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REVIEW ARTICLE

The Spectrum of Airway Disease Associated with Rheumatoid Arthritis

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Abstract: Airway involvement results from long-standing rheumatoid arthritis leading to severe pulmonary complications, correlated with increased mortality and socioeconomic costs. Different types of pulmonary lesions, including pulmonary rheumatoid nodule, pulmonary arteritis, diffuse interstitial fibrosis, and rheumatoid pneumoconiosis or Caplan's syndrome, are believed to be related to rheumatoid arthritis (R.A.). The above changes may indicate the increased susceptibility to the infection, toxins from a disease, or chronic immunity activation. The symptoms vary from asymptomatic to severe life-treating conditions, and the prognosis varies depending on the genre and severity of involvement. Our study aims to assess the prevalence and characteristics of airways association in rheumatoid arthritis as these data provide a brief insight into early diagnosis and treatment, which could be applied to minimize complications of airways diseases in rheumatoid arthritis.

Keywords: Rheumatoid arthritis, upper airway disease, lower airway disease, pulmonary involvement, obstruction, pulmonary dysfunction.

1. INTRODUCTION

Rheumatoid arthritis (R.A.) is a chronic systemic inflammatory disease with an unknown origin characterized by peripheral symmetric erosive polyarthritis [1]. In 1948, F. Ellman described the pulmonary involvement in three cases of convoying pulmonary lesions as an intrinsic part of "Rheumatoid State" [2]. Pulmonary involvement in frequent extra-articular manifestation of Rheumatoid Arthritis (R.A.) is assessed as rare pulmonary vacuities, interstitial involvement, airway disease, pleurisy, and parenchymal nodules [3]. Caplan Antony reported chest radiological appearance in the rheumatoid infected coal mine workers later in 1953 [4]. Different types of manifestation were seen in rheumatoid arthritis patients, along with airways disease. As per Geddes D. M. *et al*., the initial few patients in the absence of emphysema or chronic bronchitis exhibited rapidly progressive airway obliteration.

In approximately 39% to 60% of patients, the airways disease's pervasiveness in rheumatoid arthritis is high with the involvement of any part of the airways, including the distal small airways and the upper and the lower part of the larger airways [5]. The most common forms of appearance are cricoarytenoid arthritis, bronchiectasis, airway hyperreactivity, and bronchiolitis. Upper airway involvement is more common in females and people with prolonged or severe malady and includes rheumatoid nodules of the vocal cords. Vasculitis of the recurrent laryngeal or vagus nerves resulting in vocal cord paralysis is rare in the Cricoarytenoid joint arthritis [6]. However, it is worthy of consideration because the clinical spectrum ranges from delicate dysphagia, throat pain, or dyspnea to abrupt glottic stenosis, stridor, and acute respiratory failure requiring immediate surgery [7]. Although small airway involvement might supervise airflow obstruction, these were initially reported in 1977 in 6 patients, of which 5 of them already had R.A. [8, 9]. In a few other studies, 60% of the patients were reported to have obstructive lung disease. Fully contrasting etiologies have been propounded for this high prevalence, including synchronic use of cigarettes, the existence of rheumatoid diseases like Sjögren syndrome, bronchiectasis, and side effects of antirheumatoid medicine, notably corticosteroids [10, 11].

Doran *et al*. delineated that the use of DMARDs didn't increase the chance of initial mild or serious ailment. The lower airway involvement can exist as follicular bronchiolitis or constrictive bronchiolitis obliterans. In each of these cases, the lumen's constriction is ascertained. However in follicular bronchiolitis, it emerges from bronchial associated lymphoid tissue (BALT) hyperplasia, whereas in constrictive

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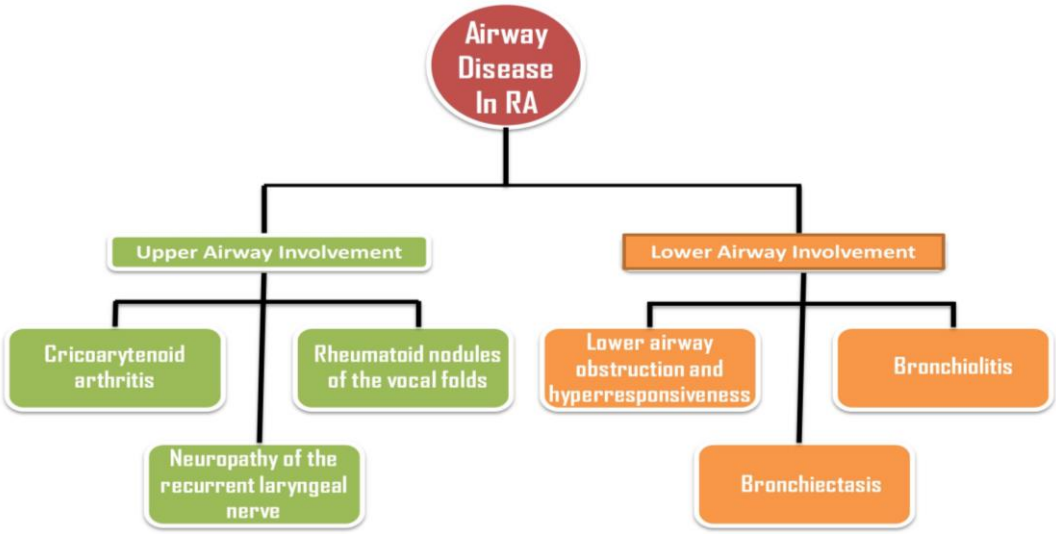


Fig. (1). Step-down flow chart illustration showing the association of Airways disease of rheumatoid arthritis with interstitial lung disease. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

bronchiolitis obliterans, it evolves from the progress of concentric fibrosis.

Numerous pathophysiological contrivances have been recommended for respiratory disorders in rheumatoid arthritis. Based on the underlying anatomical location, upper airway involvement, and lower airway involvement, the two main types of airway disease feature different clinical symptoms and instrumental features (Fig. **1**).

2. METHODS AND MATERIALS

A literature search for English-language systematic reviews and guidelines regarding airway disease and rheumatoid arthritis was performed in PubMed, Google Scholar, and Medline. Searches were carried out using combinations of the following keywords: upper airway involvement in R.A., lower airway involvement in R.A., laryngeal involvement, lung function tests, flow volume loops, rheumatoid arthritis, bronchiectasis, bronchiolitis, and airway obstruction with relevant research articles and case reports were reviewed, and the information was retrieved and stratified based on epidemiology, clinical symptoms, instrumental findings, diagnosis, and treatment. PubMed was searched using the narrow diagnosis, clinical queries and the systematic review filter. Only diagnosis and treatment approaches currently available in clinical practice were included. When identified reviews did not cover relevant topics, articles were selected based on the informal consensus of relevance and rigor.

3. UPPER AIRWAYS INVOLVEMENT

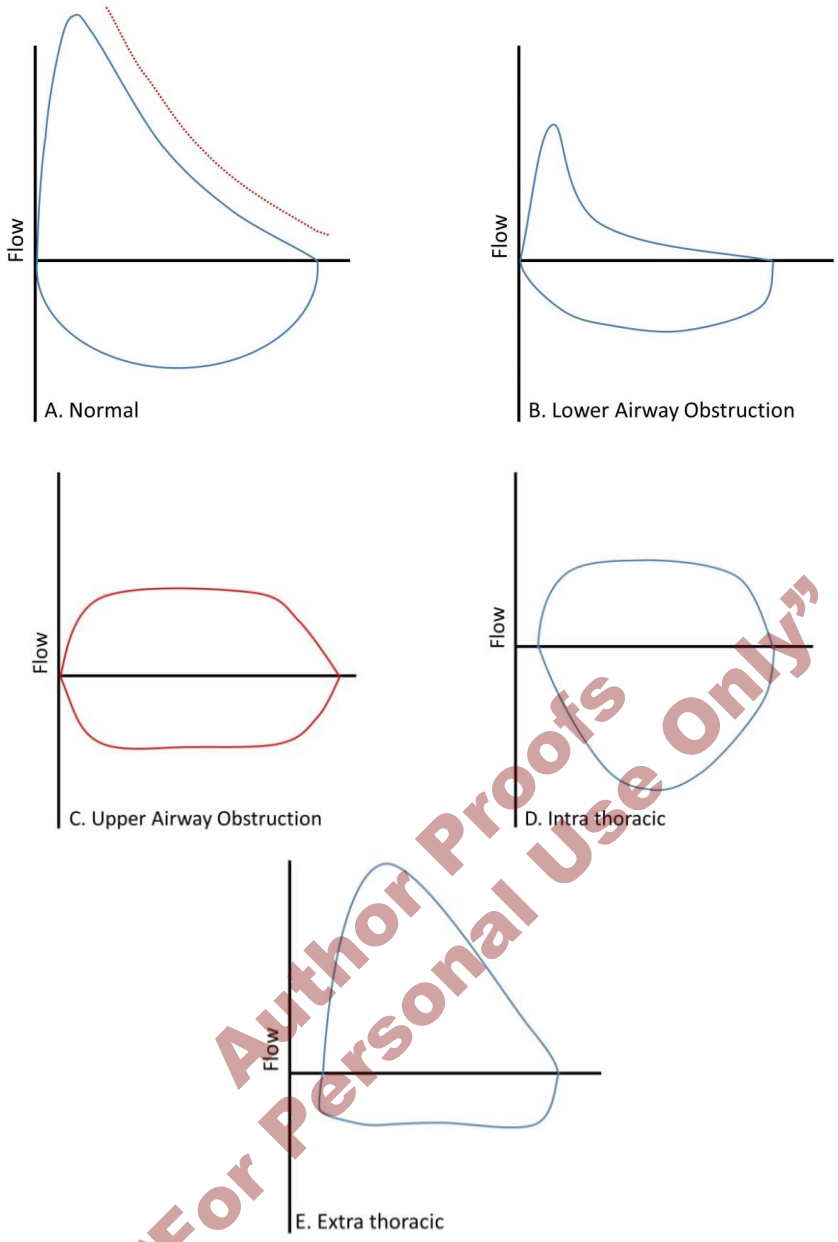
The airway pathways can further be divided into lower airways and upper airways, which further have various subdivisions, including the larynx and the pharynx that includes the nasopharynx, the oropharynx, and the hypopharynx. The larynx, commonly known as the voice box composed of various intrinsic muscles, three large unpaired cartilages (i.e., epiglottis, thyroid, cricoid), and three pairs of smaller cartilages (*i.e.*, arytenoids, corniculate, cuneiform), comprises essential organs for producing sound and protecting the lower respiratory tracts [12].

Approximately 13% to 75% of individuals with rheumatoid arthritis have symptoms in the throat and larynx, whereas postmortem investigations reveal that 45% to 88% of people and about 15% of patients have laryngeal involvement as a distinct symptom of RA [13]. Several studies reported the most common clinical features that patients generally complain of, which include hoarseness, dyspnea, pain in the throat radiating to the ears, stridor or dynodysphagia, upper esophageal dysmotility, dyspnea during the workout, or intense physical activity, which is due to the reduction of airway less than 8 mm in diameter. In contrast, dyspnea at rest or stridor develops when reduced to less than 5 mm in diameter [14-17].

A rare case of Cricoarytenoid arthritis was reported by Kavitha Masilamani *et al*. as croup in juvenile rheumatoid arthritis patients [18]. The most significant and available investigation of upper airways involvement involves the use of fiber optic laryngoscopy or video laryngoscopy [19].

The myositis of intrinsic laryngeal muscles, edema, inflammation, swelling of the arytenoids, inter arytenoid mucosa, aryepiglottic folds and epiglottic folds and epiglottis; edema or erythema of the vocal cords and impaired mobility or fixation of the cricoarytenoid joint is diagnosed with confirmed laryngoscopic examination [20].

The radiological results show sturdiness and expansion of the articular cartilage with erosion of the C.A.J., and the changes in the cricoarytenoid motion restrict complete lateral rotation [21]. Most cricoarytenoid arthritis cases can be diagnosed on chest radiography, with erosion and sclerotic fragments of cricoarytenoid joint (C.A.) displaced anteromedially, ankylosis, slandering the space jointly, and the congestion of vocal fold [22]. Upper airway obstruction and lung efficiency could be significantly measured with pulmo-



Graph 1. (**A-E**) Graphical representation of flow-volume-loops showing the pattern of various pulmonary dysfunctions. A normal loop is shown in Graph A, followed by Graph B showing lower airways obstruction, Graph C shows Upper airway obstruction, Graph D shows Intra thoracic, and Graph E shows the Extra thoracic. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

nary function tests (PFTs). The measurement and changes in the flow-volume loops on spirometry can aid us in diagnosing and localizing airway obstruction. (Graph **1A-E**) The flow-volume loop plot for the upper-airways obstruction in the expiratory curves or inspiratory curves was presented as a biphasic, plateau, or flattening shape for possible diagnosis and upper airway examination obstruction [23-25]. Several authors proposed importance for the early monitoring of upper airway obstruction with the Empey Index (FEV1ml/ P.F.R. L/min> 8) [26-28].

COPD and asthma both induce airway blockage and are linked to long-term inflammation of the lungs' respiratory tracts. Nevertheless, the kind of inflammation and its locations vary from disease to disease, leading to various pathophysiology, clinical symptoms, and therapeutic responses [29]. As a result of these variations, asthma and COPD present clinically different symptoms and respond differently to a treatment. It's fairly uncommon for people with asthma and COPD to have characteristics in common, although this is either due to a coincidence of two common illnesses or due to different phenotypes within each disease [30, 31]. Differential diagnosis of upper airway involvement, particularly with obstruction, should be carried out between lower airway obstruction in asthma and COPD. In upper airway obstruction, typically stridor is noted and as in case of asthma and COPD, wheezing is reported. Stridor is heard

mainly during inspiration and is prominent over the neck, whereas wheezing sound is heard mainly during expiration [32]. In the differential diagnosis of a laryngeal mass, Hee Won Seo *et al*. suggested that for patients with laryngeal mass, the possibility of rheumatoid nodules, as well as laryngeal malignancy, should be considered [33]. Asthma management is difficult for certain individuals due to their resistance to the anti-inflammatory effects of corticosteroids. The majority of people with COPD, on the other hand, are resistant to corticosteroids, prompting a quest for new anti-inflammatory treatment options.[34] For novel asthma and COPD therapies to be developed in areas of high need, including severe asthma, curative asthma therapy, and effective anti-inflammatory medications for COPD, it is critical to understand the cellular and molecular processes that underlie these diseases [35, 36].

4. LARYNGEAL INVOLVEMENT IN RHEUMATOID ARTHRITIS

The range of laryngeal-related cases in rheumatoid arthritis is from 0.3% to approximately 12%. The symptoms of laryngeal-related cases in rheumatoid arthritis patients are usually subclinical and benign resulting in either anatomical or functional laryngological alteration [37]. These include laryngeal nodules, cricoarytenoid joint fixation, neuropathy of the recurrent laryngeal nerve, and myositis diagnosed only through micro-video laryngoscopy or histopathology. Grossman *et al*. reviewed that half of the patients with R.A. had laryngeal symptoms [38].

Several other studies report that up to 50% of the patients show positive laryngeal involvement as the only result of this disease. The clinical manifestation mainly relies on the bilateral or unilateral involvement and the orientation of vocal cords [39]. Initial symptoms are hoarseness or change in voice quality, odynophagia, and upper oesophageal dysmotility. Sometimes it may remain quite asymptomatic and recognized only through autopsy [40].

Surgical management, including tracheostomy, adenoidectomy, or arytenoidopexy, may be prescribed if progressive airway obstruction occurs despite medical management. Acute stridor is life treating condition occurring in the later phase of disease due to severe airway obstruction, which requires an urgent tracheostomy as a life-saving measure [41].

The rheumatoid nodules in patients' vocal folds with seropositive nodular rheumatoid polyarthritis presented with chronic productive cough. The bamboo nodes or rheumatoid nodules are the laryngeal deposits of autoimmune complexes without any pathological or clinical differences. In seropositive rheumatoid arthritis, the presence of different-sized rheumatoid nodules in the larynx could be detected [42]. The three essential risk factors that aid in the bamboo nodes' development include the expression of an existing autoimmune disease, use of voice, and female sex [43]. In fibrinoid necrosis adjoining through resisting histiocytes and in the submucosa, various nodules could be seen histologically. In many of the cases, only after the rheumatoid arthritis diagnosis; the bamboo nodes were detected. The dismissal of these nodules *via* cordotomy by microdissection engenders prompts vocal folds decompression [44].

Carcinoid joint (C.J.) involvement is rare, but it deserves attention; it can lead to paralysis of the vocal cord leading to upper airway obstruction. One of the distinctive features of rheumatoid synovitis could be seen in patients' joint manifestations due to the cricoarytenoid joint's arthritis [45]. Different symptoms could be seen as per the severity of the cricoarytenoid joint, nonspecific and subclinical, and due to the involvement of C.A. joints, acute airway obstruction could be noted with the progression of the disease. Hoarseness and stridor may be the first complaint in patients not previously diagnosed with autoimmune diseases [46]. A study by Bienenstock *et al*. summarized clinically undetectable variants of rheumatoid cricoarytenoid arthritis. Laryngoscopy in acute cricoarytenoid arthritis shows red swelling in the region of arytenoids and epiglottis [47].

A rare case of C.A. rheumatoid joint arthritis was presented by Pradhan P *et al*. which showed a patient with stridor and hoarseness, confirmed for C.A. joint arthritis corresponding to the histopathological examination of the forearm and laryngeal nodules, which was efficaciously countered by medical treatment. After approximately six months, the relapse of laryngeal symptoms was reported, which requires another tracheostomy [48]. The paralysis of vocal cords, neural atrophy of laryngeal muscles, and degenerative changes in laryngeal nerves caused by vasculitis or arthritis of the cricoarytenoid joint were reported [49].

5. COMPLICATIONS OF UPPER AIRWAY INVOLVEMENT

Acute respiratory failure (A.R.F.) is a life-treating condition that requires immediate emergency treatment. Due to vocal folds nodules or cricoarytenoid arthritis, the obstruction in the upper airways is its considerable pathophysiological mechanism. The most common cause can be an acute exacerbation of crico-arytenoid arthritis associated with an upper respiratory tract infection [50]. A report by Mc Geehan D. F *et al*. described the onset of severe stridor of less than one h in duration in an inpatient and low oxygen saturation in a patient with an 8-year history of generalized seropositive rheumatoid arthritis. A flexible fiber-optic laryngoscope showed the vocal cords to be fixed in a midline position and no movement could be elicited and reported uncomplicated recovery after cervical tracheotomy. Another complication is cricoarytenoid arthritis with upper esophageal ulceration [51]. A difficult manageable complication of laryngeal involvement noted extra-airways obstruction due to laryngeal deviation associated with cervical vertebra ankylosis in R.A. One of the harmful states in laryngeal involvement reviewed choking during vocal cord paresis (Fig. **2**).

6. LOWER AIRWAYS INVOLVEMENT

Lower airways include the larynx portion below the vocal folds, trachea, bronchi, bronchioles, and alveolar is the last part of the airway encased with a single-cell layer of

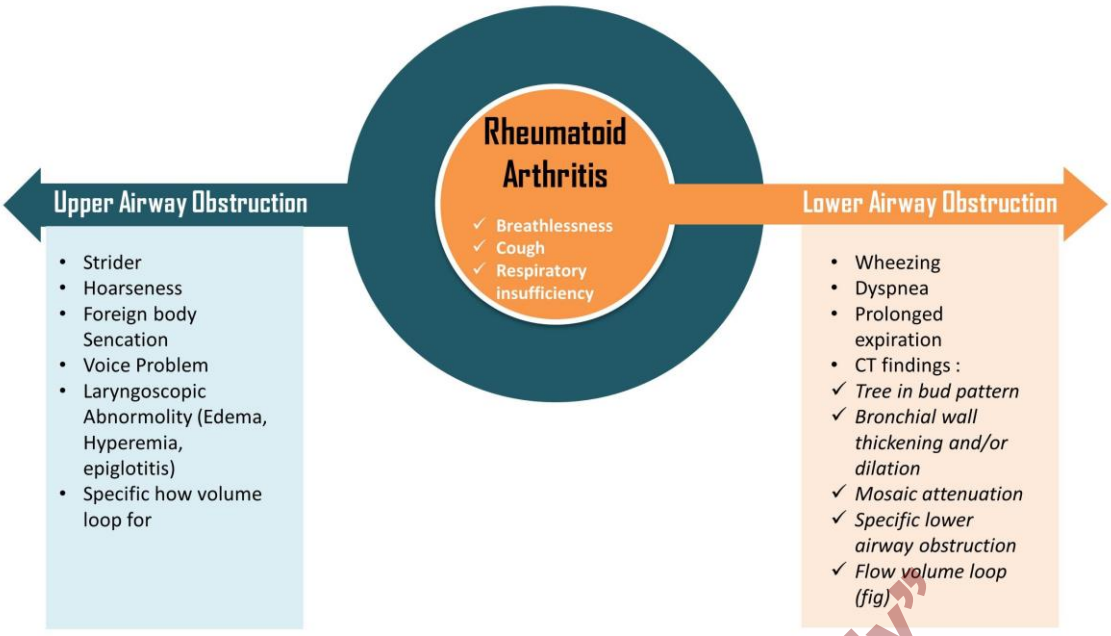


Fig. (2). Schematic illustration and summary of the symptoms and the clinical findings of the rheumatoid arthritis, upper airway obstruction and lower airway obstruction. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

pneumocytes. Although, lower airways are further divided into large airways with >2mm in diameter and small airways with <2mm in diameter. Any anatomical or pathophysiological abnormality in these organs is defined as lower airway involvement. The airways' most vital and significant function is to allow free air access to the distal endobronchial segment. They also play a significant role in immune defense, humidification, and filtration of the inhaled air in the lungs [52]. In worldwide literature, the lower airways' main pathological conditions are bronchial hyperresponsiveness or bronchial obstruction, the inflammatory process of bronchus and bronchioles as the small airways' involvement, and abnormal dilation of the bronchus or bronchiectasis. The pervasiveness of bronchiolar complicity ranges in extent from < 10% to >60% [53].

The most common pulmonary symptoms can be chronic cough, sputum production, and wheezing. Pulmonary examination reveals crackles and wheezing [54]. Diagnosis of lower airway involvement is based on pulmonary function test (PFTs) and high resolution computed tomography (HRCT). Recommended PFT findings in airways involvement are obstruction, and air trapping,/elevated residual volume [55]. The diagnosis for airway obstruction is generally considerable based on the results of the ratio of the Forced Expiratory Volume in 1 second (FEV_1) to Forced Vital Capacity (F.V.C.) that is below 70%, and FEV_1 also predominantly manifests the obstruction in the large airways. The inspection and analysis of the mid-portion of the expiratory flow may reveal more details about the small airways' pathology. Between 25% to 75%, the Forced Expiratory Flow of the F.V.C. (FEF_{25-75}) is a considerable specific index of small airway function. Several studies suggested a significant decrease in FEF25%, FEF50%, and FEF75% as small airway obstruction in rheumatoid arthritis [56-58]. Another study shows the drawback is the FEF_{25-75} sensitivity because it shows unremarkable results if FEV_1/FVC is more than 75% [59]. The study of airway obstruction in rheumatoid arthritis by Geddes *et al*. determined the presence of airflow obstruction in a patient having a normal X-ray of the chest [60].

When it comes to rheumatoid arthritis and airway involvement, the results of a high-resolution C.T. scan and a lung function test have been almost significantly linked. French researchers found that the most frequent HRCT findings were: bronchiectasis (30.5%), pulmonary nodules (28%), and air trapping (25%). In contrast, a retrospective study by G. Devouassoux showed bronchiectasis (40%), diffuse lung infiltrates (44%), and diffuse pulmonary hyperinflation (64%). Nodular shadows and diffuse alveolar opacities were noted with a slight frequency of 16% and 32% in each case [8]. Assessed radiological criteria of the airway involvement were mosaic attenuation and hyperinflation, bronchial wall thickening, cylindrical bronchiectasis, and centrilobular pulmonary nodules. Mosaic attenuation is well recognized during expiration as patchy areas of hyperlucency due to air trapping from bronchiolar obstruction [61, 62].

7. AIRWAY OBSTRUCTIVE DISORDERS AND HYPERRESPONSIVENESS

The overall frequency of airway obstruction appeared as inflated in rheumatoid arthritis diseases. Thierry Perez *et al*. showed an increased number of airway involvement cases in patients with R.A. Further, they found an obstructive pattern through a reduced FEV_1/VC ratio being 18%. A retrospective cohort study by Shen TC *et al*. reported patients with R.A. to have a significantly higher risk of developing COPD than the control population [63]. A prospective study from

the United Kingdom suggested that airflow obstruction and bronchial reactivity were significantly increased in patients with R.A. and explained one of the possible mechanisms of airway obstruction being the mucosal edema secondary to pre-existing airway inflammation rheumatoid arthritis. As per Nouvet *et al*., 50% of the rheumatoid arthritis cases had obstructive bronchial disorders. The results of other prospective case-control studies showed the increased number of obstructive syndrome cases among rheumatoid arthritis patients [64].

8. BRONCHIOLITIS IN R.A.

Bronchiolitis can be presented as constrictive bronchiolitis obliterans or follicular bronchiolitis. The narrowing and the shrinkage of the lumen are observed in both of these cases. However, bronchial-associated lymphoid tissue (BALT) results in follicular bronchiolitis. It is a placid state determined by an inflammatory pattern and the germinal center-like structure with distinct histopathological characteristics. A mild restrictive disease diagnosed with the pulmonary function test (PFTs) does not need any precise treatment other than R.A., and HRCT assists in the detection of centrilobular peribronchial nodules and thickening of the wall [65].

On radiographs, dyspnea and cough progress with no evidence of parenchymal lung illness characterized as obliterative bronchiolitis (O.B.). Inhaled bronchodilators usually do not reverse an obstructive ventilatory impairment shown by pulmonary function tests. In most instances, clinical, physiological, and radiological data eliminate the necessity for open lung biopsy's higher risk.[66] Transbronchial biopsies are not sensitive enough to provide a diagnosis. A number of exposures have been linked to this diagnosis, including fragrance plant gases, fire pit smoke, and ambient sulfur gas [67, 68]. In most cases, R.A. patients with bronchiolitis are asymptomatic or low-symptomatic. [69].

Airflow blockage is shown by spirometry and does not improve after an inhaled bronchodilator challenge, as expected. The FEV1 (forced expiratory volume in one second) and FEV1/FVC (forced vital capacity to forced expiratory volume in one second) ratios would be decreased. Air trapping has the potential to raise T.L.C. by causing hyperinflation.[70] In most cases, the DLCO (diffusion-limited capacity) is decreased. Bronchiolitis obliterans syndrome stage in lung transplant is determined by the amount of FEV1 decrease from the post-transplant value [71, 72].

Imaging tests such as chest radiographs may reveal no abnormalities or show indications of hyperinflation in the early stages of illness. Bronchial wall thickening, mosaic pattern, and patchy hypoattenuation are all possible findings on chest C.T. scans [73]. Because of air trapping from small airway illness, a mosaic pattern will remain in dynamic pictures with inspiratory and expiratory films. This leads to increasing airflow obstruction as well as debility because of immunologic and non-immunologic processes in all cases [74].

A substantial percentage of patients will not react to immunosuppression enhancement, although it is sometimes helpful in delaying or reversing the course of illness. Every time this disease is discovered, other immunomodulatory treatments have been tried. There are still many unknown facts about O.B., which leads to rapid disease progression and the need for transplantation as a last resort (or retransplantation) [75].

The formation of lymphoid follicles with germinal centers in the walls of tiny airways is a characteristic of Follicular bronchiolitis (F.B.), which is also known as hyperplasia of associated lymphoid tissue (BALT) or bronchiolar nodular lymphoid hyperplasia. Polyclonal lymphoid hyperplasia follows antigenic stimulation of BALT in the development of F.B. Lymphoproliferative pulmonary illnesses are a category of reactive pulmonary lymphoid disorders (L.P.D.s) [76]. The diagnostic "F.B." is used to describe many medical conditions, including connective tissue diseases (CTDs), immunological deficiencies (AIDS), autoimmune disorders (A.D.s), infections (I.A.I.s) and obstructive airway illnesses (O.A.I.s) (I.L.D.s). There are considerable variations in therapy and prognosis of different types of L.P.D.s. Therefore its features must be carefully recognized and distinguished from those of other closely similar illnesses [77].

9. THE PATTERN OF IDIOPATHIC PULMONARY FIBROSIS AND USUAL INTERSTITIAL PNEUMONIA:

Pneumonary fibrosis can manifest itself in a wide range of medical conditions and ailments other than asthma [78]. The identification of whether or not there is an indication of systemic disease or exposure to environmental irritants is critical in the examination of patients. Since the natural history and potential therapeutic responses to pulmonary fibrosis vary based on the etiology, classification performance is critical [79]. Pulmonary fibrosis is usually associated with connective tissue illnesses, including rheumatoid arthritis and systemic sclerosis (scleroderma), and the diagnostic is generally established with reasonable certainty [80]. On the other hand, other connective tissue illnesses are less well understood, and the lung is often the first organ to show symptoms of connective tissue disease. Since some sorts of connective tissue disease-related fibrosis are reversible, it is essential to evaluate whether or not an underlying connective tissue problem exists. A biopsy of the surgically removed lung tissue reveals a uniform pattern of fibrosis and chronic inflammation, as well as a scarcity of healthy lung tissue in the area. There were no foci of fibroblasts seen. Fibrotic nonspecific interstitial pneumonia is the medical term for this type of fibrosis (NSIP) [81].

The reticular opacities on chest C.A.T. scan are distinct in individuals with I.P.F., who also suffer from lung disease. Traction bronchiectasis thickened interlobular septae, and subpleural honeycombing are all shown on standard imaging. I.P.F. may be diagnosed with certainty when all three of these symptoms are observed, and there is no

evidence suggesting a related connective tissue illness or environmental exposure [82]. It follows, then, that in the event of a surgical lung biopsy, a (U.I.P.) will almost certainly be seen (>90 percent). In U.I.P., fibroblastic foci, microscopic honeycombing, and a variegated pattern of chronic interstitial fibrosis with accentuation underneath the pleura are all features that identify the condition as having U.I.P [83, 84]. The treatment with immunosuppressive medication such as prednisone and Azathioprine is unsuccessful if these patterns are shown on the chest C.A.T. scan and a bronchial biopsy. Prednisone, Azathioprine, and N-acetyl cysteine were all ineffective when combined in an NIH-sponsored research. The study was discontinued midway through for lack of results [85].

Even in individuals who do not have an idiopathic illness, a U.I.P. pattern can be detected on lung biopsies; in particular, patients with hypersensitivity pneumonitis and connective tissue disorders may exhibit a U.I.P. pattern. This can complicate pulmonary fibrosis clinical treatment [86]. An abnormal chest C.A.T. scan in patients with the illness exhibits lower-lobe predominance reticular opacities and traction bronchiectasis. Changes in the subpleural honeycomb, on the other hand, are inconclusive. There were no microscopic honeycomb alterations and few fibroblastic foci in the surgically performed lung biopsy, which revealed a varied pattern of chronic interstitial pneumonia [87]. Mononuclear inflammation also occurred away from the site of the developed collagen deposit. Clinically, connective tissue serologies failed to identify the presence of the illness, but immunosuppressive treatment stopped it in its tracks, keeping lung function constant while improving oxygen desaturation when walking [88]. This particular kind of pulmonary fibrosis has not been thoroughly studied, and it serves as a reminder of the complexity of pulmonary fibrosis' phenotypes. For doctors to correctly identify patients who would benefit from immune-modulating treatment, the capacity to discriminate between I.P.F. and U.I.P. and other types of pulmonary fibrosis is critical [89].

10. BRONCHIECTASIS IN R.A.

The term bronchiectasis was first described by Laennec in 1819 as an abnormal and permanent widening of bronchi, resulting in vulnerability to infection due to mucous accumulation. The significant clinical features include the non-productive and productive cough, though it can be clinically silent. High-resolution computed tomography (HRCT) is considered to be more accurate and precise for the diagnosis. The diagnostic criterion of HRCT includes the bronchi visualization in the outer 1-2 cm of the lung fields and the bronchus diameter wider than its pulmonary artery [90].

Pulmonary function test (PFT) is nonspecific. Several authors documented obstructive and restrictive pattern PFT. There have been a large number of factors that have been related as contributive to bronchiectasis. One of the important etiologic factors described rheumatoid arthritis. The association between bronchiectasis and R.A. has been described since 1940. The prevalence of bronchiectasis in patients with R.A. has been estimated to be between 0.6±3.1% [91]. NA Shadick proposed that bronchiectasis can be a feature of rheumatoid arthritis and is often found in patients with the severe, long-standing and nodular disease. A study by M. Kristen Demoruelle *et al*. reported airways abnormalities in R.A.-related autoantibody-positive individuals without apparent inflammatory arthritis, suggesting that the lung is an early target or potentially a site of initial generation R.A. related autoimmunity [92]. Controversially MJ McMahon explained that bronchiectasis is not an extra-articular manifestation of rheumatoid disease and it does not lead to a more aggressive disease course in R.A. In an observational study from Arabia using HRCT scan of the chest, 35% of cases of bronchiectasis in R.A. patients were found, which suggested that bronchiectasis is often asymptomatic [93].

The association among anti-CCP, R.F., and bronchiectasis propounded that bronchiectasis patients' screening for R.F. and R-F positive patients for anti-CCP will empathize the possibility for the further development of R.A. [94]. Also, the risk of infection in the lower airways is a bit higher during the course of disease-modifying treatment and biologics for rheumatic disease [95, 96].

11. MANAGEMENT OF AIRWAY INVOLVEMENT IN R.A.

The treatment in the acute phase of upper airway involvement may be medical, phoniatric, or surgical and consists of administration of steroids, cool tracheostomy humidification of inspired air, anti-inflammatory agents, and logopedic therapy. In chronic cases, mainly arytenoidectomy with lateral cord fixation is recommended [97]. Treatment of cricoarytenoid arthritis should be directed against systemic disease and treatment of current infection. Oral steroids are the first-line treatment both for autoimmune disease and for laryngeal lesions. Prednisone and methotrexate are most frequently used. Jelena Todic *et al*. suggest that an effective and first-line treatment is speech therapy. Tracheotomy indicates severe laryngeal obstruction. Relief of acute respiratory symptoms suggested corticosteroids and use of topical hydrocortisone spray [98]. Habib *et al*. reported improved vocal cord abduction and swelling of the arytenoids region after Intra-articular (intra-cricoarytenoid joint) steroid injection [99].

There are no standard treatment- guidelines for managing lower airway involvement in R.A. in the literature. The management recommended a focus on minimizing R.A. disease activity. Proposed recommendation patients suspected with respiratory tract involvement should undergo a review by chest physician with regular 3-6 months' monitoring with clinical examination, PFT, screening for bacterial colonization by sputum culture, and radiological assessment. Symptomatic treatment is suggested for lower airway disease with bronchodilators, antibiotics for bacterial infection, and oxygen therapy, and airway clearance physiotherapy in case of sputum production. Several authors analyzed that treatment with bronchodilators, and oral corticosteroids remained ineffective in most of the cases [100, 101].

CONCLUSION

Mechanisms of airway involvement have been attributed to genetics, environmental exposure, and airway colonization by pathogenic microorganisms. The PFT is helpful in the diagnosis of upper airway obstruction, however nonspecific in lower airway involvement. It should be correlated with specific clinical symptoms and radiological findings. Every condition accompanying stridor or hoarseness, voice problem or cough, and dyspnea should be seen by a specialist or undergo an immunologic check-up. Special attention should be paid to the clinical symptoms and purposeful treatment plan in primary settings.

AUTHORS' CONTRIBUTIONS

All the authors read, edited, and approved the manuscript.

LIST OF ABBREVIATIONS

A.R.F.	=	Acute Respiratory Failure
ANTI-CCP	=	Anti-Cyclic Citrullinated Peptides
BALT	=	Bronchial Associated Lymphoid Tissue
CA	=	Cricoarytenoid Joint
COPD	=	Chronic Obstructive Pulmonary Disease
DLCO	=	Diffusing Capacity of Carbon Monoxide
F.E.F.	=	Forced Expiratory Flow
F.E.V.	=	Forced Expiratory Volume
F.V.C.	=	Forced Vital Capacity
FB	=	Follicular Bronchiolitis
HRCT	=	High Resolution Computed Tomography
NSIP	=	Non-Specific Interstitial Pneumonia
OAI	=	Obstructive Airway Illness
OB	=	Obliterative Bronchiolitis
PFTS	=	Pulmonary Function Test
R.F.	=	Rheumatoid Factor

CONSENT FOR PUBLICATION

Not Applicable.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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