FOCUSED REVIEW

Airway Disease in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a common condition affecting approximately 1% of the general population. RA is a multisystem disorder that causes progressive articular destruction through synovial inflammation. One of the most common extraarticular manifestations of RA is pulmonary involvement, where all compartments of the pulmonary system can be impacted (e.g., pulmonary vasculature, pleura, parenchyma, and the airways). Although it has been known for decades that a portion of patients with RA develop interstitial lung disease, and recent advancements in understanding the genetic risk and treatment for RA-interstitial lung disease have drawn attention, more recent data have begun to highlight the significance of airway disease in patients with RA. Yet, little is known about the underlying pathogenesis, clinical impact, or optimal treatment strategies for airway disease in RA. This review will focus on airway disease involvement in patients with RA by highlighting areas of clinical inquiry for pulmonologists and rheumatologists and discuss areas for future research. Finally, we discuss a potential screening algorithm for providers when approaching patients with RA with respiratory complaints.

Keywords: rheumatoid arthritis; asthma; COPD; bronchiectasis; bronchiolitis

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Rheumatoid Arthritis: Autoantibodies and Airway Disease Overview

Rheumatoid arthritis (RA) is the most common autoimmune arthritis, affecting 1% of the general population (1). Manifestations of RA lead to significant morbidity and mortality and are costly to the healthcare system and the patient suffering from the disease (2). End-organ damage is induced by antibody-mediated inflammation during the clinical phase of disease in RA. Antibodies to citrullinated protein antigens (ACPAs) have been shown to play a pathogenic role in synovial disease and are associated with worse RA parenchymal lung disease (3–6).

ACPAs are measured clinically through anticyclic citrullinated peptide tests (anti-CCP). In addition to their presence in individuals with established RA, ACPAs can also be detected in serum 3–5 years before the onset of joint disease in at-risk individuals who develop RA (7). Citrullinated peptides develop via the activity of peptidyl arginine deiminase, a calcium-dependent enzyme that catalyzes the citrullination of arginine to citrulline (3). Multiple citrullinated peptides have been associated with RA (e.g., citrullinated filaggrin, fibrinogen, vimentin, histones, α-enolase), and these citrullinated autoantigens are then taken up by the adaptive immune system through dendritic cells, followed by T and B cell interactions, which ultimately generate ACPAs. This process is often mediated by the "shared epitope," which confers genetic RA risk via the HLA-DRB1 allele of the major histocompatibility complex, which increases the affinity of HLA for citrullinated peptides (8). ACPAs are suggested to exert their pathologic effects in the synovium through several indiscriminate mechanisms; for instance, ACPAs have been shown to bind to Fc receptors of myeloid lineage cells and activate the complement system *in vitro* (9). Also, ACPA has been shown to stimulate macrophages via Toll-like receptor 4 and Fcy receptor to induce TNF (tumor necrosis factor) production, which is also likely potentiated by rheumatoid factor (10, 11). ACPAs have also been shown to induce osteoclastogenesis via direct binding of osteoclasts (12).

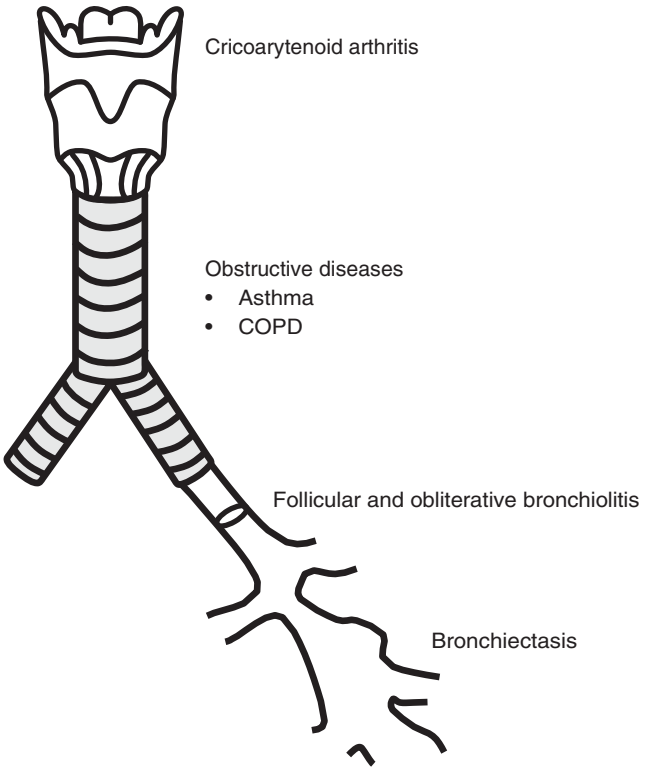

Figure 1. Graphic representation of the manifestations of airway disease in patients with rheumatoid arthritis. COPD = chronic obstructive pulmonary disease.

Primary clinical manifestations of RA are musculoskeletal in nature, leading to a debilitating, erosive synovial arthropathy. RA is a multisystem, autoimmune, inflammatory condition that impacts multiple systems. Historically, RA pulmonary involvement has been synonymous with lung parenchymal disease; however, this review highlights another pulmonary compartment often overlooked in RA: the airways.

Airway disease is a heterogenous set of disorders that comprises asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and inflammatory bronchiolitis syndromes (Figure 1). The underlying pathogenesis of these conditions varies; however, the nomenclature of airway disease applies to these disorders. This section describes what is known about each airway manifestation in RA, the epidemiology of these conditions in RA, the treatment impact for patients with RA, and the impact on clinical outcomes for patients with RA.

One component of RA airway involvement is synovitis of the cricoarytenoid joint. Cricoarytenoid arthritis presents with laryngeal symptoms such as dysphonia (13), hoarseness, change in vocal quality, or a foreign body sensation (14); in rare cases it can progress to acute respiratory failure requiring emergent tracheostomy (15). Given that cricoarytenoid arthritis represents a synovial manifestation of RA, we chose not to further highlight the entity in this review, although it is a recognized airway manifestation seen in patients with RA.

Asthma

Asthma is an inflammatory airway disorder typically mediated by an inciting antigen that leads to a heterogenous, hyperinflammatory response. Recent advances in expanded biologic therapy directed at various upstream inflammatory mediators highlight the importance of emerging endotypes in asthma (16). These biologic treatment pathways can be divided roughly into two primary divisions: high and low T-helper cell type 2 (Th2) (termed type 1 and type 2 immune response as well), based on their expression of interleukin-4 (IL-4), IL-5, and IL-13, which are classically secreted by Th2 cells (cluster of differentiation 4^+ [$CD4^+$]) (16). Type 2 asthma, as triggered by these upstream cytokines (IL-4, IL-5, and IL-13), leads to high antibody titers and eosinophilia, which results in a cellular phenotype typified by eosinophils, mast cells, basophils, group 2 innate lymphoid cells, and immunoglobulin E (IgE)-producing B cells (16). Treatment of asthma typically consists of a regimen including antiinflammatory therapy directed at the specific inflammatory endotype of the patient and bronchodilator therapy aimed at reducing airway obstruction through bronchiolar smooth muscle relaxation.

Asthma is more common in RA cohorts than population controls (17, 18). The overall incidence of asthma in a Taiwanese RA cohort was 2.07-fold greater than their non-RA cohort controlling for age and sex (17). In addition, investigators using the Nurses' Health Study data have shown that subjects with elevated RA autoantibodies who developed RA during observation were more likely to develop asthma as well (19). The Nurses' Health Study data also show that the presence of baseline COPD or asthma at study enrollment increases the hazard ratio for incident RA development during the course of prospective evaluation, even when adjusting for important confounders (20). Although these recent large studies show a robust correlation between asthma and RA, previous observational data from smaller studies found no such link (21, 22).

RA and asthma both have a female preponderance (in adulthood). In adulthood, asthma is more common in women than men, increasingly nonatopic, and more likely to be classified as severe, when compared with age-matched men (23–25). Interestingly, in childhood asthma this paradigm is commonly reversed, and more young males are affected by asthma and have worse asthma severity (24). In RA, women are impacted in a 2:1 ratio compared with men, and RA-specific measures of disease severity are worse in women (26, 27). The role of female sex in RA and asthma in disease incidence severity implicates a potential role of sex hormones in disease pathogenesis in both conditions.

RA and Asthma: Clinical Implication of Codiagnosis

It is unknown if asthma in a patient with RA represents a unique inflammatory endotype mediated by autoantibody-associated inflammation, but there is some clue that patients with asthma with RA have worse outcomes (28). Luo and colleagues describe outcomes in the National Inpatient Sample and found that subjects with asthma with RA had worse in-hospital mortality and increased hospitalizations for asthma

exacerbations when compared with subjects with asthma without RA (28). These data highlight the potential for RA to impact asthma-specific outcomes; however, to date, there are no published data that explore the impact of asthma on RA symptoms or RA disease control.

Little is known about the impact of asthma in patients with RA or the optimal approach to therapy in the individual patient with both diagnoses. Although there is a propensity for asthma within RA cohorts, there is no clinical guideline or society recommendation that guides screening for obstructive lung disease in patients with RA.

The role of biologic therapy is well explored in patients with RA, where adaptive and innate immune pathways have long been understood in the pathogenesis of synovial disease. Biologic therapy in RA consists of monoclonal antibody therapy directed at different components of these pathways, such as TNF-α, IL-1, IL-6, $CD20^+$ B cells, and CD80/86 on antigen-presenting cells (29). Use of disease-modifying anti-rheumatic drugs (DMARDs) has been explored in populations with moderate to severe asthma following promising animal data; however, results have been largely negative or retracted in nearly all instances (30–32), with the exception of methotrexate. Methotrexate use in asthma has been shown to lead to modest reduction in daily steroid dose; however, there was no associated decrement in asthma control or forced expiratory volume in 1 second (FEV_1) in these studies (33, 34).

As mentioned earlier, recent advances in biologic therapy in asthma have revolutionized the clinical approach to this condition. However, in contrast to RA, these biologic therapies in asthma are typically directed at Th2 inflammatory cascades. For instance, biologic therapies in asthma consist of antibodies directed at IgE, IL-4, IL-5, IL-13, and associated receptor antagonists (16).

Given the high coincidence of RA and asthma (17, 18, 20, 35), it is of paramount importance to the clinician to understand the impact that these diagnoses and discordant treatments have on pulmonary and joint-based outcomes. In addition, given the new frontier of biologic therapy in asthma endotypes and the potential implications of these therapies in patients with RA, there is reason to explore these important clinical considerations.

RA and Asthma: Possible Pathogenic Link

RA is caused by genetic–environmental interactions likely initiated at mucosal sites, such as within the lung airway. Although the exact etiology of RA remains unknown, it is known that the majority of patients with RA exhibit a systemic immune response to citrullinated peptides that leads to an autoantibody-mediated acute inflammatory response in the synovium (36). Clinically, ACPAs have high specificity for RA, and, when present in the absence of inflammatory arthritis, they strongly predict the future development of RA (3). This induction of abnormal immune responses to citrullinated peptides is hypothesized to occur in the lung in response to environmental insults, including smoking, where studies have reported the presence of ACPAs in sputum and bronchoalveolar lavage fluid from patients with RA and individuals at high risk of developing RA (37–39). Given the role that airway inflammation likely plays in the generation of ACPAs (35) and the role of ACPAs in RA pathogenesis, the association of asthma and RA leads to interesting scientific inquiry into a possible causal link.

Classically, RA inflammation is mediated through Th1 lymphocyte activity, and asthma is typically Th2 mediated. Conventional theory states that Th1 and Th2 diseases are inversely related, which has previously led to the assumption that RA and asthma are comorbidities and not biologically related disease states. However, multiple genetic and genomic studies have identified a Th1 phenotype within asthma populations (40–42). In addition, several studies have shown that Th1 and Th2 inflammation can occur simultaneously (43, 44), which indicates a potential role of systemic Th1 inflammatory states in subsets of subjects with asthma and thus a possible role for RA-related inflammation in asthma disease.

These interesting data regarding the role of the airway in production of ACPAs highlight the potential role of conditions like asthma as a risk factor for RA, which is supported by epidemiologic studies (20, 35, 45). However, it is important to point out that ACPAs and RA-mediated inflammation may also play a direct role in airway inflammation; therefore, it is also reasonable to consider the inverse: in some cases RA may lead to obstructive lung diseases such as asthma, which is also supported indirectly in epidemiologic studies (19, 46).

RA and COPD

COPD has a 10.1% prevalence worldwide (47). COPD is a clinical syndrome that encompasses a chronic respiratory disease typified by complete reversibility of airflow obstruction and alterations in pulmonary architecture. These structural alterations of COPD can manifest as emphysema, airway disease, or both. Although genetic conditions such as alpha-1 antitrypsin result in these same pathologic changes as COPD, most cases develop as a manifestation of inhalational smoke exposure (cigarettes or biomass).

Smoking is a shared risk factor for COPD and RA. In RA, smoking has been shown to be a modifiable risk factor in multiple studies (48–50). Interestingly, studies have also shown, in identical twin pairs with variable RA expression, that those twins who smoked were at higher risk for the development of RA, further supporting the role of environmental–gene interactions for RA and smoking (51, 52). Shared environmental risk factors certainly explain the high coincidence of many disorders with COPD, such as ischemic heart disease, atrial fibrillation, heart failure, osteoporosis, lung cancer, anxiety, and depression (53). In many cohorts of patients with RA, high rates of COPD have been found. Meta-analysis of these data shows the pooled prevalence of COPD in RA was 6.2% (95% confidence interval, 4.1–8.3%) (54). Although smoking is associated with RA and COPD, multiple analyses have found the risk for COPD in patients with RA remains significant after adjusting for smoking history (55, 56). Regardless, the presence of COPD in patients with RA has significant impact on morbidity and mortality (57).

Treatment of COPD and RA

There are clinical endotypes associated with COPD, although fewer than asthma. The two clinically important COPD endotypes are the aforementioned alpha-1 antitrypsin–deficient patients and those patients with COPD with elevated serum eosinophils. Elevated serum eosinophilia predicts response to corticosteroid therapy in COPD (53). Primary prevention is the most important intervention for COPD globally, and in the individual patient, where smoking cessation reduces risk of death and improves quality of life (53).

Despite the significant worldwide prevalence of COPD and poor clinical outcomes, there is very little clinical insight into COPD immunophenotypes, and as a result there are no effective immunomodulatory treatments aside from corticosteroids for patients with COPD. Given these limitations, it is unclear how treatment considerations for one disease should impact the other in coincident cases of RA and COPD (57). There has previously been concern regarding the use of biologic DMARD therapy in COPD, given potential risk for increased exacerbations; however, a large-scale, real-world trial design assessed this question and found no clear association between biologic DMARD use and poor COPD-specific outcomes (58). Like asthma, the use of conventional DMARDs has been explored in COPD populations, and methotrexate may exert a modest steroid-sparing effect in small studies. However, other conventional DMARD trials in COPD have been largely negative (59, 60). Clinicians should offer smoking cessation–directed interventions; however, it remains to be seen if more aggressive immune suppression for patients with RA with COPD impacts the airway disease manifestations or vice versa.

Shared Pathogenesis between COPD and RA

There are overlaps between RA and COPD in terms of autoimmune pathogenesis. For instance, higher levels of ACPAs have been detected in the serum of heavy smokers without RA at higher rates than control subjects (61). In addition, serum from patients with COPD has been shown to produce autoantibodies that react to antigens associated with known autoimmune conditions, including RA (62). Most interestingly, researchers identified a group of subjects with positive serum ACPAs before the development of RA who were also at increased risk for developing COPD when compared with a control population, which indicates a potential role for ACPAs in the pathogenesis of COPD in these patients (19).

RA and Bronchiolitis

Bronchioles are lower divisions of the airways that are typified by the absence of hyaline cartilage. These small airways are frequently involved in inflammatory disorders termed bronchiolitis.

Follicular Bronchiolitis

Follicular bronchiolitis (FB) develops in the setting of hyperplasia of bronchiole-associated lymphoid tissue. This bronchiole-associated lymphoid tissue hyperplasia is seen in many connective tissue disorders, including RA (63). Diagnosis of this condition is typically made on lung tissue examination after a surgical lung biopsy; however, there are imaging findings that are associated with FB, such as centrilobular nodules, hyperinflation, mosaicism, and air trapping, although these findings are nonspecific (64). Of interest, high-resolution computed tomography (HRCT) findings of bronchiolitis have several overlapping features with asthma, which can make the two diseases difficult to distinguish radiographically (64–66). Typically, FB requires surgical lung biopsy for diagnosis, given this nonspecific radiographic phenotype. On histopathology, FB is typified by lymphocytic proliferation and lymphoid follicles, with reactive germinal centers around the bronchioles accompanied by narrowing of the bronchiole lumen (67).

Given the rarity of RA-related FB, little is known about the expected clinical course; however, the primary clinical manifestations are a reduction in FEV_1 and associated dyspnea. RA-FB is believed to be a progressive obstructive disease that responds briskly to immune suppression, given the cellular nature of its histopathology, although there are reports of a positive response to macrolide therapy as well (68, 69).

RA is also associated with obliterative bronchiolitis (OB) (also known as constrictive bronchiolitis and bronchiolitis obliterans). Like FB, OB occurs typically in secondary fashion and most commonly in the post–lung transplant and post–bone marrow transplant populations. However, RA is the most implicated connective tissue disease for OB (70). Imaging findings of OB are diffuse pulmonary infiltrates, bronchial wall thickening, and lobular areas of decreased attenuation with mosaicism indicating air trapping (70). The diagnosis of OB is clinical, based on the presence of an inciting event or condition (e.g., RA, lung transplantation, noxious chemical inhalation), marked airflow obstruction not believed to be related to COPD (for instance, the absence of smoking history), with or without biopsy evidence of bronchiolitis. Histopathologic examination of OB reveals concentric fibrosis of the bronchial wall with severe narrowing of the bronchiole lumen, occasionally associated with lymphocytic infiltrates within the walls of the bronchioles (70).

Outcomes in OB are generally worse when compared with FB, including cases associated with RA. In one case series of patients with RA who developed OB, all patients were on immunomodulatory therapy for RA at the time of OB onset. Of the 24 patients in the series, 52% had worsening symptoms despite directed therapy, 48% developed acute hypoxemic respiratory failure, 4 patients died of respiratory failure in the follow-up period, and 1 patient went for lung transplantation (70).

Treatment for OB in RA is generally a combination of inhaled bronchodilator therapy combined with aggressive immunomodulatory therapy with inhaled and oral corticosteroids, macrolides, cyclophosphamide, or etanercept.

Bronchiolitis conditions in RA are rare; however, they lead to significant morbidity and mortality and their diagnosis frequently requires surgical lung biopsy and significant immune modulatory therapy with early consideration of lung transplantation. However, as mentioned previously, there are no clear guidelines for screening patients with RA for obstructive lung diseases, which likely leads some patients to experience delayed referral to centers that specialize in diagnosis and management of inflammatory bronchiolitis and/or lung transplantation evaluation.

RA and Bronchiectasis

Bronchiectasis results from long-term damage to the airways causing them to widen and thicken, with increased production of mucous creating a nidus for recurrent infection. The hallmark condition of bronchiectasis, cystic fibrosis, results from inherited genetic abnormalities in transmembrane ion conductance channels in the airways leading to inappropriate mucous clearance and long-standing recurrent infections and bronchiectasis. Bronchiectasis can develop in many systemic conditions aside from cystic fibrosis, including RA.

Rates of bronchiectasis in patients with RA vary based on the method of screening used to detect airway abnormalities. In unselected patients with RA, the rate of bronchiectasis on HRCT is 17–30.5% (71),

although the rate of symptomatic bronchiectasis in RA cohorts is much lower (between 2.4% and 3.1%) (72, 73).

Treatment Considerations of RA Bronchiectasis

Bronchiectasis in patients with RA leads to more irreversible obstruction than is seen in non-RA-related bronchiectasis (74, 75). Recurrent lower respiratory tract infections are a complex issue in patients with RA who commonly require immunomodulatory agents. Common RA regimens including corticosteroids, leflunomide, and biologic DMARDs have been shown to increase rates of lower respiratory tract infections (76, 77). The role of prophylactic antibiotics in RA-related bronchiectasis is unclear and left up to individual clinicians. It also unclear if immunomodulation has any impact on bronchiectasis severity or outcomes for patients with RA or if another approach should be used that targets possible underlying genetic or immunologic mechanisms directly (78).

Pathogenesis of RA Bronchiectasis

As referenced already, the pathogenesis of bronchiectasis in RA is unknown. There are multiple theories that outline possible mechanisms for airway manifestations of RA. Given the pathogenic role of ACPAs in RA, understanding the associations between bronchiectasis and ACPAs can offer insight into potential overlapping pathogenesis for RA and bronchiectasis. When comparing three groups—patients with early RA with ACPA positivity, ACPA-positive patients without RA, and normal ACPA-negative control subjects—there was significantly more airway thickening and bronchiectasis on HRCT in those groups who were ACPA-positive, even in the absence of RA (79). This highlights the role that the generation of ACPAs may play in the development of bronchiectasis seen on HRCT.

Another theory posits that bronchiectasis develops in RA related to an underlying genetic abnormality like the hallmark bronchiectasis condition: cystic fibrosis. In cystic fibrosis, the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene is abnormal, leading to poor performance of the associated protein, which alters transmembrane conductance of sodium ions resulting in abnormal mucous layers. Researchers evaluated a population of subjects with RA with bronchiectasis for the common genetic mutations associated with cystic fibrosis and found that 15.4% of those patients were heterozygous for delta F508, the most common *CFTR* mutation in cystic fibrosis (80, 81). These findings, combined with the association of ACPAs and bronchiectasis, leads to a hypothesis that airway inflammation from bronchiectasis, which may develop due to genetic risk such as *CFTR* mutations, leads to autoantibody generation that can then play a role in RA pathogenesis and worsening airway disease.

Other theories of bronchiectasis in patients with RA include the possibility that recurrent infection related to chronic immune suppression predisposes patients with RA to bronchiectasis. For instance, patients with RA and bronchiectasis have frequent lower respiratory tract infections, and these infections were associated with preexisting sputum colonization and biologic DMARD use (77). The truth is likely some combination of all these factors: antibody-mediated inflammation, genetics, and a predisposition to recurrent lower respiratory tract infections all play a role in bronchiectasis seen in HRCT scans of patients with RA.

Screening Approaches to Patients with RA for Airway Disease

The most important screening tool for RA airway disease is the clinical history to elicit the presence of airway-related symptoms. Our recommendation is that clinicians caring for patients with RA evaluate and obtain a thorough history for the presence of symptoms that may be attributable to airway diseases, such as hoarseness, change in voice character/quality, foreign body sensation in the throat, dyspnea or shortness of breath, fatigue, wheezing, cough, recurrent lower respiratory tract infections, or chest tightness/pain. A combination of diagnostic tools guided by clinical history such as HRCT, pulmonary function testing with bronchodilator response, and/or bronchoprovocation testing should have adequate sensitivity and specificity in the symptomatic patient with RA to diagnose or largely exclude airway involvement. We have proposed a screening algorithm for clinicians when approaching the patient with RA with undifferentiated respiratory symptoms on screening (Figure 2)

The diagnosis of any of these airway diseases in RA will have treatment implications in the symptomatic patient with RA and will typically require a multidisciplinary approach for treatment combining rheumatologists; pulmonologists who specialize in asthma, COPD, interstitial lung disease (ILD), or bronchiectasis; and/or otolaryngologists for laryngoscopy. In addition, consideration between pulmonologists and rheumatologists should focus on the role of DMARD therapy in the individual patients with comorbid RA and airway disease (for instance, consideration of nonbiologic therapy in patients with recurrent infections in the setting of bronchiectasis).

Future Directions in RA Airway Disease Research

Data have been presented so far in this review that highlight two exciting hypotheses: model 1, inflammation in the lung at the airway mucosal surface leads to the development of ACPAs and subsequent RA (Figure 3A); and model 2, systemic RA inflammation impacts airway mucosa leading to a unique autoantibody-mediated airway disease endotype (Figure 3B).

In the experimental view of airway–RA synergy represented by model 1, the airway involvement in these cases does not reflect a manifestation of inflammation from RA; instead, the underlying airway involvement predates clinical RA and leads to the generation of ACPAs. In this scenario, early identification and intervention of airway disease and immunomodulation for those patients at risk could be an important clinical step to disrupting RA pathogenesis. In addition, it is paramount that clinical investigators understand the pathobiology of disease initiation from airway inflammation to interrupt or alter the typical disease course.

This airway–RA link is intriguing, given the potential role of the lung and airway mucosa in RA disease pathogenesis via production of ACPAs, as noted previously in this review. In this model, lung injury,

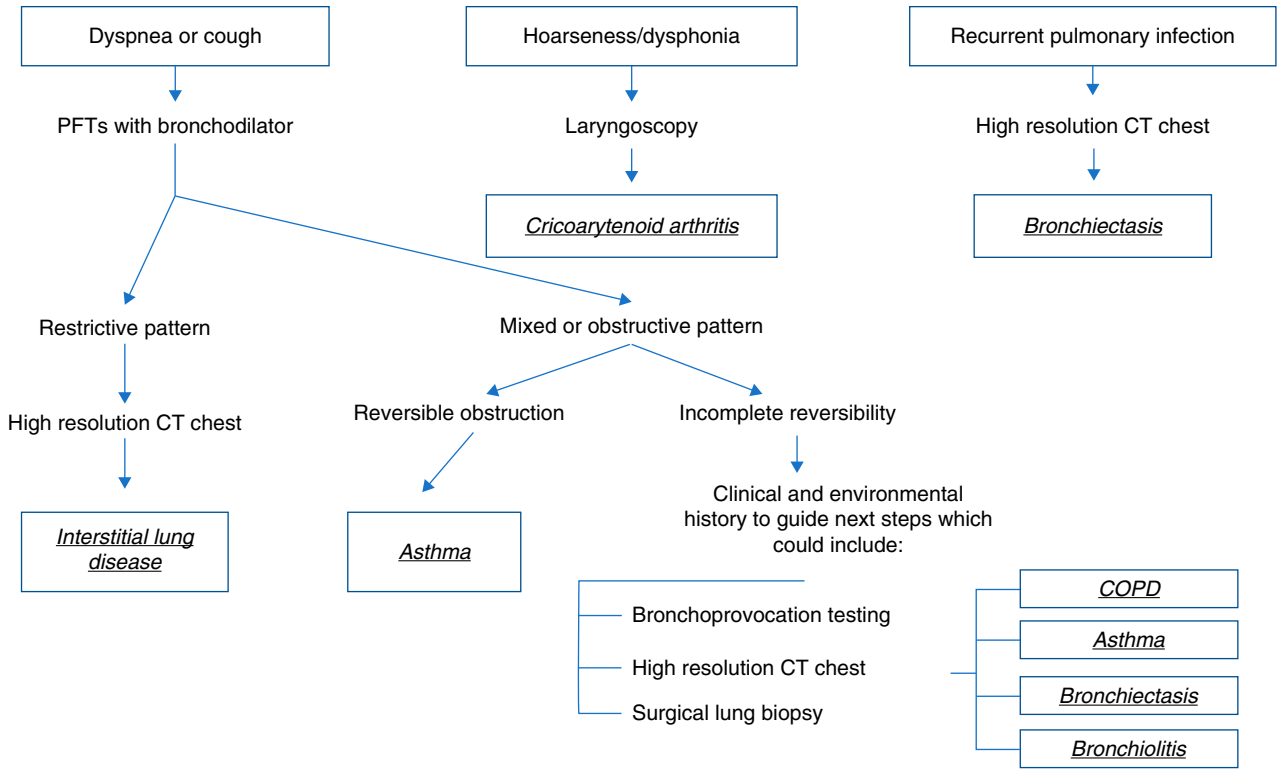

Figure 2. Proposed algorithm for evaluation of patients with rheumatoid arthritis (RA) based on positive screen during clinical evaluation for dyspnea, recurrent lower respiratory tract infections, or voice changes/dysphonia. COPD = chronic obstructive pulmonary disease; CT = computed tomography; PFTs = pulmonary function tests.

mediated by smoking or microbiota pressures such as mycobacterial disease, induce ACPAs potentially via the effect of neutrophil-mediated inflammation and neutrophil extracellular traps (NETs) (8, 39, 79, 82–84). NETs externalize digested peptides for antigen-presenting cells and serve as antigenic targets for ACPA (82).

In RA subjects, NET formation is increased in sputum neutrophils, and elevated levels of sputum ACPAs are associated with citrullinated protein containing NETs (83, 85, 86). In addition, NET peptides can be internalized by antigen-presenting cells and presented in a major histocompatibility complex class II–dependent manner to antigen-specific T cells in association with production of ACPAs (87). Together, these data support that NET peptides can be an initial antigenic trigger of ACPAs and that this process likely occurs in the lungs, but further studies are necessary to understand if there is a causal link between NETs in the lung, ACPAs, and RA (Figure 4).

Genome-wide association studies have unlocked the framework of underlying genetic risks for multiple diseases, including RA-ILD (88). RA-ILD is an interesting comparison to the other diseases discussed herein. Currently, management of RA lung disease varies significantly; RA-ILD is treated with aggressive immune suppression targeted at pulmonary manifestations of RA inflammation, whereas asthma or COPD in a patient with RA is thought of exclusively as a comorbidity. Meanwhile, the recent genetic insights into RA-ILD found shared genetic risks with a similar ILD, idiopathic pulmonary fibrosis (IPF). Might it be that RA-ILD is a more similar condition to IPF, and something about the ongoing lung injury predisposes to the development of RA in some individuals? This field remains an active area of discussion and research but has very important implications when considering asthma in a patient with RA or RA-bronchiectasis, given the genetic associations with cystic fibrosis already discussed. Genetic and epigenetic studies are necessary to understand how the interaction of environmental factors influences the coincidence of these diseases.

These RA-ILD and RA-bronchiectasis genetic insights also raise the specter of the usefulness of DMARD therapy in RA-related lung diseases. Perhaps the efficacy of DMARD therapy in lung disease for patients with RA is blunted because of the underlying genetic risks for lung manifestations that are not primarily inflammation driven, (i.e., such as IPF, in which outcomes are worse with an immune-suppressive approach [89]). Much work is still required to understand how treatment for lung disease in RA is best approached.

When considering model 2, presented here in Figure 2B, it is important to point out that airway abnormalities in RA (based on HRCT analysis) are high (30%) but not universal (71). Therefore, many patients with RA must develop RA in the absence of underlying airway involvement. It is also important to point out that in our current understanding of the role of ACPAs in lung disease, there is evidence of worsened outcomes for RA parenchymal disease but no data to date that describe the role of ACPAs in RA airway disease (90, 91). As such, it is important to understand if these patients with RA

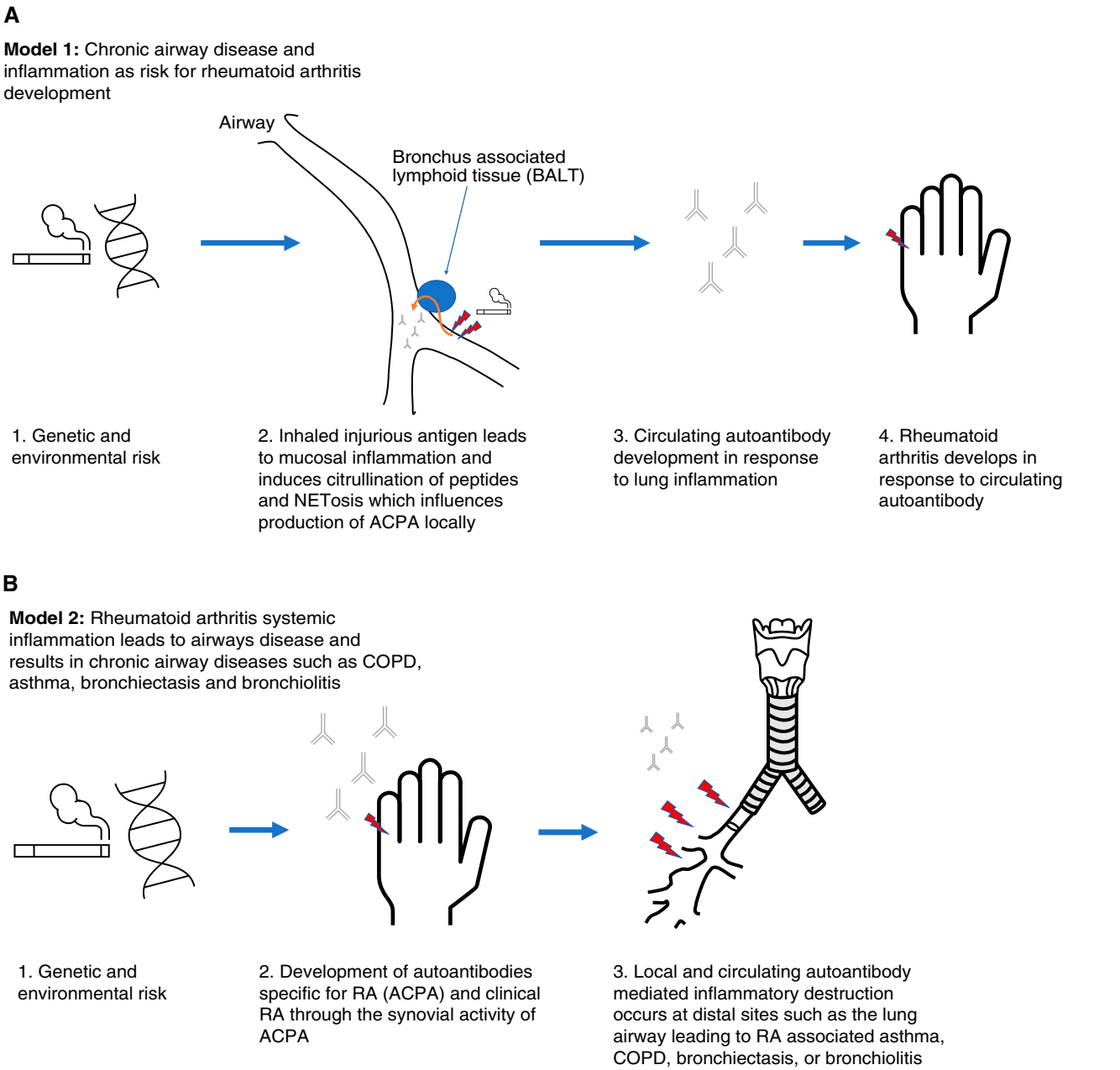

Figure 3. (*A*) Model 1: Chronic airway disease and inflammation as risk for rheumatoid arthritis (RA) development. Data that support model 1 of development of antibodies to citrullinated protein antigens (ACPAs) in chronic lung disease are found in References 7, 19, 20, 35, 38, 39, 45, 79, 80, 83, 85, and 92. (*B*) Model 2: Airway diseases such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and bronchiolitis result as a direct manifestation of RA autoantibody-mediated inflammation and represent a unique autoimmune endotype of airway disease. Data that support model 2 of RA-mediated lung inflammation causing airway phenotypes are found in References 28, 46, 56, 68, and 93–95. NETosis = neutrophil extracellular trap formation.

airway disease have distinct clinical phenotypes that lead to alterations in treatment response or other differential outcomes.

The next vital step for pulmonary physicians caring for patients with RA is to understand if airway disease in RA represents an RA manifestation (Figure 2B). Current approaches to management of these conditions (asthma, COPD, bronchiolitis, and bronchiectasis) in patients with RA largely ignores the potential that inflammation from RA contributes to the condition; however, given our limited understanding in these cases, this distinction may have important treatment considerations. Prospective, longitudinal work is required to understand this link between the airway and RA, which should include multiple specialties and research disciplines.

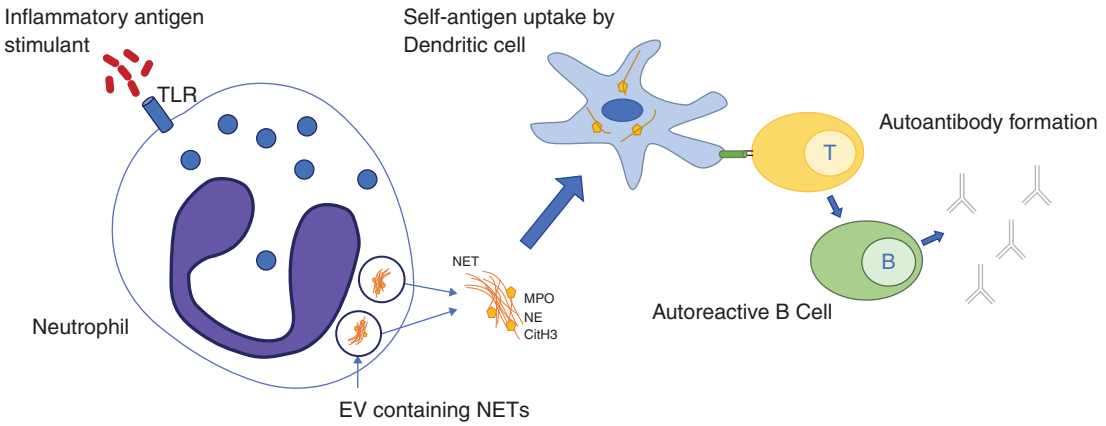

Figure 4. Neutrophil extracellular trap formation (NETosis) occurs when an antigenic stimulus, such as bacterial infection, stimulates the release of decondensed nucleolar material from the neutrophil, which, in addition to innate immune function capabilities, contains self-antigens. These self-antigens are then taken up by dendritic cells and through T and B cell interactions lead to the production of autoantibodies such as antibodies to citrullinated peptide antigens (ACPAs). CitH3 = citrullinated histone 3; EV = extracellular vesicle; MPO = myeloperoxidase; NE = neutrophil elastase; NET = neutrophil extracellular trap; TLR = Toll-like receptor.

Another current limitation to understanding the impact of these disease states on one another is the nature of clinical and translational research study design, which typically studies a single disease in isolation. For instance, most studies of RA treatment outcomes would likely exclude someone with significant asthma, COPD, or bronchiectasis. We believe that many questions raised in this review will remain unanswered unless trials specifically designed with these two models in mind are undertaken. For instance, it is paramount to include subjects with RA with lung disease in treatment study designs to understand the impact of DMARD therapy for RA on airway diseases in coexistent states and vice versa. In addition, it is vital to undertake prospective evaluation of subjects with chronic lung disease, such as asthma, COPD, and bronchiectasis, who are serially monitored for the development of autoantibodies and subsequent RA to determine if there is validity to model 1 (Figure 2A).

Nearly all the data presented in this review are associative in nature. Given this, there are limitations to the conclusions that can be drawn. We caution clinicians and investigators when approaching this issue that more mechanistic studies are needed to better address the questions that are raised herein.

This review highlights the next steps in understanding this association between RA and the airways; however, it remains clear that the current standard of care of these patients should enlist in-depth consultation with diverse specialties, and decisions about treatment risks and benefits should be made in concert with pulmonary and rheumatology providers. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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