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COEXISTENCE OF BRONCHIECTASIS RELATED WITH RHEUMATOID ARTHRITIS AND POSTTUBERCULOSIS LUNG DISEASE - AN EVERPRESENT ISSUE

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ABSTRACT

The lung is a common site of involvement both in TB and rheumatoid arthritis (RA) disease, caused by disease itself or therapy. After completion of antiTB treatment, post TB lung disease (PTLD) residual changes persist and affect heath, survival and quality of life, mainly in patients with associated collagen diseases, as RA. Bronchiectasis are described in both RA and PTLD. The purpose of this prevalence study of bronchiectasis, performed among 92 RA hospitalized patients, from June 2017 to June 2019, consists in a pictorial assessment of the lung involvement changes, noticed on chest radiography and/or computed tomography, described in relation with TB sequelae, severity and duration of RA disease. Results. A high prevalence of imagistic abnormalities was found in 77.2% of cases (n=71/92). Bronchiectasis was a frequent imagistic chest finding (24/71; 33.8%), having a lower frequency among all study group patients (n=24/92; 26%), mostly older nonsmoker females. Conclusions. In a high TB burden, as Romania, the prevalence of bronchiectasis is related with advanced RA disease, being strongly correlated with persistent respiratory symptoms (p=0.009), and coexisting PTLD calcified nodular lung sequelae (p=0.001).

Keywords: Rheumatoid arthritis, Bronchiectasis, Extraarticular manifestations, Post Tuberculosis Lung Disease

Introduction

Starting as an orphan disease, bronchiectasis is no more associated with female gender, older age and insignificantly morbidity. From the beginning of the XXth century, lung damage caused by tuberculosis (TB) disease remains an important cause of bronchiectasis (1). Increased morbidity and mortality are important characteristics of bronchiectasis. Since imagistic methods of diagnosis became available, decreased rate of mortality, among both men and women, diagnosed with bronchiectasis, had been reported, in relation with different other comorbidities than TB (2). The coexistence of bronchiectasis related rheumatoid arthritis (RA) poses significant challenges in terms of increased morbidity, more complex disease management, and higher mortality rates (3).

Bronchiectasis is more a syndrome than a disease, overlapping with many diseases and disorders, as tuberculosis (TB), a leading cause for a high morbidity and mortality caused by single infectious agent. In an overwhelming TB burden country, as Romania, post TB bronchiectasis is a health hazard for the majority of people. Post TB Lung Disease (PTLD) is strongly associated with a large variety of pulmonary conditions, including lung parenchymal lesions (fibrosis, nodules), bronchial lesions (bronchial stenosis or

dilatation, bronchiolitis), pleural thickening, or other residual changes in mediastinal lymph nodes (4). These several categorized PTLD residual changes can be minor or debilitating, even fatal, mainly in patients with other comorbidities, as RA.

Considering the greatest heterogeneity of bronchiectasis syndrome, recognizing this entity in RA patients is crucial for improving therapy and outcomes of survival and quality of life.

Materials and Methods

A prevalence study was conducted, from June 2017 to June 2019, on a cohort of RA patients, admitted to hospitalization in Rheumatology Department of Constanta County Clinical Emergency Hospital "St Andrew" and/or investigated in Constanta Clinical Pneumophtisiology Hospital. Diagnosis of rheumatoid arthritis was performed according to the ACR/EULAR 2010 criteria (5).

Data Collection of RA patients' characteristics included: demographical data, personal medical and therapeutical history, particularly clinical information, regarding respiratory symptoms, including cough, dyspnea, and sputum production, but also imagistic information. All patients underwent hands and chest X- rays, chest tomography (CT), as well as laboratory tests, such as erythrocyte sedimentation rate (ESR), C reactive protein, serum levels of anti-citrullinated protein (CCP) antibody and rheumatoid factor (RF).

RA disease activity was assessed, for all included cases, by the Disease Activity Score-28 (DAS-28), using both Erythrocyte Sedimentation Rate (DAS28-ESR) and the C reactive protein (DAS28-CRP) (6).

Statistical analysis, including descriptive reports, ANOVA analysis of means, correlations, was performed using SPSS version 20.0. Statistical significance was considered for a confidence level of 95%.

Results

The study cohort consists in 92 cases, almost completely in patients with longstanding advanced RA (98.9%), and the mean disease duration was 15.00 ± 11.55 years.

Anti-CCP antibodies and rheumatoid factor (RF) were positive in the majority of cases (81.5% and 90.2%, respectively).

Erosive RA disease was identified in 70 subjects (76.1%).

In regards to medication history, most patients (89.1%) had a history of Methotrexate use, with more than half still using this disease modifying antirheumatic drug.

The average patient age at rheumatoid arthritis (RA) onset was 63.77 ± 11.56 years (limits: 38-86).

The study subjects were predominantly female (n=73/92; 79.3%), mean aged of 62.96 ± 11.79 years (limits: 38-86). Males were less (n=19) representative in the RA cohort, having a mean age of 66.89 50.7 ± 10.31 years (limits: 46-83) (Table 1). Regarding the mean age, there was no significant difference between cases, by gender, as ANOVA analysis showed (F=1.761; p=0.188). The older age is sustained, also, by the median value of 65.5 years.

Less than half of cases were smokers (n=39/92; 42.9%), with an average smoking history of 18.19 ± 17.26 pack-years (Table 1).

Table 1. Study cohort characteristics

Variable (n=92)	Patients (%)	Mean and standard deviation
Age of cases (years)	-	63.77 ±11.56
Females	73 (79.3%)	
Men	19 (20.7)	
BMI (Kg/m²)		27,11± 5,75
History of smoking	39(42,4%)	
Smoker at RA onset	29 (31.5%)	
Current smoker	15 (16.3%)	
Disease duration (years)	-	15.00±11.55
Positive RF	83 (90,2%)	
Anti CCP Antibodies	75 (81.5%)	
Erosions	70 (76,1%)	
Current Methotrexate use	50 (54.3%)	
History of Methotrexate use	82 (89.1%)	
Respiratory symptoms	65 (70,7%)	
X-ray pulmonary findings	46 (50%)	
Chest imagistic findings	71 (77,2%)	

Legend: BMI- body mass index; RA- rheumatoid arthritis; RF- rheumatoid factor; anti CCP antibodies- anti-cyclic citrullinated peptides

Most patients were overweight or obese, with a mean body mass index (BMI) of 27.11 ± 5.758, almost equal by gender (27.603 + 5.649 in males versus 26.982 + 5.818 in females), with no significant difference by ANOVA analysis (F=1.174; p=0.678).

Table 2 Respiratory symptoms in RA patients

Variable	Patients (%)
Respiratory symptoms	65 (70.7%)
Exhertional Dyspnea	59 (64.1%)
Non-productive cough	46 (50%)
Productive cough	(16.3%)

Respiratory symptoms were present in the great majority of RA patients (n=65/92; 70.7%), with exertional dyspnea as the main complaint (64.1%), followed by non-productive cough in 46 patients (50%) and productive cough in 15 patients (16.3%). (Table 2)

The prevalence of chest imagistic abnormalities was higher revealed by chest CT (n=71/92; 77.2%) than X-ray (n=46/92; 50%). (Table 1)

The most prevalent RA-related thoracic abnormality feature was represented by fibrotic changes (40.2%), followed by bronchiectasis (26.1%), and post TB lung disease suggestive calcified nodular lesions which were also prevalent, being identified in 38 patients (41.3%). (Table 3)

Tabel 3 Chest Tomography (CT) abnormalities among study cases

CT abnormalities	Patients (%)
Pulmonary fibrosis	37 (40.2%)
Bronchiectasis	24 (26.1%)
Mediastinal adenopathy	21 (22.82%)
Pulmonary emphysema	20 (21.7%)
Rheumatoid nodules	7 (7.7%)
Pleural thickening	21 (22.8%)
Pleural effusion	6 (6.52%)
Pulmonary sequelae calcified nodules	38 (41.3%)
Fibrotic bacillary sequelae	14 (15.4%)

Bronchiectasis was identified in more than a quarter of the subjects (26.1%), with traction morphology and predilect localization in middle and lower lobes of the lungs. It was correlated with the presence of respiratory symptoms (p=0.009), dry cough (p=0.032), and with coexisting TB sequelae, both fibrous and nodular or pleural involvement (p=0.015), and especially with pleural thickening (p=0.009). (Table 4)

We did not find a correlation between bronchiectasis related to medication history or smoker history.

Table 4 Comparative analysis of rheumatoid arthritis cases with and without bronchiectasis

Variable	Bronchiectasis (N=24)	Without bronchiectasis (N=68)	P
Men	6 (25%)	13 (19.2%)	0.56
Smoking history	8 (33.3%)	31 (45.6%)	0.34
Positive RF	21 (87.5%)	62 (91.2%)	0.69
Positive anti CCP antibodies	20(83.3%)	55 (80.9%)	0.79
Respiratory Symptoms	22 (91.7%)	43 (63.2%)	0.009
Non-productive cough	17 (70.8%)	29 (42.6%)	0.03
Exertional Dyspnea	18 (75%)	41 (60.3%)	0.22
Lung fibrous tuberculous sequelae	8(33.3%)	7 (10.3%)	0.02
Lung nodular tuberculous sequelae	17 (70.8%)	21 (30.9%)	0.001
Pleural Involvement	12 (50%)	16 (23.5%)	0.015
Pleural thickening	12 (50%)	14 (20.6%)	0.009

Legend: RF- rheumatoid factor; anti CCP antibodies- anti-cyclic citrullinated peptides.

Discussions

Rheumatoid arthritis (RA) is a prevalent chronic autoimmune colagen disorder, which affects mainly the joints, but it has several extra-articular manifestations, including pleural, bronchial and lung parenchymal involvement (7-9).

In our study, we found irreversible bronchiectasis in almost a quarter of RA patients (26.1%), mostly older and nonsmoker women. Studies recognised a strong association between rheumatoid arthritis (RA) and bronchiectasis. In 1967, in non computed tomography era, Walker et al, observed a frequency of bronchiectasis related RA between 1 and 10% (10). However,

with the advent of computed tomography (CT) of the lung, after 1993, based on imagistic findings, studies reported an increased prevalence of 25–30.5%, mostly in men (11, 12). There is a significant difference between the prevalence of bronchiectasis in hospitalized RA patients comparative with general population, where it ranges between 52.3/100000 and 566.1/100000 (2, 13-17). Whilst our study cohort is small, consisting in RA hospitalized patients, mostly women, the prevalence of bronchiectasis is consistent with other data, reported by other authors, but the most frequent abnormality found in our study was interstitial lung disease (ILD).

Various hypotheses have been proposed to explain the link between RA and lung involvement, including genetic predisposition, environmental exposure to mineral dust, or smoking, susceptibility to chronic infections, that lead to airway damage and bronchiectasis, or alveolar inflammation, with consecutive fibrosis, or pleural disease, or vascular disease, or drug-related pulmonary toxicity (9, 18-22). In our study cohort, we did not find a link between the use of disease-modifying antirheumatic drugs and bronchiectasis. However, a strong correlation between tubercullous sequelae and bronchiectasis was identified in our study group of hospitalized RA patients.

It is difficult to estimate the prevalence of coexisting TB and RA bronchiectasis. Bronchiectasis can share both infectious and autoimmune etiology. The Korean registry of post TB bronchiectasis revealed a lower rate of RA among comorbidities (n=15/119; p=0.008) (1). Among European countries, Romania has a high TB morbidity. After first 2 years of COVID-19 pandemic, in 2022, TB incidence, in Romania, was reported as 52 cases per 100,000 people (23). Although, this trend marks a significant decline from previous years, such as 2003, when the incidence was 159 cases per 100,000 people, Romania is still a high TB burden country.

Patients with RA, especially those treated with biological agents, are considered a risk group for developing TB disease (24). The immune system disruptions, caused by disease itself and the use of immunosuppressive drugs, are related to TB progressive infection to TB active disease. When analysing the risk of TB disease, in RA patients, in Spain, Carmona et al found a four-fold increased TB risk in RA patients, compared to the general population (25).

Japanese cohorts have, also, a 3.2-fold increased risk of tuberculosis in patients with rheumatoid arthritis, higher in males (10-fold increased risk), but no one in women (26).

Vulnerable population to both TB and RA exist worldwide. Bronchiectasis related RA and PTLD is a real challenge and further studies and larger cohorts are required. Although the European Respiratory Society guidelines for the management of adult bronchiectasis have been published since 2017, there are less information about the management of bronchial dilatations in patients with coexisting diseases TB and RA (27). Optimal imagistic screening of bronchiectasis is mandatory recommended in all RA patients having persistent respiratory symptoms. There is a huge need for evaluating the incidence and morphology of bronchiectasis, among RA patients, mainly in TB burden countries, like Romania, estimating the impact of RA and TB as coexisting diseases.

Conclusions

The prevalence of bronchiectasis was higher among hospitalized RA patients, mostly older and nonsmoker females. Bronchiectasis is more prevalent in RA patients with TB sequelae. There is a considerable overlapping with pleural involvement.

References

1. Choi H, Lee H, Ra SW, Kim HK, Lee JS, Um SJ, et al. Clinical Characteristics of Patients with Post-Tuberculosis Bronchiectasis: Findings from the KMBARC Registry. J Clin Med. 2021 Sep 30;10(19).
2. Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. Eur Respir J. 2016 Jan;47(1):186-93.
3. Swinson DR, Symmons D, Suresh U, Jones M, Booth J. Decreased survival in patients with co-existent rheumatoid arthritis and

bronchiectasis. Br J Rheumatol. 1997 Jun;36(6):689-91.
4. Khan R, Malik NI, Razaque A. Imaging of Pulmonary Post-Tuberculosis Sequelae. Pak J Med Sci. 2020 Jan;36(1):S75-s82.
5. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology (Oxford). 2012 Dec;51 Suppl 6:vi5-9.
6. van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis. 1990 Nov;49(11):916-20.
7. Yunt ZX, Solomon JJ. Lung disease in rheumatoid arthritis. Rheum Dis Clin North Am. 2015 May;41(2):225-36.
8. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R. Extra-articular Manifestations in Rheumatoid Arthritis. Maedica (Bucur). 2010 Dec;5(4):286-91.
9. Li Y, Wang W, Zhou D, Li L. The causal relationship between rheumatoid arthritis and bronchiectasis: a bidirectional Mendelian randomization study. Front Med (Lausanne). 2024;11:1403851.
10. Walker WC. Pulmonary infections and rheumatoid arthritis. Q J Med. 1967 Apr;36(142):239-51.
11. Remy-Jardin M, Remy J, Cortet B, Mauri F, Delcambre B. Lung changes in rheumatoid arthritis: CT findings. Radiology. 1994 Nov;193(2):375-82.
12. Cortet B, Perez T, Roux N, Flipo RM, Duquesnoy B, Delcambre B, et al. Pulmonary function tests and high resolution computed tomography of the lungs in patients with rheumatoid arthritis. Ann Rheum Dis. 1997 Oct;56(10):596-600.
13. Weycker D, Edelsberg J, Oster G, Tino G. Prevalence and Economic Burden of Bronchiectasis. Clinical Pulmonary Medicine. 2005 07/01;12:205-9.
14. Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots DR. Trends in bronchiectasis among medicare beneficiaries in the United States, 2000 to 2007. Chest. 2012 Aug;142(2):432-9.
15. Ringshausen FC, de Roux A, Pletz MW, Hämäläinen N, Welte T, Rademacher J. Bronchiectasis-associated hospitalizations in Germany, 2005-2011: a population-based study of disease burden and trends. PLoS One. 2013;8(8):e71109.
16. Monteagudo M, Rodríguez-Blanco T, Barrecheguren M, Simonet P, Miravitlles M. Prevalence and incidence of bronchiectasis in Catalonia, Spain: A population-based study. Respir Med. 2016 Dec;121:26-31.
17. Chalmers J, Polverino E, Aliberti S. Bronchiectasis: The EMBARC Manual2018.
18. Wilczynska MM, Condliffe AM, McKeon DJ. Coexistence of bronchiectasis and rheumatoid arthritis: revisited. Respir Care. 2013 Apr;58(4):694-701.
19. Matson SM, Demoruelle MK, Castro M. Airway Disease in Rheumatoid Arthritis. Ann Am Thorac Soc. 2022 Mar;19(3):343-52.
20. Bendstrup E, Møller J, Kronborg-White S, Prior TS, Hyldgaard C. Interstitial Lung Disease in Rheumatoid Arthritis Remains a Challenge for Clinicians. J Clin Med. 2019 Nov 21;8(12).
21. Fragoulis GE, Conway R, Nikiphorou E. Methotrexate and interstitial lung disease: controversies and questions. A narrative review of the literature. Rheumatology (Oxford). 2019 Nov 1;58(11):1900-6.
22. Wiater R, Håkansson KEJ, Ulrik CS. A causal relationship between rheumatoid arthritis and bronchiectasis? A systematic review and meta-analysis. Chron Respir Dis. 2021 Jan-Dec;18:1479973121994565.
23. Incidence of tuberculosis (per 100,000 people) - Romania. World Health Organization, Global Tuberculosis Report. World Bank Group.
24. Ji X, Hu L, Wang Y, Man S, Liu X, Song C, et al. Risk of tuberculosis in patients with rheumatoid arthritis treated with biological and targeted drugs: meta-analysis of randomized clinical trials. Chin Med J (Engl). 2022 Jan 12;135(4):409-15.
25. Carmona L, Hernández-García C, Vadillo C, Pato E, Balsa A, González-Alvaro I, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol. 2003

Jul;30(7):1436-9.
26. Yamada T, Nakajima A, Inoue E, Tanaka E, Hara M, Tomatsu T, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan. Ann Rheum Dis. 2006 Dec;65(12):1661-3.
27. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017 Sep;50(3). Marshall, M.R. Loebinger, *et al.* European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017; 50(3):1700629