TITLE PAGE

TITLE: BRONCHIECTASIS IN RHEUMATOID ARTHRITIS – WHAT CLINICIANS SHOULD KNOW

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ABSTRACT

Bronchiectasis is defined as irreversibly damaged and dilated bronchi and is one of the most common pulmonary manifestations in patients with rheumatoid arthritis (RA).

The model of RA-associated autoimmunity induced by chronic bacterial infection in bronchiectasis is becoming increasingly acceptable, although a genetic predisposition to RA-associated bronchiectasis has also been demonstrated.

Bronchiectasis should be suspected in RA patients with chronic cough and sputum production or frequent respiratory infections and the diagnosis must be confirmed by thoracic high-resolution computed tomography.

Management of patients with RA-associated bronchiectasis includes a multimodal treatment approach. Similar to all patients with non-cystic fibrosis bronchiectasis, patients with RA-associated bronchiectasis benefit from a pulmonary rehabilitation program, including an exercise/muscle strengthening program and an education program with a specific session on airway clearance techniques. Prophylactic antibiotics are recommended for patients with frequent (3 or more infective exacerbations per year) or severe infections requiring hospitalization/intravenous antibiotics and inhaled corticosteroids and long-acting β2-agonists should be used in patients with non-cystic fibrosis bronchiectasis and associated airway hyper-responsiveness. In patients with RA-associated bronchiectasis the use of immunomodulatory drugs has to be carefully considered, as they are essential to control disease activity and pulmonary manifestations, despite being associated with an increased infectious risk. Pneumococcal and influenza vaccines are advised to all patients with RA-associated bronchiectasis in order to reduce the risk of infection.

Patients with RA-associated bronchiectasis have a poorer prognosis when compared to those with RA or bronchiectasis alone and require regular follow-up, under the joint care of a rheumatologist and a pulmonologist.

KEYWORDS: rheumatoid arthritis; bronchiectasis; prophylactic antibiotics

HIGHLIGHTS

- The presence of bronchiectasis in patients with rheumatoid arthritis can be as high as 50%, when considering subclinical disease detected on high resolution computed tomography.
- Patients with rheumatoid associated-associated bronchiectasis have a poorer prognosis when compared to those with rheumatoid arthritis or bronchiectasis alone and require regular follow-up, usually by hospital multidisciplinary teams.
- Prophylactic antibiotics might be recommended in patients with recurrent respiratory infections, particularly when concomitantly receiving immunosuppressive drugs.

MANUSCRIPT

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune rheumatic disease associated with a wide range of extra-articular manifestations, including those involving the lung.
Bronchiectasis is defined as irreversibly damaged and dilated bronchi (1) and is considered one of the most common manifestations (2–5). It can occur either isolated or secondary to traction, as a result of concomitant interstitial lung disease (ILD) (2–5). The first description of the association between RA and bronchiectasis was made in 1955 (6), but despite this the number of papers that have covered this issue is limited. The aim of this article is to synthesize what has been published in the literature regarding RA-associated bronchiectasis in order to improve the care provided to these patients.

2. Methods

We searched Medline, Embase and Cochrane databases until July 2019 using the keywords rheumatoid arthritis, bronchiectasis, lung involvement and lung disease.

3. Results

3.1 Epidemiology

The presence of symptomatic bronchiectasis in RA patients has been estimated to be between 2 and 12% (7–9). However, reflecting the fact that most patients remain clinically silent for several years, the prevalence of subclinical disease detected by high resolution computed tomography (HRCT) is as high as 30-50% (9–14).
Regarding smoking, despite the lack of studies evaluating its association with RA-associated bronchiectasis, the published data suggest that there is no association between smoking and bronchiectasis (12,15,16).

3.2 Pathogenesis

Our understaiding regarding the pathogensis of RA-associated bronchiectasis remains unsatisfactory until nowadays. However, disease seems to result from integration of several factors, which include impaired mucociliary clearance, chronic infection, persistent inflammatory response and abnormal airways' remodelling (17). In 1986 Cote et al. (18) proposed a model in which predisposed individuals may develop an extensive inflammatory reaction after a pulmonary infection, which leads to respiratory epithelial damage with mucociliary dysfunction and subsequent mucus stasis and bacterial overgrowth. This favours recurrent infections and perpetuates the inflammatory process, with production of cytokines and proteinases that further damage the underlying epithelia, resulting in a vicious cycle of damage followed by further infection.
According to the literature, bronchiectasis can occur either after (RA-bronchiectasis) (19) or before (20–24) the articular manifestations of RA (bronchiectasis-RA). Shadick et al. (19) have reported in a retrospective study a mean interval of 24.7 years between RA and RA-associated bronchiectasis diagnosis, and have suggested that immunosuppressive therapy used to control articular disease, including corticosteroids, can predispose to infection (19), initiating the Cote's vicious cycle (18). On the other hand, bronchiectasis can precede RA and the mean interval time has been reported as 19 to 28.5 years (21,23,24). In these cases, lung infection has been described as a possible trigger to RA development by allowing exposure to a range of bacterial antigenic stimuli, some of which may lead to articular disease in a genetically susceptible subject (20). The possibility of chronic bacterial infection in patients with bronchiectasis inducing RA-related autoimmunity was also proposed by Quirke et al. (25). According to their study, citrulline specificity of anti-cyclic citrullinated peptide (anti-CCP) antibodies in RA-associated bronchiectasis was increased compared to bronchiectasis alone (88% vs 48%, $p<0.001$) and its magnitude was increased compared to RA without any lung disease (25). These results suggest that infections such as

bronchiectasis induce a low-titer, low-avidity, non–citrulline-specific anti-CCP antibodies' response in the early phases of tolerance breakdown, which subsequently evolves into the higher-avidity, higher-titer, and highly citrulline-specific responses that characterize RA (25).

RA-associated autoimmunity, characterised by the presence of rheumatoid factor (RF) and anti-CCP antibodies, may also play an important role in the inflammatory process associated with the development of bronchiectasis in patients with RA. In a prospective study (26), patients with positive anti-CCP antibodies and/or RF but without inflammatory arthritis had a higher frequency of airway abnormalities when compared to autoantibody-negative controls (76.2% vs 33.3%; p=0.005) (26), but similar to seropositive RA patients (76.2% vs 91.7%; p=0.42). In the antibody-positive group, 2 (4.8%) patients eventually developed RA, 13 months after the lung evaluation (26). Similar findings were reported in another prospective study (27), where RF (25.4% vs 10.3%; p=0.01) and anti-CCP antibodies (3.3% vs 0%; p=0.03) positivity were significantly more prevalent in non-RA patients with bronchiectasis when compared to healthy controls, and independent of smoking history. Half of the patients with positive RF and anti-CCP antibodies developed RA over 12 months (27). These findings add to the suggestion that the lung may be an early site of generation of RA-related autoimmunity (28).

Some researchers have also reported a genetic predisposition to RA-associated bronchiectasis. According to a family-based association study (29), the frequency of CFTR (cystic fibrosis transmembrane conductance regulator) mutation heterozygosity was higher in family members with RA-associated bronchiectasis than in unaffected relatives (60% vs 21.1%: p<0.005) and in unrelated healthy controls (60% vs 18.%; p<0.005) (29). CFTR mutations were also more frequent in family members with RA-associated bronchiectasis than in those with RA only (OR=5.3, 95%CI 2.48-11.33; p<0.005) (29) and were associated with poorer survival in patients with RA-associated bronchiectasis (HR=7.2, 95%CI 1.4-37.1; p=0.018) (30). Besides, CFTR mutations cosegregated with RA-associated bronchiectasis in the families (sib-TDT=10.82, p=0.005) (29), demonstrating an association and linkage between non-cystic fibrosis-related bronchiectasis and CFTR mutations.

Regarding HLA variants, a case control study (31) documented a higher frequency of DQB1*0601 (p<0.005), DQB1*0301 (p<0.005), DQB1*0201 (p=0.039) and DQA1*0501 (p=0.039) in patients with RA-associated bronchiectasis, when compared to those with RA only (31). Similar results were found with DRB1*0401, which was more frequent in patients with RA-associated bronchiectasis (39%), when compared to RA without bronchiectasis (17%) and controls (6%; p<0.0001) (32). Therefore, RA patients with these alleles seem to be at a higher risk of developing bronchiectasis, but the clinical significance of these findings is still not completely clear.

Table 1 summarises the known risk factors for RA-associated bronchiectasis.

Table 1 – Risk factors for rheumatoid arthritis-associated bronchiectasis

Risk factors for rheumatoid arthritis-associated bronchiectasis
Positive rheumatoid factor
Positive anti-cyclic citrullinated peptide antibodies
Cystic fibrosis transmembrane conductance regulator (CFTR) mutations
Presence of HLA - DQB1*0601, DQB1*0301, DQB1*0201, DQA1*0501 or DRB1*0401

3.3 Clinical features

Bronchiectasis should be suspected in any patient with chronic cough and sputum production or frequent respiratory infections (1,33). Additional factors suggesting the diagnosis include daily sputum production (frequently worse in the morning due to sputum accumulation during sleep), rhinosinusitis, fatigue and haemoptysis (33). Clinical examination may reveal coarse crepitations, which change with coughing, and rarely digital clubbing (1,23).

Some patients may also report dyspnoea, which according to a study by Wilsher et al. (10) was associated with the extent and severity of bronchiectasis on HRCT. The occurrence of bronchiectasis either before or after articular symptoms had no influence on the degree of dyspnoea (24), or other symptoms such as productive cough and haemoptysis (19).

As far as articular symptoms are concerned, Perry et al. (22) reported that patients with RA bronchiectasis had higher DAS28 scores (mean 3.51 vs. 2.59, p= 0.003), were more frequently positive for anti-CCP antibodies (89% vs. 46%, p<0.005) and RF (79% vs. 52%, p=0.003) and had higher prevalence of erosive disease (78% vs. 43%, p=0.003) when compared to patients with RA alone. Different results were described by McMahon et al. in a case-control study (20), where the presence of bronchiectasis was not associated with a more aggressive RA. In this study, patients with RA-associated bronchiectasis had a higher frequency of xerophtalmia when compared to those with RA alone (p=0.01) (20).
Different results had also been reported when comparing patients with RA-bronchiectasis vs. bronchiectasis-RA symptoms. In a small retrospective study including 5 patients with bronchiectasis-RA and 18 patients with RA-bronchiectasis (19), the former group had milder arthritis, based on the number of articulations involved and morning stiffness duration (80% vs. 100%, p<0.001), lower frequency of rheumatoid nodules (20% vs. 78%, p<0.05) and a lower frequency of comorbidities (0% vs. 22%, p<0.01) (19). Different results were published by Perry et al. (24), that reported no significant difference regarding disease activity and erosive disease prevalence, when comparing patients with prior articular vs. respiratory symptoms (24).

3.4 Pulmonary function tests

Patients with RA-associated bronchiectasis have the lowest forced vital capacity (FVC), forced expiratory volume in first second (FEV1) and diffusing capacity for carbon monoxide (DLCO) of any group with bronchiectasis, except patients with bronchiectasis as a sequelae of tuberculosis (34). In particular, patients with RA-associated bronchiectasis had more pronounced airways obstruction, with less reversibility after bronchodilators (20), when compared to bronchiectasis or RA alone (20).
According to a cross-sectional cohort study (10), a reduction in FVC is weakly correlated with the extent (r=-0.29, p=0.03) and severity (r=-028, p=0.04) of bronchiectasis in RA patients. Similarly, RA patients with bronchial wall thickening on HRCT had lower FEV1 (r=-0.43, p<0.01), FVC (r=-0.32, p=0.02) and DLCO (r=-0.29, p=0.03) than RA patients without bronchial wall thickening (10).
The time relationship between RA and bronchiectasis does not seem to influence spirometry results (19,24), although patients with RA-bronchiectasis tend to have more pronounced diffusion defects when compared to patients with bronchiectasis-RA (DLCO/VA = 56.4% vs. 83.3%, p=0.06) (19).

3.5 Imaging

In all RA patients with suspected bronchiectasis a baseline chest radiograph must be performed (1), ideally when the patient is clinically stable for serial comparision purposes (1). However, diagnosis must be confirmed by HRCT, which is nowadays the imaging exam of choice to establish the diagnosis of bronchiectasis (1), allowing the identification of bronchiectasis even in a subclinical stage (35). Bronchiectasis is defined by bronchial dilatation, which in HRCT is suggested by at least one of the following: bronchoarterial ratio >1 (internal airway lumen vs adjacent pulmonary artery), lack of tapering and airway visibility within 1cm of costal pleural surface or touching mediastinal pleura (Figure 1) (1). Some indirect signs are also commonly associated with bronchiectasis, such as bronchial wall thickening, mucus impaction and mosaic perfusion/air trapping (1).
HRCT results also provide helpful information to integrate in prognostic predictive tools, such as bronchiectasis severity index (BSI) (36) and FACED score (37).
According to some published data (12,13), bronchiectasis was the most common finding in HRCT from RA patients. However, bronchiectasis is commonly found in association with other abnormalities, including diffusely interstitial changes, focal infiltrates, bullae or cysts, thickened bronchial walls, nodules, emphysema and hyperinflation (12,19).

3.6 Management

The sputum of patients with bronchiectasis is frequently found to be colonized with potentially pathogenic microorganisms and the presence of airways colonization in patients with RA-associated bronchiectasis was reported to be associated with increased risk of infection (OR=7,4, 95%CI 2.0-26,8; p=0.002) (38).

The most common bacterium found in colonized sputum from patients with RA-associated bronchiectasis were *Pseudomonas aeruginosa* and *Haemophilus Influenzae* (38), similarly to patients with non-cystic fibrosis bronchiectasis due to other causes (33,39).

In RA patients, the use of immunosuppressive therapies, including synthetic and biological disease modifying antirheumatic drugs (DMARDs), was predictive of lower respiratory tract infection (OR= 8.7, 95%CI 1.7-43.4; p=0.008) (38). The risk was higher for biologics when compared to synthetic DMARDs (1.2 ± 1.6 vs. 0.2 ± 0.5 infections per patient-year; p=0.001) (38). Among these, etanercept and rituximab were associated with less frequent infections (0.8 ± 1.4 and 0.3 ± 0.7 infections per patient-year, respectively) (38), although patients treated with rituximab must have antibodies regularly checked (2-3 monthly), as hypogammaglobulinemia might lead to recurrent airway injury with bronchiectasis' exacerbation (40). Similar results were reported in a retrospective study including patients with various rheumatic diseases, including RA (39), in which pulmonary adverse events (most commonly respiratory infections) were higher in patients on immunosuppressive therapy, particularly methotrexate (39). Nine (19.6%) patients were started on azithromycin due to recurrent bronchial infections and pneumonia with no recurrence afterwards (39).

However, despite the infectious risk associated with immunosuppression, bronchiectasis' pathogenesis foresees a persistent inflammatory response (17) and immunomodulatory drugs might be part of a multimodal treatment approach (17). In fact, in patients with bronchiectasis associated with immune-mediated diseases, immunomodulatory drugs are essential to control disease activity and pulmonary manifestations (41), and their risk-benefit ratio should always be considered.

Due to this higher risk of infection, clinicians should be vigilant and advise patients with RA-associated bronchiectasis to get pneumococcal and influenza vaccines, particularly before immunosuppressive treatment (9). Influenza vaccination is recommended annually (9,42,43) and a single pneumococcal revaccination might be considered, 5 years after the first dose (42,43), since vaccination with pneumococcal polysaccharide antigens may induce hyporesponsiveness and a less robust antibody response on subsequent doses (44). However, clinicians must be aware that patients with RA (45,46), can have an impaired response to vaccination, particularly under specific immunosuppression like methotrexate and rituximab (47).

The use of prophylactic antibiotics should also be considered for all patients with non-cystic fibrosis bronchiectasis, including RA-associated, and frequent (3 or more infective exacerbations per year) or severe infections requiring hospitalization/intravenous antibiotics (1). Macrolides have been used in several chronic lung diseases, such as bronchiectasis, not only due to its immunomodulatory effects, but also because they can alter the lung microbiome and consequently modulate the intensity of lung inflammation(48).

In a randomized-control trial (RCT), including 68 patients with bronchiectasis (49), azithromycin (as a single 1000mg weekly dose) over 12 weeks was associated with a reduction in the 24-h sputum volume ($p<0.01$), which was maintained for the following 12 weeks without treatment, and with lung function stability during the 24-weeks period (49). In another RCT study (50), azithromycin (250mg daily) reduced the rate of infectious exacerbations in non-cystic fibrosis bronchiectasis after 12 weeks of treatment (HR 0.29, 95%CI 0.16-0.51) (50), and also led to an increase in FEV1 (1.3% over 3 months) (50).

The promising results of macrolides as prophylactic antibiotics was also highlighted in two meta-analyses (51,52) in which the use of these drugs was associated with a reduction in the number of acute exacerbations and in the 24-h sputum volume, as well as with an improvement in dyspnoea and in FEV1 and FVC in some of the studies included. There were no significant adverse reactions associated with the use of macrolides (51,52), despite the higher incidence of gastrointestinal events (51).

According to British Thoracic Guidelines (1), most commonly used regimens include azithromycin 250 mg 3 times a week, which can be increased to 500 mg 3 times a week according to clinical response and side effects (1), and erythromycin 250 mg twice daily. In patients colonised with microorganisms other than *Pseudomonas aeruginosa*, doxycycline 100mg twice daily can be an alternative in patients intolerant of macrolides or in whom they are ineffective (1). These patients should be reviewed biannually with assessment of efficacy, toxicity and continuing need (1).

Regarding inhaled therapy, one RCT including children and adults with non-cystic fibrosis bronchiectasis demonstrated that a 3-months association of inhaled corticosteroids and long-acting β2-agonists (LABA) significantly improved the dyspnoea index (mean difference 1.29, 95%CI 0.4-2.18), as well as the cough-

free days (mean difference 12.3, 95%CI 2.38-22.2), compared to those who received a 3-month course of ICS (53). Both groups were previously treated with inhaled corticosteroids for 3 months (53). These results suggest that a combination of inhaled corticosteroids and LABA should be considered in patients with non-cystic fibrosis bronchiectasis and associated airway hyper-responsiveness.

Patients with RA-associated bronchiectasis are also advised to undergo a pulmonary rehabilitation program, which should include an exercise/muscle strengthening program and an education program with a specific session on airway clearance techniques. After 6 to 8 weeks of pulmonary rehabilitation, patients with non-cystic fibrosis bronchiectasis developed significant improvement in a 6-minute walking test (6MWT; mean change 53.4 m, 95%CI 45.0-61.7) and dyspnoea index (54). After 12 months there was a non-significant decline in 6MWT distance compared to the immediate evaluation post intervention (p=0.104), but it remained significantly higher than baseline (p=0.036) (54). There were no significant differences between outcomes obtained by patients with non-cystic fibrosis bronchiectasis and those with chronic obstructive pulmonary disease (54). A RCT including patients with non-cystic fibrosis bronchiectasis (55) also reported an increase in 6MWT distance, dyspnoea and fatigue after exercise training, when compared to baseline. However, improvement in 6MWT distance was not maintained at 6 and 12 months (55). Exercise training was also associated with a reduction in the number of acute exacerbations median 1 [IQR 1–3]) compared to the control group (2[1–3]) over 12 months follow-up (p=0.012) (55), with a longer time to first exacerbation (8 months, 95%CI 7-9 months vs. 6 months, 95%CI 5-7 months; p=0.047) (55).

Despite the absence of clear association between smoking and RA-associated bronchiectasis, smoking cessation is recommended for these patients, as it not only may help to control the RA disease activity, but also prevents further damage in the lung (14).

Taking into consideration the previously reported association between CFTR mutations and outcomes in patients with RA and bronchiectasis, it has been suggested that drugs which modulate CFTR protein function might be a promising treatment for these patients (56). However, further studies are needed to support this hypothesis.

3.7 Prognosis

According to a 5-year follow-up international multicentre cohort analysis including outpatients with bronchiectasis (57), multimorbidity is frequent in this clinical condition and can negatively affect survival. Connective tissue diseases in general were associated with poorer outcomes (HR=1.78, 95%CI 1.19-2.68, p = 0.005), with higher prevalence of RA in non-survivors than in survivors (57).

In a 5-year prospective study involving 95 patients (32 with RA-associated bronchiectasis, 32 with RA alone and 31 with bronchiectasis alone), those with RA-associated bronchiectasis were 5 times more likely to die than the RA group alone and 2.4 times more than the bronchiectasis group alone (58). In all groups the cause of death was mainly pulmonary (58). An increased risk of death within the RA-associated bronchiectasis group was associated with a history of smoking, more severe RA and steroid use (58). In addition, when compared to the general population, patients with RA-associated bronchiectasis 7.3 times more likely to die, with an estimated mortality rate of 31.3% over 5 years (58).

Similar data was reported in a multicentre retrospective study (59), where RA was associated with an increased mortality in patients with bronchiectasis (OR=2.03, 95%CI 1.19-3.44; p=0.009) (59). This relationship was not associated with higher rates of bronchiectasis exacerbations or bronchiectasis-related hospitalizations (59).

A prospective family-based cohort study (30) also identified the presence of heterozygous CFTR mutation as a predictor of mortality in RA patients with bronchiectasis (HR=7.2, 95%CI 1.4-37.1; p=0.018), as well as the early development of bronchiectasis (HR=15.4, 95%CI 2.1-113.2, p=0.007) (30).

In view of the poorer prognosis of patients with RA-associated bronchiectasis, a close follow-up in secondary care units is recommended, under the joint care of a rheumatologist and a pulmonologist (1,9)

4. Conclusion

The presence of symptomatic bronchiectasis has been estimated at between 2 and 12% of RA patients. However, this number increases to as much as 50% when considering subclinical bronchiectasis detected on HRCT, which has become the imaging exam of choice to establish bronchiectasis diagnosis.
Bronchiectasis can precede or succeed the articular symptoms, although prospective studies with a larger number of patients will be important for a better understanding of the influence of bronchiectasis on RA disease activity and vice versa.
Patients with RA-associated bronchiectasis have a poorer prognosis when compared to those with RA or bronchiectasis alone and require regular follow-up, usually by hospital multidisciplinary teams. Apart from the general recommendations applied to non-cystic bronchiectasis, special attention must be given to the use of prophylactic antibiotics in these patients, as most of them are on immunosuppressive therapies and have, therefore, a higher risk of respiratory infections.

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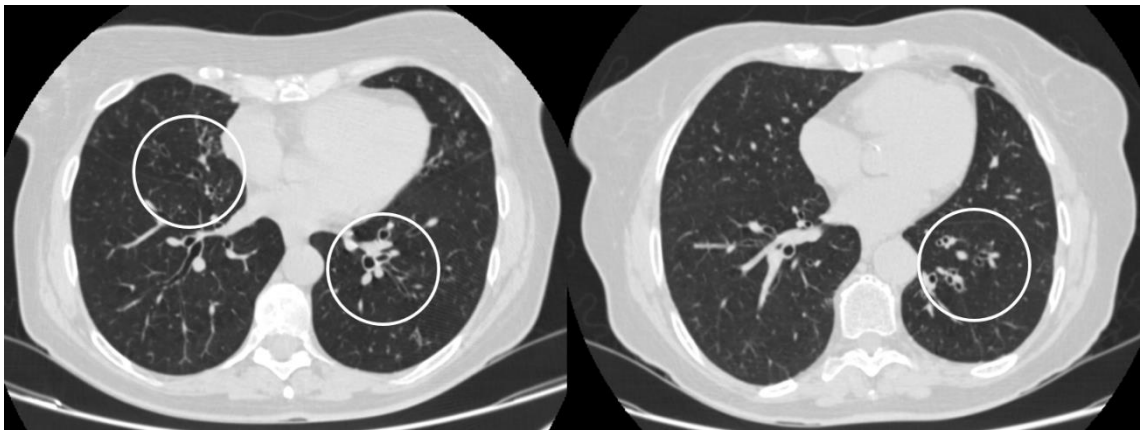

Figure 1 – Thorax high resolution computed tomography from patients with rheumatoid arthritis showing bronchoarterial ratio >1, in relation to bronchiectasis (circle)

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