SD	Range of age (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 fibro-caseous 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 active 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	-	-	-	-
Inactive fibrous TB (n = 11) and inactive fibro-caseous TB (n = 4)	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
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

Table 1: *Sex, mean age with SD, range, onset and disease duration (in years) of 161 RA patients with fibrous, fibro-caseous or miliary TB or without TB.*

Remarks to table 1

Fibrous, fibro-caseous or miliary tuberculosis go with RA in both sexes, and 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 women were more likely to be affected by TB.

In our autopsy population women were involved only by miliary TB. The risk of miliary dissemination was particularly high in elderly women with fibro-caseous TB who died earlier than women without miliary TB (9.67 vs. 14.64 years p < 0.076 - NS).

RA: Rheumatoid Arthritis; TB: Tuberculosis; SD: Standard Deviation.

At the time of death there was no significant difference in lifespan, onset or duration of RA between patient cohorts with fibrous, fibro-caseous inactive or active military TB and without TB, except in mean age of patients with fibrous TB and without TB (70.92 years versus 64.77, $p < 0.043$).

There was no significant difference in the mean age of female and male patients at death with fibrous, fibro-caseous inactive or active military TB and without TB; TB complicated RA in both sexes, and at any time in the course of the disease.

Figure 1 demonstrates the mean age, onset and duration of RA in patients with fibrous, fibro-caseous inactive or active military TB and without TB at death.

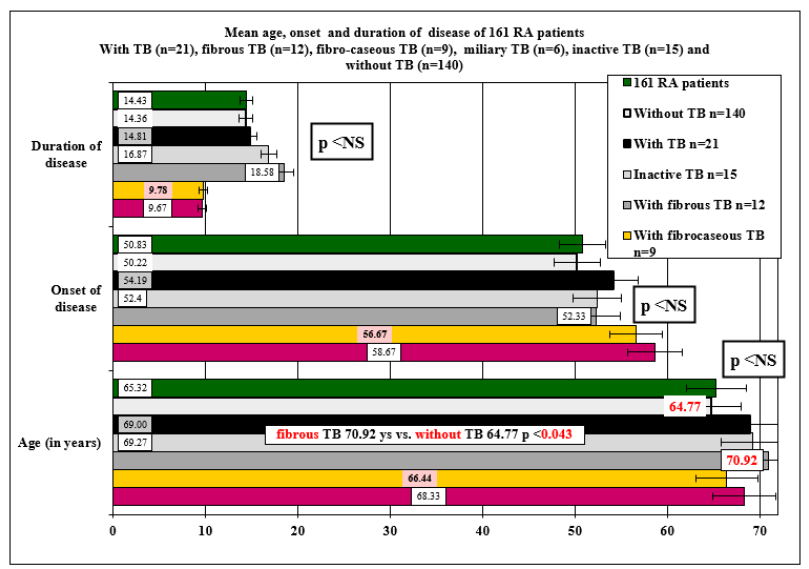

Figure 1: *Mean age, onset and duration of RA in patients with fibrous, fibro-caseous inactive and active miliary TB at death with (error bars in %).*

Legends to figure 1

There was no significant difference in the mean age of patient cohorts with fibrous, fibro-caseous inactive or active military TB and without TB; except patient cohorts with fibrous TB and without TB (70.92 years versus 64.77, $p < 0.043$).

The onset and duration of RA in patient cohorts did not influence the prevalence and features of coexistent TB (fibrous, fibro-caseous or miliary TB). The patients with fibro-caseous TB (9.78 years) and miliary TB (9.67 years) died earlier than the patients without TB (14.36 years); but these differences were not significant.

(Detailed analyses of statistical correlations between patient cohorts has been published in EC Pulmonology and Respiratory Medicine, 2020; 9.12: 73-88. [19], and Journal of Clinical Trials and Research (JCTR), 2021; 4(1): 219-236. [20]).

Glossary to figure 1

RA: Rheumatoid Arthritis; TB: Tuberculosis.

Prevalence of systemic autoimmune vasculitis

Systemic autoimmune vasculitis complicated RA in 33 (20.497%) of 161 patients.

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 was present in all 33 patients, in combination (mixed) with fibrinoid necrotic vasculitis in 17 (51.51%) and combined with granulomatous vasculitis in 10 (30.30%) patients.

Systemic autoimmune vasculitis led to death in 19 (57.57%) of 33 patients, due to coronary arteritis and thrombosis of the main coronary artery with a large myocardial infarct in 1, coronary arteriolitis and multiple focal microinfarctions of the myocardium (myocardiocytolysis) in 11, pulmonary arteriolitis and multifocal pneumonia in 3, cerebral vasculitis and multifocal brain necrosis in 2, thrombovasculitis of renal artery and renal necrosis in 1 or thrombovasculitis of mesenteric artery and intestinal hemorrhagic necrosis in 1 cases.

AV was recognized clinically in 4 (21.05%), and missed in 15 (78.95%) of 19 patients with the lethal complication of AV.

Ns vasculitis alone or combined (mixed) contributed to the mortality in 19 of 33, Fn vasculitis in 11 of 17, and the Gr vasculitis in 8 of 10 cases.

Demographics, onset and duration of RA patients with and without AV

Table 2 and figure 2 summarize the demographics, onset and disease duration of RA with nonspecific (n = 33), fibrinoid necrotic (n = 17) or granulomatous (n = 10) AV, and without AV (n = 125); three cases of systemic vasculitis of septic origin were not tabulated.

Sex	Number of autopsies	Mean age in years at death ± SD	Range of age (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 nonspecific AV	33 of 161	67.18 ± 10.64	32 - 83	56.94 ± 14.63	11.68 ± 10.34
Female	20	66.95 ± 11.11	32 - 82	59.47 ± 10.15	10.63 ± 7.46
Male	13	67.46 ± 9.87	53 - 83	52.92 ± 19.07	13.33 ± 13.55
With fibrinoid necrotic AV	17 of 33	68.24 ± 7.31	53 - 82	54.00 ± 16.64	14.88 ± 12.44
Female	10	68.90 ± 6.41	58 - 82	55.67 ± 7.39	14.44 ± 8.76
Male	7	67.29 ± 8.34	53 - 78	51.86 ± 23.55	15.43 ± 15.96
With granulomatous AV	10 of 33	65.70 ± 14.81	32 - 82	54.00 ± 17.04	15.44 ± 11.84

Female	7	65.71 ± 16.71	32 - 82	56.33 ± 17.04	15.00 ± 7.57
Male	3	65.67 ± 8.96	53 - 72	49.33 ± 26.41	16.33 ± 17.46
Without AV	125 of 161	65.02 ± 13.48	16 - 88	49.04 ± 17.39	15.45 ± 10.47
Female	94	64.82 ± 11.84	16 - 87	48.08 ± 16.15	16.03 ± 11.03
Male	31	65.65 ± 17.51	19 - 88	52.21 ± 20.65	13.54 ± 8.05

Table 2: *Sex, mean age with SD, range, onset and disease duration (in years) of 161 RA patients with nonspecific, fibrinoid necrotic or granulomatous type of AV and without AV.*

Remarks to table 2

Nonspecific, fibrinoid necrotic or granulomatous vasculitis complicated RA in both sexes, and at any time in the course of the disease, elderly (especially female) patients were more likely to be affected by AV than younger or male patients.

RA: Rheumatoid Arthritis; AV: Autoimmune Vasculitis; SD: Standard Deviation.

RA with nonspecific vasculitis started at a later age compared to the total population (56.94 years vs 50.83 years; $p < 0.050$) or compared to the patients without AV (56.94 years vs 49.04 years; $p < 0.016$).

These differences were more prominent in women than in women of the total population (59.47 years vs 50.19 years; $p < 0.003$) or compared to women without AV (59.47 years vs 48.08 years; $p < 0.000482$).

Elderly (especially female) patients were more likely to be affected by AV than younger ones or male patients; the women with nonspecific vasculitis died earlier than the women of the total population (10.63 years vs 16.03 years; $p < 0.052$ - NS), and significantly earlier than women without AV (10.63 years vs 16.03 years; $p < 0.017$).

Figure 2.1 demonstrates the differences with a level of significance between patients with nonspecific, fibrinoid necrotic and granulomatous AV, compared to the total population or to patients without AV.

Figure 2.2 demonstrates the differences with level of significance between female patients with nonspecific, fibrinoid necrotic and granulomatous AV, compared with the total population or with patients without AV.

Comparing the age, onset and duration of disease in males the differences were not significant, and were not demonstrated.

There was no significant difference in the mean age of female and male patients at death with and without AV; AV complicated RA in both sexes, and at any time in the course of the disease.

The relationship ("p" values of correlation) of demographics, onset and duration of disease between RA patients with nonspecific, fibrinoid necrotic or granulomatous vasculitis and without vasculitis are summarized in table 3.

Comparing the age, sex, onset and duration of RA there was no significant difference between patients with nonspecific, fibrinoid necrotic or granulomatous vasculitis and fibrous, fibrinoid necrotic inactive or active miliary TB; AV or TB affected both genders and at any time of the disease.

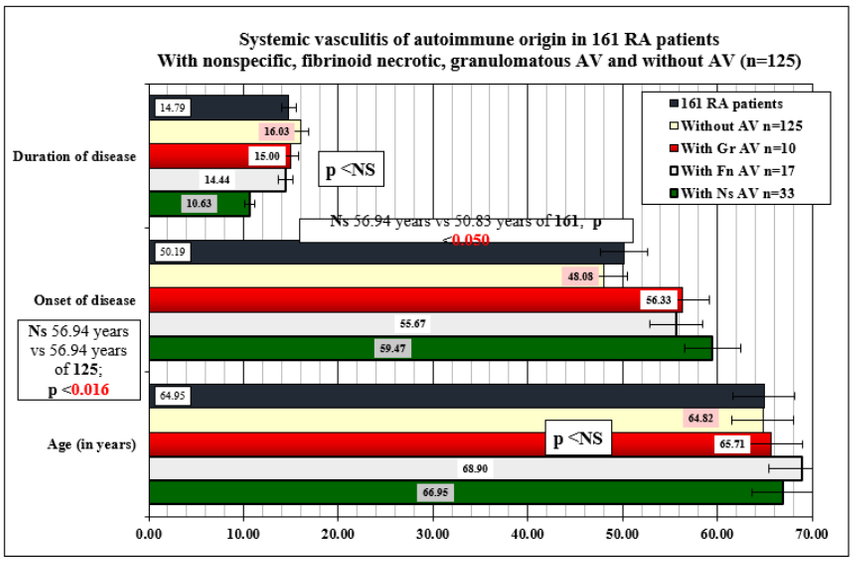

Figure 2.1: *Mean age onset and duration of disease of RA patients with and without AV (Error bar in %).*

Legend to figure 2.1

RA with nonspecific vasculitis started significantly later in life compared with the total population (56.94 years vs 50.83 years; p < 0.050) or with the patients without AV (56.94 years vs 49.04 years; p < 0.016).

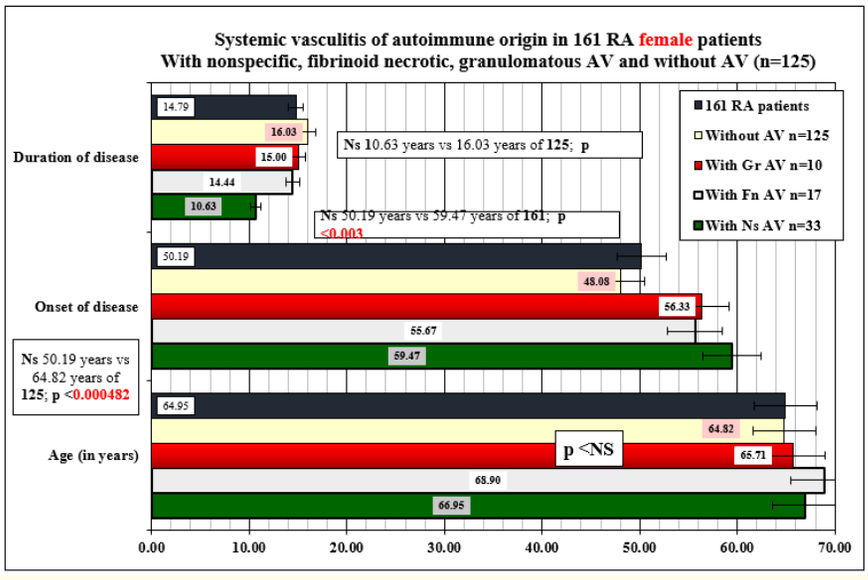

Figure 2.2: *Mean age onset and duration of disease of women with and without AV (Error bar in %).*

Legend to figure 2.2

RA started at a later age in women with nonspecific vasculitis compared with the women of the total population (56.94 years vs 50.19 years; p < 0.003) or compared with the women without AV (56.94 years vs 48.08 years; p < 0.000482).

The women with nonspecific vasculitis died earlier than the women of the total population (10.63 years vs 14.79 years; p < 0.052 - NS), and significantly earlier than women without AV (10.63 years vs 16.03 years; p < 0.017).

RA patients n = 161	Age	Onset of disease	Disease duration
Nonspecific vasculitis n = 33 versus total n of RA pts. n = 161	p < 0.389	p < 0.050	p < 0.195
Female n = 20 of 33 versus n = 116 of 161	p < 0.477	p < 0.003	p < 0.052
Male n = 13 of 33 versus n = 45 of 161	p < 0.737	p < 0.959	p < 0.978
Nonspecific n = 33 versus Fibrinoid necrotic vasculitis n = 17 of 33	p < 0.690	p < 0.567	p < 0.399
Female n = 20 of 33 versus n = 10 of 17	p < 0.563	p < 0.295	p < 0.303
Male n = 13 of 33 versus n = 7 of 17	p < 0.955	p < 0.926	p < 0.790
Nonspecific n = 33 versus Granulomatous vasculitis n = 10 of 33	p < 0.784	p < 0.664	p < 0.429
Female n = 20 of 33 versus n = 7 of 10	p < 0.870	p < 0.498	p < 0.286
Male n = 13 of 33 versus n = 3 of 10	p < 0.806	p < 0.869	p < 0.835
Nonspecific n = 33 versus without vasculitis n = 125 of 161	p < 0.338	p < 0.016	p < 0.086
Female n = 20 of 33 versus n = 94 of 125	p < 0.458	p < 0.000482	p < 0.017
Male n = 13 of 33 versus n = 31 of 125	p < 0.661	p < 0.922	p < 0.963
Fibrinoid necrotic vasculitis n = 17 of 33 versus total n RA pts. n = 161	p < 0.176	p < 0.494	p < 0.896
Female n = 10 of 17 versus n = 116 of 161	p < 0.122	p < 0.093	p < 0.918
Male n = 7 of 17 versus n = 45 of 161	p < 0.813	p < 0.946	p < 0.779
Fibrinoid necrotic n = 17 of 33 versus Granulomatous vasculitis n = 10 of 33	p < 0.639	p < 1.000	p < 0.915
Female n = 10 of 17 versus n = 7 of 10	p < 0.669	p < 0.887	p < 0.906
Male n = 7 of 17 versus n = 3 of 10	p < 0.835	p < 0.912	p < 0.952
Fibrinoid necrotic n = 17 of 33 versus without vasculitis n = 125 of 161	p < 0.153	p < 0.296	p < 0.867
Female n = 10 of 17 versus n = 94 of 125	p < 0.118	p < 0.029	p < 0.645
Male n = 7 of 17 versus n = 31 of 125	p < 0.729	p < 0.974	p < 0.788
Granulomatous vasculitis n = 10 of 33 versus total n RA pts. n = 161	p < 0.942	p < 0.622	p < 0.818
Female n = 7 of 10 versus n = 116 of 161	p < 0.915	p < 0.176	p < 0.955
Male n = 3 of 10 versus n = 45 of 161	p < 0.933	p < 0.879	p < 0.838
Granulomatous n = 10 of 33 versus without vasculitis n = 125 of 161	p < 0.897	p < 0.448	p < 1.000
Female n = 7 of 10 versus n = 94 of 125	p < 0.901	p < 0.085	p < 0.785
Male n = 3 of 10 versus n = 31 of 125	p < 0.998	p < 0.893	p < 0.843

Table 3: *The statistical correlations ("p" values of significance) between female and male RA patients with and without AV.*

Remarks to table 3

Nonspecific, fibrinoid necrotic or granulomatous vasculitis complicated RA in both sexes, and at any time in the course of the disease.

The risk of AV was higher in elderly RA patients than in younger ones, especially elderly females were more likely to be affected by AV.

RA: Rheumatoid Arthritis; AV: Autoimmune Vasculitis.

Table 4 summarizes the relationships ("p" values of correlation) of demographics, onset and duration of RA in patients with nonspecific, fibrinoid necrotic or granulomatous vasculitis and in patients with nonspecific, fibrinoid necrotic inactive or active miliary TB.

RA patients n = 161	Age	Onset of disease	Disease duration
Ns vasculitis n = 33 versus TB n = 21 of 161	p < 0.530	p < 0.548	p < 0.357
Female n = 20 of 33 versus n = 15 of 21	p < 0.390	p < 0.366	p < 0.232
Male n = 13 of 33 versus n = 6 of 21	p < 0.734	p < 0.958	p < 0.901
Ns vasculitis n = 33 versus fTB n = 12 of 21	p < 0.251	p < 0.415	p < 0.126
Female n = 20 of 33 versus n = 7 of 12	p < 0.200	p < 0.312	p < 0.113
Male n = 13 of 33 versus n = 5 of 12	-	-	-
Ns vasculitis n = 33 versus fcTB n = 9 of 21	p < 0.863	p < 0.967	p < 0.641
Female n = 20 of 33 versus n = 8 of 9	p < 0.868	p < 0.784	p < 0.931
Male n = 13 of 33 versus n = 1 of 9	-	-	-
Ns vasculitis n = 33 versus inactive TB n = 15 of 21	p < 0.502	p < 0.426	p < 0.225
Female n = 20 of 33 versus n = 9 of 15	p < 0.295	p < 0.361	p < 0.164
Male n = 13 of 33 versus n = 6 of 15	p < 0.734	p < 0.958	p < 0.901
Ns vasculitis n = 33 versus mTB n = 6 of 21	p < 0.835	p < 0.711	p < 0.496
Female n = 20 of 33 versus n = 6 of 6	p < 0.810	p < 0.858	p < 0.736
Male n = 13 of 33 versus n = 0 of 6	-	-	-
Fn vasculitis n = 17 versus TB n = 21 of 161	p < 0.789	p < 0.973	p < 0.988
Female n = 10 of 17 versus n = 15 of 21	p < 0.711	p < 0.837	p < 0.802
Male n = 7 of 17 versus n = 6 of 21	p < 0.794	p < 0.896	p < 0.715
Fn vasculitis n = 17 versus fTB n = 12 of 21	p < 0.403	p < 0.799	p < 0.467
Female n = 10 of 17 versus n = 7 of 12	p < 0.357	p < 0.576	p < 0.298
Male n = 7 of 17 versus n = 5 of 12	p < 0.884	p < 0.857	p < 0.853
Fn vasculitis n = 17 versus fcTB n = 9 of 21	p < 0.675	p < 0.718	p < 0.297
Female n = 10 of 17 versus n = 8 of 9	p < 0.804	p < 0.801	p < 0.417
Male n = 7 of 17 versus n = 1 of 9	-	-	-
Fn vasculitis n = 17 versus inactive TB n = 15 of 21	p < 0.737	p < 0.808	p < 0.687
Female n = 10 of 17 versus n = 9 of 15	p < 0.528	p < 0.641	p < 0.438
Male n = 7 of 17 versus n = 6 of 15	p < 0.794	p < 0.896	p < 0.715
Fn vasculitis n = 17 versus mTB n = 6 of 21	p < 0.986	p < 0.421	p < 0.195
Female n = 10 of 17 versus n = 6 of 6	p < 0.919	p < 0.522	p < 0.229
Male n = 7 of 17 versus n = 0 of 6	-	-	-
Gr vasculitis n = 10 versus TB n = 21 of 161	p < 0.551	p < 0.979	p < 0.901
Female n = 7 of 10 versus n = 15 of 21	p < 0.558	p < 0.771	p < 0.896
Male n = 3 of 10 versus n = 6 of 21	p < 0.966	p < 0.853	p < 0.798
Gr vasculitis n = 10 versus fTB n = 12 of 21	p < 0.364	p < 0.832	p < 0.588
Female n = 7 of 10 versus n = 7 of 12	p < 0.371	p < 0.543	p < 0.342
Male n = 3 of 10 versus n = 5 of 12	p < 0.765	p < 0.831	p < 0.871
Gr vasculitis n = 10 versus fcTB n = 9 of 21	p < 0.906	p < 0.755	p < 0.315
Female n = 7 of 10 versus n = 8 of 9	p < 0.802	p < 0.880	p < 0.378

Male n = 3 of 10 versus n = 1 of 9	-	-	-
Gr vasculitis n = 10 versus inactive TB n = 15 of 21	$p < 0.528$	$p < 0.839$	$p < 0.802$
Female n = 7 of 10 versus n = 9 of 15	$p < 0.469$	$p < 0.604$	$p < 0.496$
Male n = 3 of 10 versus n = 6 of 15	$p < 0.966$	$p < 0.853$	$p < 0.798$
Gr vasculitis n = 10 versus mTB n = 6 of 21	$p < 0.713$	$p < 0.521$	$p < 0.245$
Female n = 7 of 10 versus n = 6 of 6	$p < 0.762$	$p < 0.667$	$p < 0.219$
Male n = 3 of 10 versus n = 0 of 6	-	-	-

Table 4: *The statistical correlations ("p" values of significance) between female and male RA patients with AV and TB.*

Remarks to table 4

Men and women could be affected by fibrous, fibro-caseous inactive or active miliary TB and nonspecific, fibrinoid necrotic or granulomatous AV at any time during RA; the differences were not significant between patient cohorts or between men and women of the same cohort.

The risk of TB or AV was particularly high in elderly patients (especially in women).

RA: Rheumatoid Arthritis; AV: Autoimmune Vasculitis; Ns: Nonspecific; Fn: Fibrinoid Necrotic; Gr: Granulomatous; TB: Tuberculosis; fTB: Fibrous Tuberculosis (Inactive Tuberculosis without Miliary Dissemination); fcTB - Fibro-Caseous Tuberculosis (Inactive Tuberculosis without Miliary Dissemination); mTB - Miliary Tuberculosis (Active Tuberculosis with Miliary Dissemination).

Influence of tuberculosis on coexistent autoimmune vasculitis

TB (n = 21) was associated with nonspecific AV in 9, with fibrinoid necrotic AV in 3, with granulomatous AV in 4 of 21 patients.

Fibrous TB (n = 12) was associated with nonspecific AV in 4, with fibrinoid necrotic AV in 2, with granulomatous AV in 1 of 12 patients.

Fibro-caseous TB (n = 9) was associated with nonspecific AV in 5, with fibrinoid necrotic AV in 1, with granulomatous AV in 3 of 9 patients.

Inactive TB (n = 15) was associated with nonspecific AV in 5, with fibrinoid necrotic AV in 1, with granulomatous AV in none of 15 patients.

Active miliary TB (n = 6) was associated with nonspecific AV in 4, with fibrinoid necrotic AV in 2, with granulomatous AV in 4 of 6 patients.

There was a significant and positive correlation between TB and prevalence of nonspecific vasculitis ($\chi^2 = 7.4097$, $p < 0.0065$), between Tb and prevalence of granulomatous vasculitis ($\chi^2 = 6.8309$, $p < 0.0090$), between fibro-caseous Tb and prevalence of nonspecific vasculitis ($\chi^2 = 7.1902$, $p < 0.0073$), between fibro-caseous Tb and prevalence of granulomatous vasculitis ($\chi^2 = 7.6114$, $p < 0.0058$), between mTB and prevalence of nonspecific vasculitis ($\chi^2 = 5.4751$, $p < 0.0193$), and between mTb and prevalence of granulomatous vasculitis ($\chi^2 = 29.0646$, $p < 0.0000001$.

Fibrous or inactive TB did not influence statistically the prevalence of AV, indeed in some cases the relationship was inverse.

TB (n = 21) was associated with fatal nonspecific AV in 5, with fatal fibrinoid necrotic AV in 2, and with fatal of granulomatous AV in 3 of 21 patients.

Fibrous TB (n = 12) was associated with fatal nonspecific AV in 2, with fatal fibrinoid necrotic AV in 1, and with fatal granulomatous AV in 1 of 12 patients.

Fibro-caseous TB (n = 9) was associated with fatal nonspecific AV in 3, with fatal fibrinoid necrotic AV in 1, and with fatal granulomatous AV in 2 of 9 patients.

Inactive TB (n = 15) was associated with fatal nonspecific AV in 2, with fatal fibrinoid necrotic AV in none, and with fatal granulomatous AV in none of 15 patients.

Active miliary TB (n = 6) was associated with fatal nonspecific AV in 3, with fatal fibrinoid necrotic AV in 2, and with fatal granulomatous AV in 3 of 6 patients.

There was a significant and positive correlation between mTB and mortality of nonspecific vasculitis ($\chi^2 = 5.3406$, $p < 0.0208$), and between mTB and mortality of granulomatous vasculitis ($\chi^2 = 17.7744$, $p < 0.0000249$).

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

Table 5 summarizes the statistical correlations ("p" values of significance) between RA patients with fibrous, fibro-caseous inactive or active miliary TB and with nonspecific, fibrinoid necrotic or granulomatous AV with or without fatal outcome.

Type of AV without mortality/ Character of TB	**Nonspecific n = 33 of 33**	**Fibrinoid necrotic n = 17 of 33**	**Granulomatous n = 10 of 33**
TB n = 21 of 161	c: 0.5676, $\chi^2 = 7.4097$, $p < 0.0065$	c: 0.2000, $\chi^2 = 0.0463$, $p < 0.8296$ - NS	c: 0.6803, $\chi^2 = 6.8309$, $p < 0.0090$
Fibrous TB n = 12 of 21	c: -0.3483, $\chi^2 = 1.3111$, $p < 0.2522$ - NS	c: 0.2823, $\chi^2 = 0.5117$, $p < 0.8201$ - NS	c: 0.1715, $\chi^2 = 0.0930$, $p < 0.7603$ - NS
Fibro-caseous TB n = 9 of 21	c: 0.6940, $\chi^2 = 7.1902$, $p < 0.0073$	c: 0.0303, $\chi^2 = 0.2527$, $p < 0.6152$ - NS	c: 0.8239, $\chi^2 = 7.6114$, $p < 0.0058$
Active miliary TB n = 6 of 21	c: 0.7936, $\chi^2 = 5.4751$, $p < 0.0193$	c: 0.6471, $\chi^2 = 1.3762$, $p < 0.2408$ - NS	c: 0.95, $\chi^2 = 29.0646$, $p < 0.0000001$
Inactive TB n = 15 of 21	c: 0.3563, $\chi^2 = 1.6726$, $p < 0.1959$ - NS	c: -0.2656*, $\chi^2 = 0.2654$, $p < 0.6065$ - NS	c: -1.000*, $\chi^2 = 1.2755$, $p < 0.2587$ - NS
Type of AV with mortality/ Character of TB	**Nonspecific n = 19 of 33**	**Fibrinoid necrotic n = 11 of 17**	**Granulomatous n = 8 of 10**
TB n = 21 of 161	c: 0.4754, $\chi^2 = 2.1505$, $p < 0.1425$ - NS	c: 0.2102, $\chi^2 = 0.0037$, $p < 0.9518$ - NS	c: 0.6364, $\chi^2 = 2.4603$, $p < 0.1168$ - NS
Fibrous TB n = 12 of 21	c: -0.2166, $\chi^2 = 0.0061$, $p < 0.9378$ - NS	c: 0.1165, $\chi^2 = 0.1447$, $p < 0.7036$ - NS	c: 0.2968, $\chi^2 = 0.0177$, $p < 0.8942$ - NS
Fibro-caseous TB n = 9 of 21	c: 0.6190, $\chi^2 = 2.3378$, $p < 0.1263$ - NS	c: 0.2793, $\chi^2 = 0.0244$, $p < 0.8758$ - NS	c: 0.7485, $\chi^2 = 2.7625$, $p < 0.0965$ - NS

miliary TB n = 6 of 21	c: 0.7935, χ^2 = 5.3406, p < 0.0208	c: 0.7805, χ^2 = 3.2316, p < 0.0722 - NS	c: 0.9355, χ^2 = 17.7744, p < 0.0000249
Inactive TB n = 15 of 21	c: 0.0772, χ^2 = 0.0516, p < 0.8204 - NS	c: -1.0000*, χ^2 = 0.3181, p < 0.5727 - NS	c: -1.000*, χ^2 = 0.0937, p < 0. 5957 - NS

Table 5: *Level of significance between coexistent tuberculosis and autoimmune vasculitis with and without mortality.*

Glossary to table 5

NS - Not Significant.

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

Association's coefficient was positive in all of the cases except inactive TB and fibrinoid necrotic or granulomatous AV.

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.*

Figure 3-5 show post-primary exudative, fibro caseous and fibrous TB with concomitant (incidental, isolated) non-autoimmune vasculitis.

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.

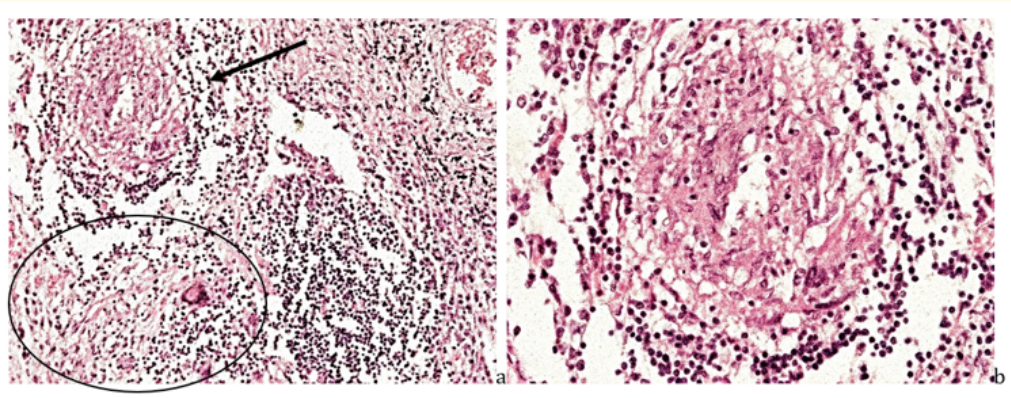

Figure 3a and 3b: *RA, post-primary exudative tuberculosis in the lung with concomitant incidental (non-systematic) vasculitis. (a) Exudative (black ellipse) miliary epithelioid granuloma with concomitant nonspecific tuberculous vasculitis (black arrow), HE, x 100, (b) same as (a) x200.*

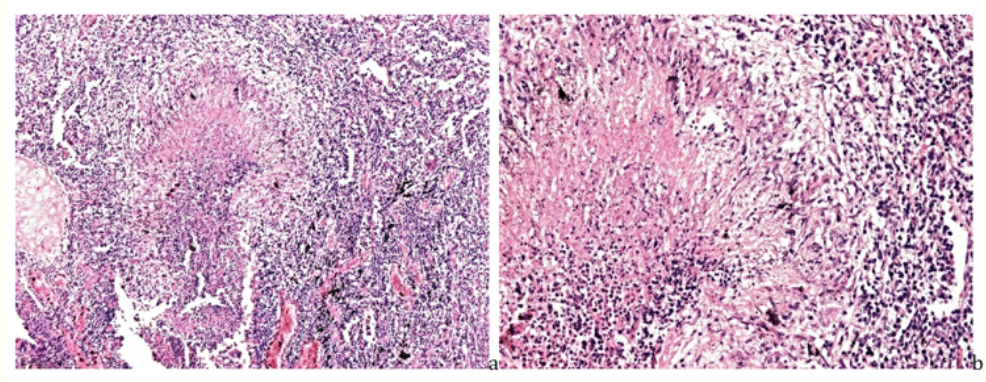

Figure 4a and 4b: *RA, Post-primary caseous tuberculosis in the lung. Coalescent caseous cores of tuberculotic foci are surrounded by a moderately cellular zone of histiocytes not respecting the borders of lobular-sublobular units of the lung. (a) HE, x 40, (b) same as (a) x100.*

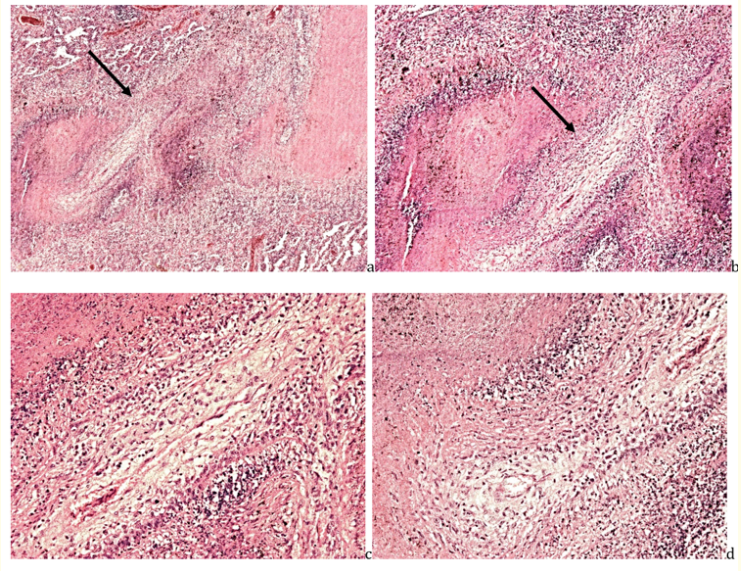

Figure 5a-5d: *RA, Post-primary fibro-caseous tuberculotic foci in the lung with concomitant occlusive arteritis of a small artery (black arrow). (a) HE, x 20, (b) same as (a) x40, (c) same as (a) HE, x 100, (d) same as (a) x100.*

Figure 6-9 demonstrate nonspecific, fibrinoid necrotic and granulomatous AV of RA patients AV.

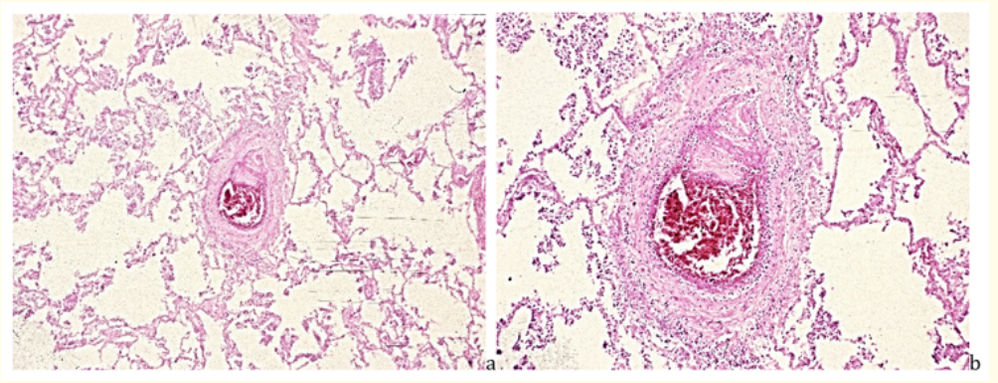

Figure 6a and 6b: *RA (not associated with TB), systemic autoimmune vasculitis, lung, small artery, nonspecific arteritis. (a) HE, x 20, (b) same as (a) x50.*

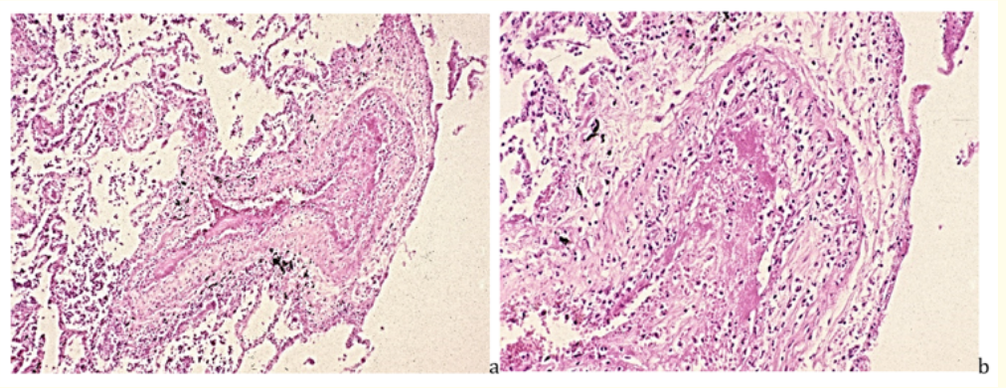

Figure 7a and 7b: *RA (not associated with TB), systemic autoimmune vasculitis, lung, small artery, fibrinoid necrotic arteritis. (a) HE, x 20, (b) same as (a) x50.*

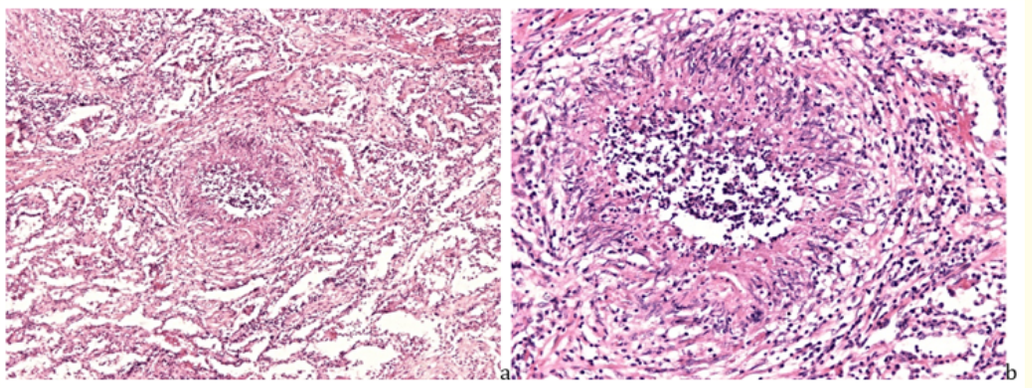

Figure 8a and 8b: *RA, systemic autoimmune vasculitis in association with co-existent TB complicated by mTB, lung, small artery. Granulomatous autoimmune arteritis. (a) HE, x 20, (b) same as (a) x50.*

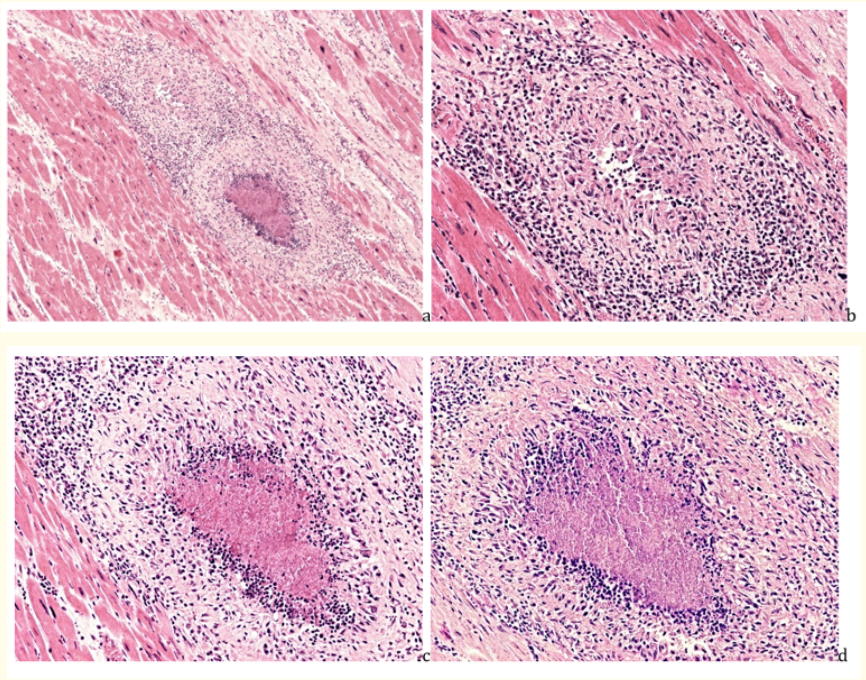

Figure 9a-9d: *RA, systemic autoimmune vasculitis in association with co-existent TB complicated by mTB; heart, small artery. Granulomatous necrotizing autoimmune vasculitis with typical rheumatoid nodule in the next segment of the same artery. (a) HE, x 40, (b) same as (a) x100, (c) same as (a) x100, (d) PAS, same as (a) x100.*

Discussion

In our RA patients tuberculosis and autoimmune vasculitis occurred at any age, in both sexes, and at any time in the course of the disease.

The risk of TB and AV was higher in elderly RA patients than in younger ones, especially elderly women were more likely to be affected by TB or AV.

Global Tuberculosis reports 1997 - 2022 of the World Health Organization suggested that the number of people with undiagnosed and untreated TB has grown, based on the increased number of TB deaths in 2020 and 2021 [1].

The true prevalence of dormant TB to estimate is difficult, even in an autopsy population, because of the gradually decreasing number of autopsies in recent years.

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 [21], 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 [22].

Beside patient history or targeted X-ray "histopathology remains one of the most important methods for diagnosing tuberculosis" [23,24].

Epithelioid granuloma can be associated to many diseases i.e., sarcoidosis, leprosy, schistosomiasis, histoplasmosis, cryptococcosis, cat-scratch disease, rheumatic fever, Crohn's disease, listeriosis, leishmaniasis, etc.

Epithelioid granulomas can be caused by 'infectious organisms (bacteria and fungi), products of plants and animals (pollen, sporangia, proteins), and metallic compounds, drugs or may be of unknown etiology' [25,26].

Therefore, the presence of epithelioid granulomas does not mean automatically a miliary dissemination of tuberculosis.

In case of TB or mTB additional histological sections were stained according to Ziehl-Neelsen, using a strong (massive) positive control (Figure 10). Our RA patients with co-existent TB were negative for mycobacteria by Ziehl-Neelsen stain.

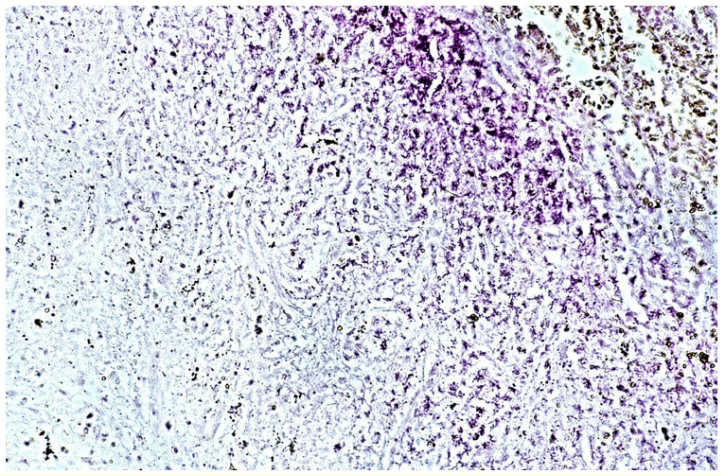

Figure 10: *TB, lung, cavernous tuberculosis, positive control tissue sample for Ziehl-Neelsen stain. (a) Ziehl-Neelsen stain, x 600.*

A negative Ziehl-Neelsen stain does not rule out tuberculosis, especially if the dissemination is terminal or the granulomas contain only a few mycobacteria.

In our RA patients the mentioned diseases with epithelioid granulomas were clinically excluded.

The tuberculous origin of epithelioid granulomas was supported by the fact that epithelioid granulomas occurred in all cases only together with post-primary TB (there were no granulomas without post-primary TB).

Tuberculotic foci can be accompanied with incidental isolated vasculitis (Figure 3).

Hematogenic miliary dissemination of TB can be accompanied with subendothelial miliary granulomas of the blood vessels without AV (Figure 11).

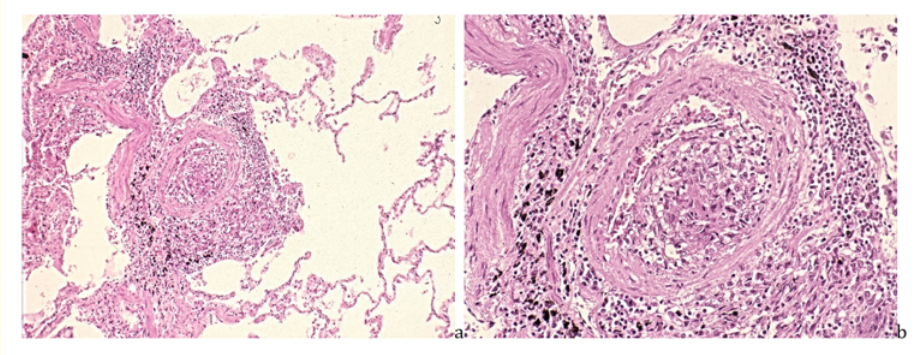

Figure 11a and 11b: *RA, TB complicated by miliary dissemination, lung. Subintimal miliary granuloma in the wall of a small artery is the sign of hematogenic dissemination of tuberculosis (distinct of granulomatous autoimmune vasculitis). (a) HE, x 50, (b) same as (a) x125.*

Landouzy typhobacillosis (sepsis tuberculosa acutissima) can be complicated by systemic vasculitis without microscopic characteristics of AV (Figure 12).

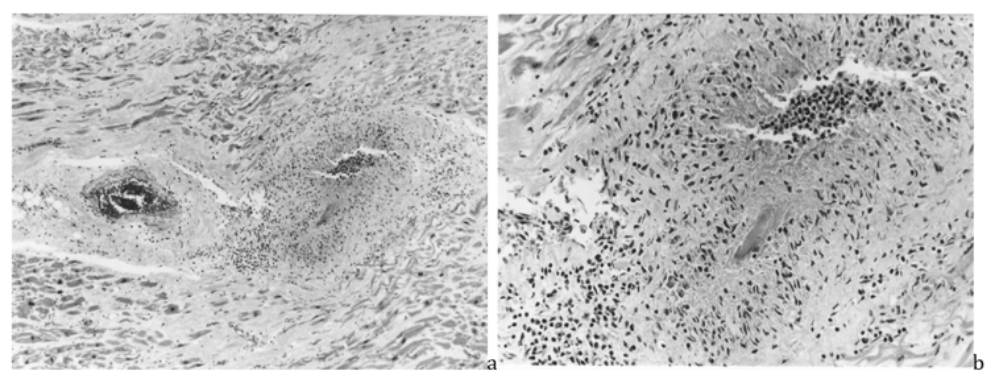

Figure 12a and 12b: *TB, Landouzy typhobacillosis, heart. Hyperacute terminal stage of systemic septic tuberculous vasculitis, reminiscent of granulomatous vasculitis of autoimmune origin (but should be distinguished from granulomatous autoimmune vasculitis). (a) HE, x 50, (b) same as (a) x125.*

The clinical diagnosis of systemic vasculitis of autoimmune origin is as difficult as the diagnosis of dormant TB. The diagnosis of vasculitis is based mostly on visible skin involvement, e.g. urticaria, infiltrative erythema, petechiae, purpura, purpuric papules, hemorrhagic vesicles and bullae, nodules, racemose livedo, deep (punched out) ulcers and/or digital gangrene [27].

Contemporary studies recommend that 'a definitive diagnosis of vasculitis should be made upon biopsy of involved tissue' [28].

Different (nonspecific, fibrinoid necrotic and granulomatous) types of autoimmune vasculitis are discussed in details by Sokoloff (1964) [29] and others [30-32].

The granulomatous autoimmune vasculitis was associated in all of our cases with nonspecific form of vasculitis.

In our RA patients we found a close relationship between TB or mTB and granulomatous autoimmune vasculitis. We assume that granulomatous vasculitis can be regarded as an indirect histological sign of miliary dissemination of TB, based on the significant link between them.

Granulomatous AV by itself can of course occur without TB, and does not mean necessarily in all cases TB.

According to Koizumi (1979) the rheumatoid nodule (without TB) is the most serious form of granulomatous necrotizing vasculitis [33].

We also consider rheumatoid nodules to be the most severe form of necrotizing granulomatous vasculitis, based on adjacent granulomatous segments and nodules within the same vessel [34-37].

According to Carlson (2010) granulomatous vasculitis means a high risk, and is a signal of coexistent serious systemic disease [27].

The contribution of nonspecific, fibrinoid necrotic and granulomatous vasculitis to mortality in our study supports Carlson's view; Ns vasculitis alone or combined contributed to the mortality in 19 of 33, Fn vasculitis in 11 of 17, and the Gr vasculitis in 8 of 10 patients.

The probability of lethal outcome was high in cases of fibrinoid necrotic (64.70%) or granulomatous (80.0%) vasculitis compared to the nonspecific vasculitis (31.58%); Fn or Gr vasculitis represent the more serious types of AV with an increased risk of fatal outcome.

Conclusion

RA can associate with TB or can complicate by autoimmune vasculitis at any age, in both sexes, and at any time in the course of the disease.

The risk of TB (without significance) and AV (at a significant level) is higher in elderly RA patients than in younger ones, especially elderly women are more likely to be affected by TB (without significance) or AV (at significant level).

Recognition of dormant TB without radiological sign and diagnosis of AV without visible skin involvement is a great diagnostic challenge.

A definitive diagnosis of vasculitis should be made upon biopsy of involved tissue.

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. The histological diagnosis should alert clinicians to make further efforts to identify a possible co-existent TB.

Disclosure

It has not been published elsewhere or communicated for the purpose of any other publication.

Conflict of Interest

There is no conflict of interest.

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