Chapter 13

Bronchiectasis and autoimmune disease

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Summary

The association between bronchiectasis and autoimmune disease is well recognised, and best described with rheumatoid arthritis. The prevalence of bronchiectasis in rheumatoid arthritis varies considerably in studies, with obliterative bronchiolitis a common feature. The prognosis of rheumatoid arthritis with bronchiectasis seems to be worse than either condition alone. The advent of high-resolution computed tomography has increased the sensitivity of detecting bronchiectasis, but this should be assessed for clinical significance. Traction bronchiectasis results from interstitial fibrosis pulling the airway wider, rather than damage weakening the bronchial wall, and is less likely to lead to bronchial suppuration. Bronchial wall damage in bronchiectasis is caused by inflammation, but it is difficult to differentiate damage caused by severe or recurrent infections, predisposed to by immunosuppression related to the autoimmune disease itself or its treatment, from damage caused by the autoimmune process. Increased use of new immunomodulatory or immunosuppressive agents has proved successful in modifying autoimmune disease processes, but has also led to emergence of infective complications that can cause bronchiectasis or exacerbate pre-existing disease.

Keywords: Autoimmune, bronchiectasis, immunosuppression, rheumatoid arthritis, Sjögren’s syndrome, vasculitis

An association between bronchiectasis and autoimmune disease has long been recognised. The main autoimmune diseases in which bronchiectasis has been described are discussed in this chapter with emphasis on rheumatoid arthritis, for which there is best evidence of a true association. When information is available we discuss estimated prevalence, pathogenesis, clinical features and management where this differs from that in usual bronchiectasis and prognosis. In addition, we have discussed screening and risk stratification in the context of immunosuppression following the use of biological agents such as anti-tumour necrosis factor (TNF) in autoimmune disease.
There are several recurring themes that are worth noting: 1) high-resolution computed tomography (HRCT) scanning, which has increased the sensitivity of imaging bronchiectasis; 2) presence of radiological bronchiectasis versus symptomatic disease; and 3) the use of retrospective data in analyses of complex often heterogeneous populations. Another theme is traction bronchiectasis that may be present in patients with lung fibrosis due to involvement of the lung parenchyma by autoimmune disease-causing fibrosis. The scarring pulls the airways apart as it contracts. The airway mucosa is normal with intact mucociliary clearance and possibly for this reason patients are not usually prone to bacterial infections. However, in some cases with traction bronchiectasis there will be involvement of the bronchial wall due to disease-causing factors that may be present in patients with lung fibrosis due to autoimmune disease. The parenchyma by autoimmune disease. There are several recurring themes that are worth noting: 

Table 1. Summary of the features of bronchiectasis in different autoimmune diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Approximate prevalence in main studies</th>
<th>Patient selection and study type</th>
<th>Comments</th>
<th>[Ref.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>2–50%</td>
<td>Mixed selected and unselected</td>
<td>Largest body of data, variable conclusions but largest evidence base of autoimmune diseases</td>
<td>[1–12]</td>
</tr>
<tr>
<td>Sjögren's</td>
<td>&lt;10–46%</td>
<td>Mixed selected and unselected</td>
<td>Most data based on incidental findings on HRCT, patients often asymptomatic</td>
<td>[13–16]</td>
</tr>
<tr>
<td>SLE</td>
<td>&lt;2–21%</td>
<td>Various, including large prospective and cross-sectional</td>
<td>Frequent finding of bronchiectasis on HRCT but poor correlation with symptoms; complications of infection and thrombosis are significant and may dominate over clinically meaningful bronchiectasis</td>
<td>[17–19]</td>
</tr>
<tr>
<td>AS</td>
<td>7–23%</td>
<td>Mixed selected and unselected</td>
<td>Traction bronchiectasis common, but usually asymptomatic; morbidity usually through non-respiratory complications</td>
<td>[17, 20–24]</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>≤59%</td>
<td>Mixed selected and unselected</td>
<td>NSIP, pulmonary hypertension and traction bronchiectasis common; primary bronchiectasis less so and perhaps more in 'diffuse' disease</td>
<td>[25–29]</td>
</tr>
<tr>
<td>RP</td>
<td>≤50%</td>
<td>Mixed selected and unselected</td>
<td>Several old studies pre-1986 and pre-HRCT so likely gross overestimate</td>
<td>[30–34]</td>
</tr>
<tr>
<td>MCTD</td>
<td>12%</td>
<td>Various selected</td>
<td>Where present, traction bronchiectasis more likely than primary bronchiectasis, again usually asymptomatic</td>
<td>[35–37]</td>
</tr>
<tr>
<td>PM/DM</td>
<td>Rare</td>
<td>Primary bronchiectasis not described</td>
<td>NSIP and organising pneumonia common, traction bronchiectasis rarely reported and primary bronchiectasis rare</td>
<td>[38–40]</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Various according to type</td>
<td>Mixed selected and unselected</td>
<td>Granulomatosis with polyangiitis (Wegener's) and MPA most common of primary vasculitides; BPI-ANCA linked to Pseudomonas</td>
<td>[41–49]</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; AS: ankylosing spondylitis; RP: relapsing polychondritis; MCTD: mixed connective tissue disease; PM/DM: polymyositis/dermatomyositis; HRCT: high-resolution computed tomography; NSIP: nonspecific interstitial pneumonia; MPA: microscopic polyangiitis; BPI-ANCA: bactericidal/permeability-increasing protein-antineutrophil cytoplasmic antibodies.
nonspecific but high levels do characterise a group of patients with prominent small airways disease in whom immunosuppression should be considered. Anti-cyclic citrullinated peptide which is more specific for rheumatoid arthritis has not as yet been investigated in relation to bronchiectasis.

Rheumatoid arthritis

The association of rheumatoid arthritis and bronchiectasis is well described [1, 51] and it is the major autoimmune condition associated with bronchiectasis. One important question which remains unanswered is how the two conditions are related and how one develops in the context of the other. One hypothesis is that the initial event is recurrent antigen stimulation from recurrent lower respiratory tract infections, and the immunopathological sequence of events that follows leads to the development of a multi-system inflammatory disorder with a predilection for arthropathy. An alternative hypothesis is that bronchiectasis arises from the immunosuppression associated with rheumatoid arthritis itself and/or its treatments.

Prevalence

The reported prevalence of rheumatoid arthritis with bronchiectasis varies considerably largely due to patient selection and study type. Reports describe between approximately 2% and 50% prevalence of bronchiectasis in the largest studies of rheumatoid arthritis published between 1967 and 2006 [1–12]. A major issue is whether radiological evidence of bronchiectasis, either by chest radiography or by HRCT scanning, represents disease that is clinically significant. Studies that have tried to explore this demonstrate poor correlation with radiology [3, 8, 9, 52]. In most studies, the prevalence is calculated on the HRCT findings rather than on clinical evidence of bronchiectasis and patients may be entirely asymptomatic with incidental HRCT findings.

Most reports of prevalence have used heterogeneous populations and so carry several potential confounding characteristics including duration of illness, age (mean age of 45–64 yrs across studies), cigarette smoking history and drug-treatment schedules, which might include corticosteroids and immunosuppressants, such as methotrexate, which could influence susceptibility to infection. Moreover, the data is typically retrospective bringing with it recall and reporter bias. DESPAUX et al. [8] report prospective data on 46 unselected patients with rheumatoid arthritis (34 females, 12 males; mean age 60.1 yrs) collected over an 18-month period. In this study in which all patients had a HRCT, they found 23 (50%) patients with radiological evidence of bronchiectasis, 18 of whom were previously undiagnosed. 13 (57%) of these 18 patients were asymptomatic, thus giving a total of 22% (10 out of 46 patients) with clinically significant bronchiectasis. In two other prospective studies of 75 consecutive patients [10] and 63 consecutive patients [12] with rheumatoid arthritis, 19% and 29% of patients, respectively, were found to have bronchiectasis on HRCT, although it is not clear what proportion of these were symptomatic. A retrospective uncontrolled study of 20 life-long nonsmokers showed a high proportion of bronchiectasis with five (25%) out of 20 demonstrating basal bronchiectatic changes, but whilst three of these five gave a past history of pleurisy or pneumonia none had ongoing symptoms [3]. In other more heterogeneous studies, sub-group analysis has not been able to demonstrate a relationship between smoking and bronchiectasis in rheumatoid arthritis [8, 9, 52]. We are not aware of any study that has attempted to correlate the severity of bronchiectasis using one of the accepted scoring systems with severity of arthritis, either in terms of joint damage or immunological measures.

The immunological diagnosis of rheumatoid arthritis may also complicate prevalence data. In particular, there may be other autoimmune diseases present within the population studied, such as Sjögren’s syndrome [53, 54]. With modern day biochemical and immunological markers, there is a more robust system to better differentiate autoimmune diseases from one another, which will allow better definition of disease in the future.
Finally, the patient’s ethnic status may have an additional impact on the development of bronchiectasis with rheumatoid arthritis. This is rarely mentioned within studies. The largest cohorts are described in France close to the Alps [8] and close to the North Atlantic [4], North Africa [9], New England in the USA [2] and in central and northern England, UK [3]. The antigenic stimulation by community pathogens is likely to vary markedly in these different settings.

Pathogenesis

Whilst the association of bronchiectasis and rheumatoid arthritis has long been recognised [1, 8, 51], the mechanisms of how one condition develops in the context of the other remains unclear. While the co-existence of the two separate conditions is possible, the frequency of bronchiectasis in rheumatoid arthritis is well above that found in the non-rheumatoid arthritis population and suggests that these are not chance findings [4, 7, 8]. Three mechanisms have been considered: 1) bronchiectasis gives rise to the development of rheumatoid arthritis; 2) bronchiectasis and rheumatoid arthritis are caused by similar immunological processes, or because of immunosuppression due to rheumatoid arthritis or its treatments; and 3) other diagnoses and/or comorbid conditions drive the development of rheumatoid arthritis or bronchiectasis. These will be discussed in turn, although in reality there may well be several mechanisms interacting in a particular case.

 Bronchiectasis gives rise to the development of rheumatoid arthritis

The nature of the complex immunological mechanisms present in the bronchiectatic airways has been studied. The neutrophil plays a central role in what has been called “the vicious circle hypothesis”, but in addition abnormal mucus clearance and cellular immune responses are important [55–58]. In this context, one proposed mechanism is that persistent immunological pressure stimulated by chronic bacterial infection drives a sequence of events that leads to the formation of autoantibodies to “self” components and ultimately the development of a systemic inflammatory disorder. For this mechanism to operate lung disease would need to precede rheumatoid arthritis. Most reports suggest that this is the case. DESPAUX et al. [7] described from an extensive literature review that 90% of 289 reports published since 1928 document respiratory symptoms prior to articular symptoms. While this study combines old reports with variable diagnostic criteria for both rheumatoid arthritis as well as bronchiectasis, in an era before computed tomography (CT) imaging, the temporal sequence is in fact corroborated in several individual and more recent studies [4, 5, 54]. Even in newly diagnosed rheumatoid arthritis present for <1 year, with normal chest radiographs and normal respiratory function tests, 58% of patients were found to have HRCT evidence of bronchiectasis. This study demonstrates established bronchiectasis, albeit subclinical, by the time of a formal diagnosis of rheumatoid arthritis [59]. However, since the bronchiectasis was subclinical, sufficient antigenic stimulation by bacterial infection seems unlikely.

 Bronchiectasis is caused by similar immunological processes or by immunosuppression due to rheumatoid arthritis or its treatments

HRCT has made it clear that airway disease is common in rheumatoid arthritis (fig. 1). Follicular bronchiolitis is due to lymphoid aggregates, with or without germinal centres, which lie in the wall of bronchioles and sometimes compress their lumens. This appears as centrilobular nodules, peribronchial nodules and patches of ground-glass shadowing [60]. Airway wall thickening (indicating bronchitis without dilatation) and bronchiectasis (fig. 1a and b) are both more common in patients than matched controls [61].

There is a recognised association of rheumatoid arthritis and obliterative bronchiolitis, also known as “constrictive bronchiolitis”, in which bronchioles are destroyed and replaced by scar tissue (fig. 1c).
Several associations have been observed with obliterative bronchiolitis outside of the well-known association with tissue rejection in heart and lung transplantation. Drug treatment, especially with gold and penicillamine, has been implicated in the development of obliterative bronchiolitis [62, 63] but it also occurs in patients who have had neither drug. Obliterative bronchiolitis is well-documented post-infection and although more recognised in children, has been documented with adenovirus, measles, influenza and Mycoplasma [64–69]. Not only could such an outcome easily go unnoticed until later in life, but this could represent a plausible mechanism for the later development of formal bronchiectasis or rheumatoid arthritis. Early toxin exposure might also account for obliterative bronchiolitis and later bronchiectasis or rheumatoid arthritis in a similar step-wise mechanism [70]. Certain human leukocyte antigens (HLA) have been associated with obliterative bronchiolitis, including the presence of HLA-DR1 in obliterative bronchiolitis with rheumatoid arthritis, while a large population fail to have an identifiable cause [71–73]. Bacterial infection may complicate the picture by itself provoking inflammation in the lung and causing damage to the airway wall, as well as exciting rheumatoid arthritis-driven inflammatory processes. Mosaic perfusion and gas trapping are present on HRCT. In the context of the above, patients complain of progressive breathlessness, develop irreversible airflow obstruction and subsequently carry a poor prognosis with death due to respiratory failure [74, 75].

It is interesting to speculate whether these different manifestations of airway disease in rheumatoid arthritis are a single inflammatory process affecting different parts of the bronchial tree, or whether they are discrete inflammatory conditions. In favour of the former suggestion, all manifestations described previously can be seen in the HRCT scan of some patients. However, it is usually necessary to postulate that constrictive obliterative bronchiolitis has been preceded by exudative bronchiolitis, rather than being able to demonstrate this by sequential radiology. However, bronchiectasis could develop in the context of additional local structural damage caused by bacterial infection as a consequence of functional immunosuppression. Devouassoux et al. [75] report a study of 25
patients with rheumatoid arthritis and obliterative bronchiolitis and demonstrate HRCT evidence of bronchiectasis in 44% of the cohort. All patients were breathless and bronchorrhoea was present in 44%. They go on to report that in a follow-up of approximately 4 years, treatment was poorly effective, chronic respiratory failure occurred in 40% and death in four patients.

Rheumatoid arthritis itself is associated with increased morbidity and specifically an increased risk of infection when compared with the general population [76–78]. In a predisposed individual, regular infection with poor immunological clearance of microbes could subsequently lead to formation of bronchiectasis. In contrast to the reports described previously, Shadick et al. [2] describes 23 patients with rheumatoid arthritis and bronchiectasis, in whom 18 (78%) patients had rheumatoid arthritis symptoms prior to the diagnosis of bronchiectasis. These patients had a mean duration of arthritic symptoms of 25 years prior to bronchiectasis, 17 out of 18 patients had used corticosteroids and respiratory symptoms were present for an average of 4.3 years prior to the formal diagnosis of bronchiectasis. When compared with the five patients who described bronchiectasis before rheumatoid arthritis, those with late bronchiectasis used more disease-modifying agents, had more severe joint disease, were more likely to have rheumatoid nodules and carried a greater morbidity. This would support the idea that advanced rheumatoid arthritis disease and increasingly immunosuppressive medications might contribute to the development of “secondary” bronchiectasis as a late complication of rheumatoid arthritis.

Methotrexate forms part of many rheumatoid arthritis treatment regimens and despite early clinical impressions, probably does not significantly increase the infection risk in patients with poorly controlled rheumatoid arthritis [79–81]. This may be because the immunosuppressive nature of unchecked inflammation in rheumatoid arthritis in the absence of methotrexate is greater than that conferred by methotrexate itself. However, long-term corticosteroids, cyclophosphamide and azathioprine certainly do lower the threshold for opportunistic infection and with the emergence of biological agents such as anti-TNF, the complication of serious infection and ensuing bronchiectasis becomes more likely [82]. In patients with recurrent infections on rheumatoid arthritis-treatments it is difficult to define the nature of any immune paresis, and where specific functional defects are demonstrated it is difficult to ascribe them to the disease or the therapy that has been prescribed. Gold has been associated with functional antibody defects, but in a study of rheumatoid arthritis patients with and without bronchiectasis, evidence of antibody deficiency was apparent in those with bronchiectasis as well as those without, and independent of any co-incident gold therapy [83]. Other reports of late bronchiectasis may have case-specific explanations, where resistant pathogens, abnormal airways and/or impaired clearance lead to unchecked infection and inflammation and usually localised bronchiectasis [84].

Other diagnoses or comorbid conditions that drive the development of rheumatoid arthritis and bronchiectasis

In most cases today, a clear diagnosis of rheumatoid arthritis and bronchiectasis can be made that is based upon the history, clinical features and immunology profile. However, in older studies it is worth noting that either the diagnosis of rheumatoid arthritis may be incorrect, or there may be significant comorbid conditions that drive the disease phenotype. For example, the finding of greater numbers of abnormal Schirmer’s tests (test of tear production) by McMahon et al. [54] in a case-controlled study of 32 patients with rheumatoid arthritis and bronchiectasis when compared with rheumatoid arthritis without bronchiectasis did increase the possibility that Sjögren’s syndrome was involved in the pathogenesis of one or both conditions, possibly by affecting mucociliary clearance in the lung. However, this finding was not reproduced by McDonagh et al. [52], and Kelly and Gardiner et al. [53] who found no significant difference in abnormal tear production in their rheumatoid arthritis patients with bronchiectasis (six out of 10 patients) compared with those without bronchiectasis (18 out of 30 patients).

The cystic fibrosis transmembrane conductance regulator (CFTR) mutation ΔF508 present in cystic fibrosis (CF) has been implicated through a study of a French cohort that has demonstrated
its increased presence in rheumatoid arthritis with bronchiectasis [85]. In this study, four (15.4%) out of 26 Caucasians with a median age of 59 years with rheumatoid arthritis and bronchiectasis carried the heterozygote genotype compared with none from 29 consecutive rheumatoid arthritis patients without bronchiectasis, and none from 29 patients with diffuse bronchiectasis. This is a striking difference when noted in the context of a 2.8% allelic frequency in the general Caucasian European population. In addition, those with the mutation demonstrated more frequent sinusitis, lower nasal potential differences and a trend towards more severe lower respiratory tract disease, while there was no relationship to the severity of articular features.

HLA associations are well characterised for rheumatoid arthritis and the HLA-DRB1 gene locus from the DR4 “family” is perhaps the most closely associated susceptibility locus implicated in rheumatoid arthritis [86]. In a large case-controlled study of patients’ HLA associations in a UK cohort, HILLARBY et al. [87] demonstrated the predicted DR4 association in 79% of rheumatoid arthritis alone patients but no pattern of DR4 subtypes in those with rheumatoid arthritis and additional respiratory features, including pulmonary fibrosis and bronchiectasis. However, there was a significant association of rheumatoid arthritis and bronchiectasis with DQB1*0601, DQB1*0301, DQB1*0201 and DQA1*0501 when compared with rheumatoid arthritis alone. The group of patients with bronchiectasis in a separate prospective HRCT study of 68 consecutive rheumatoid arthritis patients showed a low prevalence of DQA1*0501 when compared with the rheumatoid arthritis group without bronchiectasis [6].

Immune dysregulation is seen in both bronchiectasis and rheumatoid arthritis, and a shared defect in both rheumatoid arthritis and bronchiectasis may impact upon the shape of the final disease phenotype. Common variable immunodeficiency (CVID) is the most common primary immunodeficiency and is frequently associated with both respiratory tract infections and autoimmune conditions including rheumatoid arthritis [88]. Defective antibody production has been recognised in rheumatoid arthritis and with rheumatoid arthritis treatments. A UK study of 80 patients was carried out and comprised of 20 patients with rheumatoid arthritis and bronchiectasis, 20 patients with each disease separately and 20 healthy matched controls. Three out of 20 from the rheumatoid arthritis-bronchiectasis group demonstrated an impaired antibody response post-immunisation, two out of 20 rheumatoid arthritis alone patients showed a poor response (both groups of patients contained individuals on gold therapy) and the control group demonstrated neither. Immunological defects, when investigated, are likely to be more common than is currently believed and may play important roles as co-factors in the developing bronchiectasis [89].

Yellow nail syndrome (YNS) is a heterogeneous disorder that includes bronchiectasis and has been associated with rheumatoid arthritis-drug therapy, particularly penicillamine. YNS does occur in rheumatoid arthritis and other autoimmune diseases independent of drug therapy and its aetiology remains unclear [90, 91]. Abnormal T-cell responses that are thought to drive disease in YNS may similarly drive a specific phenotype in the presence of rheumatoid arthritis and act as a co-factor in development of bronchiectasis.

**Management of bronchiectasis in the presence of rheumatoid arthritis**

There are no specific features in the management of bronchiectasis associated with rheumatoid arthritis. We have not identified any patients requiring antibody replacement in our own group of rheumatoid arthritis-bronchiectasis patients, but it would be reasonable to measure total antibody levels and specific antibody responses to polysaccharide (pneumococcal and *Haemophilus influenzae* type b and protein (tetanus)). Some patients have progressive obliterative small airways disease. Our own experience is that there is a poor response in these patients to increasing immunosuppression, and this approach to treatment creates more problems by making infections worse. Once the patient is established by the rheumatologist on a regimen that may include methotrexate, we have adopted the strategy of trying to reduce the level of bronchial infection by using antibiotic prophylaxis, including the ketolide antibiotic azithromycin as a putative
immunomodulator [92], and treating exacerbations aggressively. We hypothesise that avoiding the antigenic stimulation of bacterial infections may reduce the inflammatory processes causing obliterative bronchiolitis.

**Prognosis**

The presence of bronchiectasis with rheumatoid arthritis appears to carry a significantly worse prognosis, although only one report examines mortality and morbidity in this specific context. Swinson et al. [93] studied a UK cohort of 32 rheumatoid arthritis patients with bronchiectasis alongside matched controls with either rheumatoid arthritis alone or bronchiectasis alone. They found the mortality in the group with both diseases to be considerably higher, with a standardised mortality ratio five times and 2.4 times greater than that of the rheumatoid arthritis alone and bronchiectasis alone groups, respectively. The groups shared similar scores of physical activity and of radiological destruction (Larsen score). While several parameters carried high relative risks of mortality including grip strength and presence of rheumatoid nodules, the finding of a raised white cell count and the presence of circulating immune complexes carried the highest relative risks, the latter being the only one which demonstrated confidence intervals outside parity (relative risk 4.5, 95% CI 1.4–13.9). The 5-year survival rate in the combined rheumatoid arthritis-bronchiectasis group can be calculated at 69%. Finally, it is interesting to note that those in the combined disease group did have a lower baseline forced expiratory volume in 1 s (FEV1), as well as lower forced vital capacity (FVC) and fewer patients with signs of reversibility. Airflow obstruction in the presence of lung restriction has been identified in one large bronchiectasis study as a risk factor for mortality. In this study, carried out over 13 years, 29.7% of patients with bronchiectasis of many different aetiologies died [94]. In contrast, McMahon et al. [54] reported no significant effect of bronchiectasis on the activity and outcome measures of arthritis when compared with those with rheumatoid arthritis alone.

**Sjögren’s syndrome**

The study of the association of Sjögren’s syndrome and bronchiectasis has been made more difficult by: the presence of primary, secondary and mixed syndromes; serological overlap with systemic lupus erythematosus (SLE; in particular, Sjögren syndrome-related antigen A) and also systemic sclerosis; and the inconsistencies in the literature about how the diagnosis of bronchiectasis was made. The diagnosis of Sjögren’s syndrome includes the presence of dry eyes and dry mouth for 3 months, a positive Schirmer’s test, anti-Ro and anti-La autoantibodies and a minor salivary gland biopsy demonstrating a focus score >1. While the use of this definition was not clear across all studies, an international consensus was obtained to rectify the differences [95]. Clinically significant bronchiectasis is uncommon and so most information on the prevalence of bronchiectasis in Sjögren’s syndrome necessarily comes from imaging studies of patients with respiratory symptoms or from studies in those who are asymptomatic. Bronchiectasis is variably reported in such studies ranging from <10% to 46% [13–16]. In a study of 24 German patients with primary Sjögren’s syndrome (excluding smokers and those with other autoimmune disease or other unrelated bronchopulmonary disorders), 19 were found to have HRCT abnormalities and 11 of these bronchiectatic changes (46% of all patients) [14]. These changes were more central, predominantly lower lobe, bilateral in eight cases and unilateral in three cases. The precise symptoms of these patients are not given but the cohort comprised of patients referred for investigation over a 10-year period to a tertiary referral centre.

The aetiology of Sjögren’s syndrome is unknown but viral infection is implicated, including Epstein–Barr virus (EBV), cytomegalovirus and retroviruses such as HIV and human T-lymphocyte virus, with good evidence from animal studies [96]. Both B- and T-cells are recognised to infiltrate exocrine glands but the pathogenesis is likely to involve a complex interplay of glandular epithelial and endothelial cells, dendritic cells and B- and T-cells in the context of an environmental insult in a predisposed individual [97]. Hydration of the airways may be impaired
together with inspissations of secretions as a result of atrophied respiratory tract mucus glands. Bronchiectasis is proposed to develop subsequently due to recurrent bacterial infections which are predisposed to by impaired mucociliary clearance. Neutrophilic inflammation provoked by infection leads to thickened dilated lower airways and eventually bronchial wall destruction. Amyloid has been recognised in Sjögren’s syndrome and may be implicated in the development of bronchiectasis with its presence confirmed in peribronchial walls, as well as the interstitium [98].

**Management of bronchiectasis associated with Sjögren’s syndrome**

There are no clinical studies reported in the literature. In our own practice we have attempted to improve mucus clearance by nebulising normal saline regularly several times per day and emphasising to patients the importance of physiotherapy. Recently we have begun to nebulise 7% hypertonic saline which has an osmotic effect, with success in individual cases. Optimal antibiotic management of lower respiratory tract infections may shorten the length of infective exacerbations and so reduce airway wall damage.

**Systemic lupus erythematosus**

The first reports of bronchiectasis in SLE emerged in the early 1960s with the use of bronchograms and pulmonary function tests [99–101]. With the advent of CT imaging, there has been a greater understanding of the radiological abnormalities in SLE. However, there remains some uncertainty about the significance of the reported abnormalities and the prevalence of clinically significant bronchiectasis. Fenlon et al. [17] prospectively studied 34 patients with SLE with HRCT data alongside various clinical and lung function data. Of note, they found seven (21%) patients with bronchiectasis on HRCT, second only to interstitial lung disease (ILD) (11 patients), mediastinal or axillary lymphadenopathy (six patients) and pleuroperticardial abnormalities (five patients). However, while the presence of HRCT abnormalities was high they found no correlation with symptoms or disease activity, and none of the patients had recurrent respiratory infections. In a separate cross-sectional study of 60 Norwegian adults of childhood-onset SLE, any HRCT abnormality was found in only five patients and in just one (<2%) was there radiological evidence of bronchiectasis; none had clinical evidence of bronchiectasis [18]. These patients had a median duration of 11 years of disease by the time of cross-sectional imaging. In contrast, Bankier et al. [19] reported a much higher frequency of CT abnormalities with 17 out of 48 patients with SLE showing abnormalities (45 of whom had normal chest radiographs). They went on to show correlation of extent of disease radiologically with duration of clinical history (r=0.93), gas transfer (r=0.8) and ratio of FEV1/FVC (r=0.77). However, once again there was poor correlation of bronchiectasis on CT scans and clinical symptoms of the disease. Lung fibrosis may cause traction bronchiectasis and it is not clear in reports whether bronchiectasis is present in parts of the lung not affected by fibrosis.

As with other systemic diseases, it has been suggested that confounding factors might explain the association of bronchiectasis with SLE, including the increased risk of infection associated with a multi-system disease and use of immunosuppressive treatments to control the disease. Mannose-binding lectins (MBL) have been suggested to play a role in SLE in a report of two patients with SLE who went on to develop CVID [102]. The infrequent MBL haplotype 4Q-57Glu was present in both, while the haplotype 4P-57Glu in the second case was associated with recurrent respiratory infections, bronchiectasis and low circulating levels of MBL. This report raises the possibility of MBL polymorphisms in the development of autoimmune disease and significant infections which cause bronchiectasis.

The clinical features of bronchiectasis in SLE are not described in the literature. However, it is apparent that the most common pulmonary complications are infection and vascular events [103]. While the reported frequency of clinical bronchiectasis is low, as described previously, there may be under-diagnosis of post-infective bronchiectasis in patients who have not had HRCT examination.
Respiratory function tests frequently demonstrate reduced spirometry (typically subclinical), reduced gas diffusion and, depending on severity of disease, decreased lung capacity. These changes appear to be independent of cigarette smoking [103–105].

HRCT features reported in SLE include pleuritis with or without pleural effusion, acute interstitial pneumonia and acute pulmonary haemorrhage and thrombosis [17, 106]. Morbidity and mortality in SLE are associated with infection and vascular complications [107, 108]. There is greater mortality in the first 5 years, partly linked to the use of immunosuppressive therapy in aggressive SLE disease and the subsequent complications of infection surrounding this.

### Ankylosing spondylitis

There are several pulmonary manifestations of ankylosing spondylitis which include apical fibrobulbous disease, secondary infection, chest wall restriction, obstructive sleep apnoea, spontaneous pneumothorax and bronchiectasis [109]. A typical course is the development of chronic bi-apical fibrobulbous areas with nodules that eventually coalesce to form cysts, cavities and bronchiectasis, and later superadded infection with *Aspergillus* and environmental *Mycobacteria* species may occur. Abnormalities evident on HRCT in those either asymptomatic or with early disease are well documented with frequencies of all abnormalities in the region of 40% to 80% [20–22, 110]. However, little is published regarding bronchiectasis specifically. HRCT evidence of bronchiectasis has been found in 7–23% of ankylosing spondylitis patients in the largest cohort studies performed to date [17, 20, 21–24]; in most studies, patients do not report symptoms of bronchiectasis. Traction bronchiectasis is the most likely explanation in this context caused by pleuropulmonary fibrosis. Fenlon et al. [111] reported a total of six (23%) cases of bronchiectasis from their prospective cohort study of 26 patients with ankylosing spondylitis from an out-patient setting in Ireland, of which four were primary bronchiectasis and two had traction bronchiectasis. The four with primary bronchiectasis consisted of three patients with significant smoking histories, two each with disease in the upper and lower lobes and only one with symptoms of cough and breathlessness. The latter patient with bronchiectasis had ankylosing spondylitis for significantly longer duration of 28 years, and had an abnormal plain chest radiograph (demonstrating upper lobe bronchiectasis) with restrictive respiratory function tests. Three out of four patients with bronchiectasis in a separate study from Brazil were also current smokers, although this population with several radiological abnormalities may have had other infective causes [23].

Tracheobronchomegaly or Mounier–Kuhn syndrome, which is due to a congenital cartilage abnormality, has also been reported with ankylosing spondylitis and this mechanism may influence the development of bronchiectasis in some cases [112]. HLA-B27 does not appear to correlate with general HRCT abnormalities where this has been assessed, and while it is possible that ankylosing spondylitis disease severity correlates indirectly with respiratory abnormalities in general, there are too few cases with bronchiectasis to assess any relationship with this specifically [23, 113, 114]. There is insufficient data to comment on the timing of bronchiectasis compared with the development of ankylosing spondylitis, although it appears that the majority of those found to have bronchiectasis are asymptomatic with incidental findings on imaging only [20–24, 110, 115]. Ankylosing spondylitis mortality is usually caused by non-respiratory illnesses such as cardiovascular disease, renal failure and amyloid and through complications of treatment, and only occasionally through respiratory disease [116–118].

### Scleroderma/systemic sclerosis

Lung involvement in scleroderma or systemic sclerosis is very common. HRCT has played an important role in better characterising and following up abnormalities, and disease has also been well documented by post mortem examination with the identification of pulmonary disease in systemic sclerosis in 80% of one cohort [25–27]. The findings of an ILD, typically a nonspecific
interstitial pneumonia (NSIP) pattern and pulmonary hypertension, are quite common on HRCT. Any honeycombing is usually mild and localised and the more typical pattern is the near-confluent ground-glass opacification, fine reticular markings and associated traction bronchiectasis. Primary bronchiectasis is uncommon [28, 29], as are reports of clinically significant disease.

In one of the larger studies of systemic sclerosis patients alone, ANDONOPoulos et al. [29] investigated 22 patients with a full history, respiratory function tests, blood tests and HRCT imaging. Cylindrical bronchiectasis was evident in 13 (59%) out of 22 patients and was more common in diffuse rather than limited systemic sclerosis disease, although this finding fell short of statistical significance and did not correlate with gas transfer, ground-glass opacification or with the patient’s duration of illness. In another single case report of clinically significant bronchiectasis, there were other potential causes including Sicca syndrome and immunosuppressant treatment [119].

**Relapsing polychondritis**

The tracheobronchial tree is affected and typically leads to thickened and sometimes narrowed airways, impaired clearance and the development of airway infection and inflammation. Lower respiratory tract symptoms and significant disease developed after the initial diagnosis of relapsing polychondritis in an early and one of the largest prospective studies of 23 patients with relapsing polychondritis [30]. However, this was not the case in the only other smaller prospective series 20 years later where in six out of nine patients the respiratory symptoms were the presenting symptoms of relapsing polychondritis [31]. Cohort studies since 1966 report a prevalence of respiratory symptoms in up to 50% of those with relapsing polychondritis, although given the nature and time of these studies, accurate prevalence of bronchiectasis is not possible to estimate. A small number of cohort studies have analysed the natural history, morbidity and mortality of patients with relapsing polychondritis. Respiratory infection appears to play a significant part. Bronchiectasis is not defined by today’s standards of HRCT imaging given that these studies were carried out between 1966 and 1986. However, it can be implied that together with vasculitis and valvular heart disease, respiratory infection carries a worse prognosis [30, 32, 33]. Michet et al. [32] describe their single-centre experience of 112 patients in the US in which they identified respiratory infection as one of the leading causes of death alongside vasculitis and cancer. Of further interest is that only 10% of deaths were directly attributed to airway involvement of the disease, that anaemia was a significant poor prognostic marker and that the use of corticosteroids did not impact on survival.

Behar et al. [34] analysed past records of a cohort of 160 patients collected over 10 years from two referral centres and scrutinised records from 15 patients who had undergone any thoracic CT imaging. They identified increased attenuation in the tracheal walls of all 15 patients (with narrowing in one third of these patients), and also in the bronchial walls of 11 patients (73% of those scanned). Of the 11 patients who had complete lung view imaging, three were found to have bronchiectasis (two upper lobe, one diffuse), two demonstrated no significant airway stenoses and one showed widespread tracheal and bronchial stenoses. 12 (83%) out of 15 patients demonstrated thickened airway walls.

**Mixed connective tissue disease**

Mixed connective tissue disease (MCTD) is a distinct clinicopathological entity with unique positive antibodies against ribonucleoprotein that shares several clinical and radiological features with SLE, systemic sclerosis and polymyositis/dermatomyositis (PM/DM). The frequency of respiratory manifestations in MCTD is reported to be between 20% and 80%, more commonly the higher end of this range, although the reports are typically based upon radiological findings rather than clinical significance [35, 120, 121]. The prevalence of bronchiectasis is not available in these older studies, once again because of the absence of HRCT. MCTD is not usually associated with
primary bronchiectasis, rather with traction bronchiectasis associated with architectural distortions and the interstitial pneumonia patterns more commonly seen in this disorder [36, 37]. KOZUKA et al. [37] analysed the abnormal HRCT imaging of 41 patients with confirmed MCTD and characterised the radiological abnormalities that were observed. They identified 18 patients with traction bronchiectasis. Primary bronchiectasis was observed in five (12%) out of 41 patients, although no clinical features were reported in this study to assess the significance of this.

Polymyositis/dermatomyositis

PM/DM is typically associated with ILD with a strong correlation with anti-Jo1 antibodies, most commonly an NSIP pattern and also an organising pneumonia [38, 39]. Primary bronchiectasis is not reported and traction bronchiectasis is rarely reported, especially given that honeycombing is an infrequent finding in contrast to ground-glass opacification and patchy consolidation [38–40].

Bronchiectasis and vasculitis

It has long been recognised that immune complexes and autoantibodies can accompany bronchial infection [41, 122–125]. ABRAMOWSKY and SWINEHART [123] demonstrated renal failure associated with immune complexes in patients with CF and immune complex-mediated injury was proposed in CF patients who presented with purpuric lesions late in their disease course [124]. Immune complexes adhere to the endothelium through binding with the C1q component of complement causing vasculitis and/or the complexes interfere with the intended complement-mediated clearance of pathogens.

The vasculitic process may be localised or involve many systems with increasing severity. The extent of disease may be such as to require aggressive immunosuppressive therapy with corticosteroids and cyclophosphamide to control the vasculitis, alongside continued antimicrobial treatment for concomitant bacterial infection [126]. Evidence of immune-mediated injury and vasculitis has been demonstrated in the context of H. influenzae and Staphylococcus aureus, as well as Pseudomonas aeruginosa [2, 42, 125].

Antineutrophil cytoplasmic antibodies (ANCA) form an important component of vasculitides of which classical ANCA (c-ANCA) against the antigen proteinase-3 and perinuclear ANCA (p-ANCA) against myeloperoxidase make up the major pathogenic types [43]. Of the primary vaculitides, granulomatosis with polyangiitis (Wegener’s) with associated c-ANCA antibodies and microscopic polyangiitis (MPA) with myeloperoxidase antibodies have been most linked with bronchiectasis. A chronic pulmonary illness typically predates the development of ANCA-associated disease in various reports and although other ANCA may exist their roles may be more specific [41, 44–46]. In a retrospective cohort study of 26 patients with MPA in Japan, nine (35%) were diagnosed with bronchiectasis, four of whom had bronchiectatic symptoms prior to the diagnosis of MPA [45]. The precise role and timing of the development of autoantibodies to self-components remains unclear. FORDE et al. [47] analysed sera from a large number of patients with a wide variety of inflammatory and infective disorders in order to investigate any association of autoantibodies with acute and chronic infection. They concluded that antibodies to neutrophilic cytoplasmic components were predominantly associated with chronic bacterial infection, while antibodies to monocyte cytoplasmic components were predominantly associated with chronic granulomatous disorders such as sarcoidosis. The implication was that persistent stimulation of phagocytic cell components by bacterial infection drives the formation of autoantibodies to those components and a pathological humoral response.

More recently, studies have begun to confirm the temporal relationship of immune-complex activity with infection. MAHADEV A et al. [48] identified and characterised a new antigen bactericidal/permeability-increasing protein (BPI)-ANCA in the context of Pseudomonas infection. They went on to identify this in several patient groups including those with CF and non-CF
bronchiectasis, inflammatory bowel disease and renal failure [49]. Other groups explored its behaviour in the context of *Pseudomonas* and proposed that high levels of BPI-ANCA correlated with chronic *Pseudomonas* infection and poorer prognosis [46, 127, 128]. Of note, BPI binds with high affinity to lipopolysaccharide (LPS) on Gram-negative bacteria, and the presence of high levels of circulating antibodies to BPI may interfere with clearance of LPS bacteria giving rise to concomitant severe infection.

There are several other rare primary immunodeficiencies that are associated with bronchiectasis and vasculitis about which little is known. For example, an X-linked lymphoproliferative disorder linked to a specific T-cell defect in EBV immunity that is associated with multi-system vasculitis, bronchiectasis, respiratory failure and death [129] and an, as yet, poorly defined syndrome consisting of childhood dermatitis, profoundly elevated immunoglobulin E, severe pneumonia (and subsequent bronchiectasis) and multiple central neurological abnormalities [130].

The use of immunosuppressive agents and bronchiectasis

There is an increasing use of immunomodulatory or immunosuppressive therapy that is proving successful in modifying autoimmune disease processes [82]. However, their availability has raised fresh concerns, mainly surrounding opportunistic infection and cancer [131–135]. In the autoimmune diseases discussed herein, those drugs used frequently include steroid-sparing agents such as azathioprine and methotrexate, alternative potent immunosuppressive drugs such as leflunomide and cyclophosphamide, biological agents that include anti-TNF agents (etanercept, infliximab and adalimumab), anti-CD20 molecules (rituximab), interleukin (IL)-6 receptor antagonists (tocilizumab) and co-stimulatory inhibitor molecule (abatacept).

Reactivation of tuberculosis (TB) is a recognised risk of the use of anti-TNF therapy and the British Thoracic Society and others have issued guidelines for their use in those at risk of TB reactivation [136, 137]. TB and nontuberculous *Mycobacteria* [138] are pathogens that can both cause bronchiectasis and infect patients with existing bronchiectasis. Care must be taken to stratify the risk of reactivation following immunosuppressive therapies, and one should be aware that traditionally non-pathogenic strains can emerge as fatal infections [139]. Evidence for latent TB infection should be sought with the use of a detailed history, chest radiograph or CT, tuberculin skin testing and interferon-γ release assays (IGRA). IGRA s are now well established and should be used to “risk-stratify” in the context of anti-TNF therapy. While in theory latent viruses including herpes zoster and EBV, fungus, opportunistic bacteria and parasites are all more likely to re-emerge with immunosuppressive therapy, this has not been a consistent finding [140–145].

There may be a gradation of risks within this group of agents. Anti-CD20 therapy in the form of rituximab may generally be considered less aggressive. CD20 is expressed by haematopoietic progenitor cells and newly differentiated plasma cells, and while reactivation of latent virus is well documented, infection with other bacteria or parasites or TB is infrequently reported [146, 147]. Safety and long-term data are still emerging with tocilizumab, an IL-6 receptor antagonist found to be effective in rheumatoid arthritis and still being investigated for SLE [147–150]. To date, no surprising opportunistic infection data has emerged and meta-analyses have placed a figure of approximately six additional infections per 100 patient-years; those infections are mostly termed “pneumonia” [149, 151]. Abatacept, a newer co-stimulatory modulator that interferes with T-cell activation may not share the same documented risks of TB reactivation and may prove to be better tolerated than anti-TNF therapies, although longer term safety data on this drug is still emerging [152–155].

In general, physicians using these agents must be diligent and counsel patients about the risks of infections, particularly if patients already have susceptibility to infection due to concomitant bronchiectasis. In this case the patient should be co-managed with a respiratory physician, sputum should be screened for *Mycobacteria* sp. and other opportunistic pathogens, the patient should have an antibiotic management plan if infective exacerbations develop, and antibiotic prophylaxis
should be considered if infective exacerbations become frequent. These agents often provide marked improvement in the patient’s control of their autoimmune disease, which means that when the agents are used in bronchiectasis patients with associated autoimmune disease, treatment of chronic bronchial infection and infective exacerbations of bronchiectasis should be intensified to allow the agent to be continued when this is deemed to be safe. Good communication between the rheumatologist and pulmonologist is essential.

Statement of interest

None declared.

References


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