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Tomographic pleuropulmonary manifestations in rheumatoid arthritis: a pictorial essay

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune inflammatory and heterogeneous disease that affects several systems, especially the joints. Among the extra-articular manifestations of RA, pleuropulmonary involvement occurs frequently, with different presentations, potentially in all anatomic thoracic compartments, and may determine high morbidity and mortality. The most common pleuropulmonary manifestations in patients with RA include interstitial lung disease (ILD), pleural disease, pulmonary arterial hypertension, rheumatoid lung nodules, airway disease (bronchiectasis and bronchiolitis), and lymphadenopathy. Pulmonary hypertension and ILD are the manifestations with the greatest negative impact in prognosis. HRCT of the chest is essential in the evaluation of patients with RA with respiratory symptoms, especially those with higher risk factors for ILD, such as male gender, smoking, older age, high levels of rheumatoid factor, or positive anti-cyclic citrullinated peptide antibody results. Additionally, other etiologies that may determine tomographic pleuropulmonary manifestations in patients with RA are infections, neoplasms, and drug-induced lung disease. In these scenarios, clinical presentation is heterogeneous, varying from being asymptomatic to having progressive respiratory failure. Knowledge on the potential etiologies causing tomographic pleuropulmonary manifestations in patients with RA coupled with proper clinical reasoning is crucial to diagnose and treat these patients.

Keywords: Lung diseases, interstitial; Lung diseases; Pleural diseases; Pulmonary arterial hypertension; Arthritis, rheumatoid; Tomography.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune rheumatic disease that most commonly affects the joints. Pleuropulmonary manifestations are common and significantly contribute to increase morbidity and mortality in RA, affecting up to 60% of the patients during the disease course. All anatomic thoracic compartments can be involved in RA, including the pleura and pulmonary parenchyma, as well as small and large airways.[1-3] Clinical presentation is heterogeneous, varying from being asymptomatic to having progressive respiratory failure, and may have acute or insidious onset.[1,4] Pulmonary involvement in RA usually occurs within five years after the diagnosis of RA, but it is important to reinforce that it may precede the articular involvement.[2,3]

To evaluate the different pleuropulmonary manifestations of RA, CT is essential because it allows not only the detailing of the lesions, but also their precise location. Additionally, CT is important to assess other etiologies that may determine pulmonary lesions in patients with RA, such as infections, drug-induced lung disease (DILD), neoplasms, and response to treatment.[5]

Although there is no formal recommendation to screen patients with RA for the presence of pleuropulmonary involvement, screening may be recommended in those with respiratory symptoms and/or changes in pulmonary examinations, CT scans, or pulmonary function tests. Additionally, patients with a higher risk of pulmonary involvement due to factors such as male gender, older age, smoking, positive results for anti-cyclic citrullinated peptide antibodies, or high titers of rheumatoid factor should undergo CT and pulmonary function evaluation.

The main pleuropulmonary manifestations that may occur in patients with RA include interstitial lung disease (ILD), pleural disease, pulmonary arterial hypertension (PAH), rheumatoid lung nodules, airway disease (bronchiectasis and bronchiolitis), lymphadenopathy, and DILD.

The objective of this pictorial essay was to present the main tomographic pleuropulmonary manifestations that may be identified in patients with RA (Chart 1).

ILD

ILD is one of the most common pulmonary manifestations of RA and the second leading cause of mortality, primarily

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Chart 1. Summary of the main pleuropulmonary manifestations of rheumatoid arthritis.

Disease pattern	Radiological manifestations	Other features
Usual interstitial pneumonia	Basilar and peripheral traction bronchiectasis, with or without honeycombing	Most common ILD pattern (60%)
		Worst prognosis among all ILD patterns
	Exuberant honeycombing, straight edge sign, and anterior upper lobe involvement	
Nonspecific interstitial pneumonia	Basilar and peripheral ground-glass opacities and fine reticulation; traction bronchiectasis	Association with longer duration of joint disease, lower risk of disease progression, and greater treatment response
	Usually symmetric	
	Subpleural sparing may occur	
Organizing pneumonia	Peripheral and peribronchovascular consolidation; ground-glass opacities	Abnormalities are often fleeting or migratory
	Nodules and reversed halo sign may occur less frequently	Usually has good prognosis
Lymphocytic interstitial pneumonia	Lower lobe-predominant and peribronchovascular thin-walled cysts	More commonly associated with Sjögren's syndrome
	Ground-glass opacities and septal thickening	
Desquamative interstitial pneumonia	Ground-glass opacities and mild reticulation	Rare and may precede the onset of RA by years
	Cysts may be found	
	Basal and peripheral predominance	
Inflammatory pleural effusion	Usually unilateral with small pleural enhancement	Most patients are asymptomatic
		Usually exudative with low glucose levels, low pH levels, high LDH levels, high rheumatoid factor titers, low total complement activity, and low C3 and C4 levels
Pulmonary arterial hypertension	Enlarged pulmonary arteries, dilatation of right-sided cardiac chambers, and right ventricular hypertrophy	Rare and usually seen in older patients with long-standing RA-ILD
	Mosaic attenuation in the lungs as an indirect sign	
Rheumatoid lung nodules	Round opacities with variable size, usually multiple and cavitated	Usually asymptomatic and associated with subcutaneous nodules
	Usually in the subpleural region	
Bronchiectasis	Cylindrical, varicose, and cystic bronchiectasis may occur	Chronic suppurative infections, treatment with disease-modifying antirheumatic drugs, and genetic predisposition may be related to bronchiectasis
Constrictive bronchiolitis	Bronchial wall thickening, bronchiectasis, and mosaic attenuation pattern	More common in females and in those with long-standing untreated disease Airflow obstruction and air trapping in pulmonary function tests
Follicular bronchiolitis	Small centrilobular nodules with branching structures (tree-in-bud sign) Air trapping and peribronchovascular and septal thickening may also occur	Associated with RA or Sjögren's syndrome

Continue...▶

Chart 1. Summary of the main pleuropulmonary manifestations of rheumatoid arthritis. (Continued...)

Disease pattern	Radiological manifestations	Other features
Caplan Syndrome (rheumatoid pneumoconiosis)	Multiple peripheral lung nodules with cavitations or calcifications in some cases	Associated with exposure to coal, asbestos, or silica May precede the onset of RA by more than 10 years Most patients are asymptomatic
Lymphadenopathy	Mediastinal or axillary	Approximately 70% of patients with RA Patients may show signs of inflammatory activity
Drug-induced lung disease	Patterns suggestive of hypersensitivity pneumonitis, eosinophilic pneumonia, pulmonary edema, organizing pneumonia, and diffuse alveolar damage	Secondary to immune-mediated reaction or direct toxicity Diagnosis usually based on symptoms, tomographic pattern, and time between treatment initiation and drug discontinuation Symptoms usually improve with drug discontinuation

ILD: interstitial lung disease; and RA: rheumatoid arthritis.

owing to respiratory failure, superimposed infection, and lung cancer.[6,7] ILD is responsible for 10-20% of RA-related mortality, and approximately 10% of patients have clinically significant disease. RA-ILD may determine a variable spectrum of presentations, from acute to chronic ones, including diffuse alveolar damage (DAD), organizing pneumonia (OP), and fibrotic disorders.[8]

Risk factors for RA-ILD include smoking, male sex, older age, duration/activity of RA, and seropositivity for rheumatoid factor or anti-cyclic citrullinated peptide antibodies.[2,9] Patients with RA rarely need to undergo lung biopsy to confirm the diagnosis of ILD, which is most of the time based on tomographic patterns.

Usual interstitial pneumonia associated with RA

Usual interstitial pneumonia (UIP) is the most common ILD pattern in RA, with a prevalence of about 60%. UIP carries the worst prognosis among all patients with ILD secondary to RA, the surviving rates being quite similar to those of patients with idiopathic pulmonary fibrosis (IPF).[10] The main CT features are basilar and peripheral traction bronchiectasis and/or bronchiolectasis, with or without honeycombing, and minimal or absent ground-glass opacities.[2,11] The imaging presentation of RA-UIP and IPF may be identical. Chung et al.[12] have described three features favoring the presence of autoimmune rheumatic diseases as the etiology of UIP over IPF: exuberant honeycombing; straight edge sign, characterized as the isolation of fibrosis in the lower zones with sharp demarcation between fibrotic and normal lung in the craniocaudal plane and without substantial extension of fibrosis along the lateral margins at coronal imaging; and anterior upper lobe involvement (Figure 1).

Nonspecific interstitial pneumonia and other ILD patterns

Nonspecific interstitial pneumonia (NSIP) is the second most common ILD pattern in RA, occurring in around one-third of cases.[10] NSIP is associated with longer duration of joint disease, lower risk of disease progression, greater treatment response, and better outcomes when compared with UIP.[13] There is no difference in prognosis when comparing idiopathic NSIP with autoimmune rheumatic disease-associated NSIP.[7] CT findings in NSIP include basilar- and peripheral-predominant ground-glass opacities and reticulation, with or without immediate subpleural sparing, and traction bronchiectasis (Figure 2). The tomographic presentation of NSIP is typically homogeneous and symmetric, and traction bronchiectasis is often relatively central in comparison with UIP.[2,10,11]

The third most common ILD pattern in RA is OP, which tends to be more aggressive and to determine more symptoms than does cryptogenic OP.[7,14] Tomographic features of OP vary and commonly include peripheral and peribronchovascular consolidations, ground-glass opacities, and, less frequently, nodules (Figure 3). A reversed halo sign, characterized by a central ground-glass area surrounded by a complete or incomplete ring of peripheral consolidation, and perilobular opacities may also be identified. These abnormalities are often fleeting or migratory.[10,11]

Lymphocytic interstitial pneumonia (LIP) is a benign lymphoproliferative ILD that may occur in patients with RA, but more commonly occurs in association with Sjögren's syndrome (SS). Because secondary SS is the most common extra-articular manifestation in RA, affecting approximately 35% of patients, cases of LIP in RA may be associated with SS.[15] LIP is part of a continuum of reactive

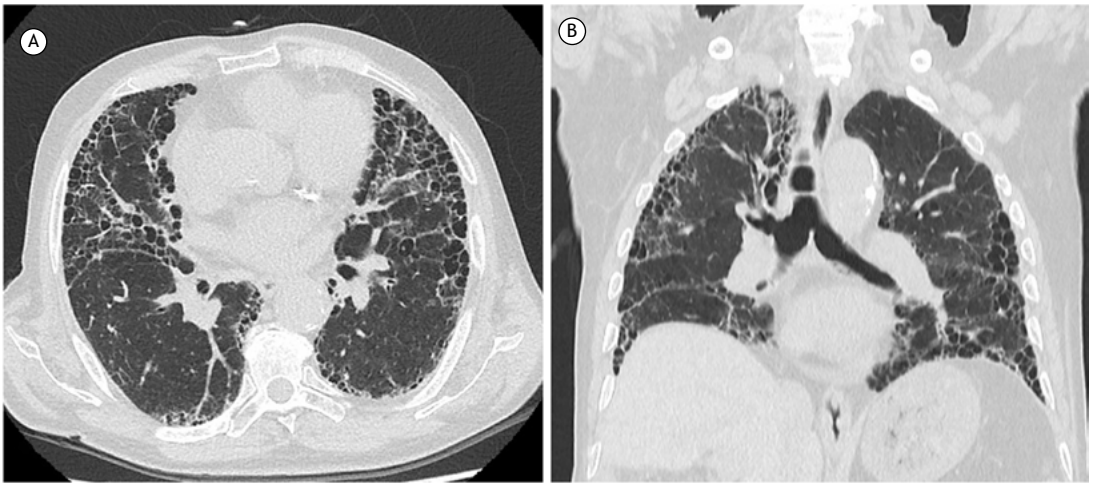

Figure 1. CT scans of an 87-year-old male patient with rheumatoid arthritis, usual interstitial pneumonia, and exuberant honeycombing. In A, axial reconstruction: large and predominantly peripheral cysts, and some areas with traction bronchiolectasis. In B, coronal reconstruction: lesions in the apicobasal axis.

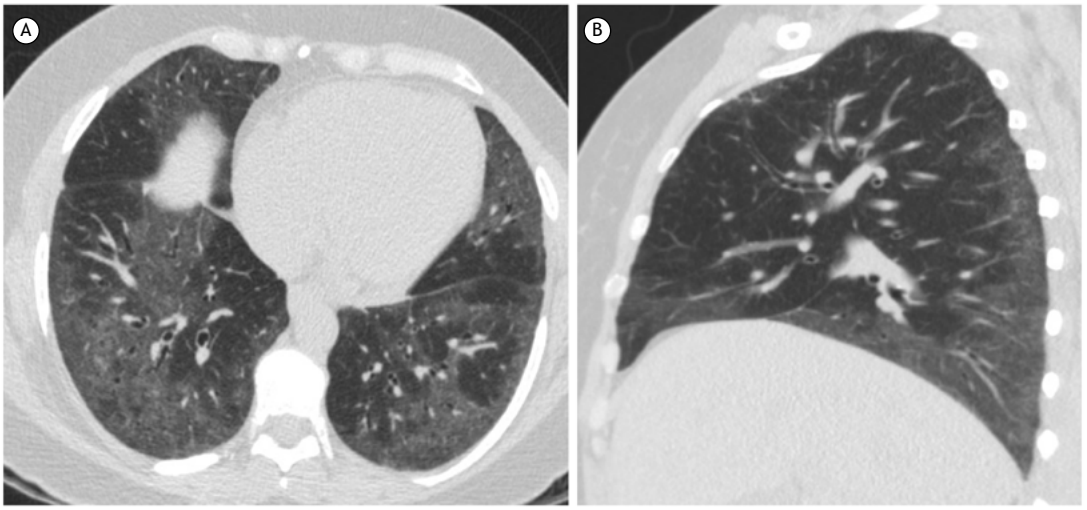

Figure 2. CT scans of a 37-year-old female patient with rheumatoid arthritis and nonspecific interstitial pneumonia. In A, axial reconstruction: diffuse ground-glass opacities and fine reticulation, predominantly in the lower lobes. In B, sagittal reconstruction showing subpleural sparing.

lymphoproliferation with follicular bronchiolitis. CT findings of LIP include lower lobe-predominant thin-walled cysts adjacent to vessels (perivascular distribution), with or without septal thickening and ground-glass opacities (Figure 4).[11,16]

Interstitial lung abnormalities (ILAs) and ILD are seen in up to 60% of individuals with RA, and some patients with such lesions may have disease progression with a significant impact on morbidity and mortality rates.[17,18] Estimates of the rate of imaging progression of ILAs range from 20% to 48% over five years. Additionally, the increase in the rate of mortality was most strongly associated with the imaging progression of ILAs, and specific imaging patterns indicative of pulmonary fibrosis were associated with earlier mortality.[19] Kawano-Dourado et al.,[17] in a retrospective study with patients with RA, quantified the initial CT pattern as compared to a second CT four years after the initial imaging. Of the 56 individuals with ILA/ILD, 21 (38%) had imaging evidence of disease progression. Subpleural distribution and higher baseline ILA/ILD extent were predictors of a higher risk of imaging progression. However, prospective longitudinal studies with patients with RA-ILA are necessary to better the understanding of the impact and the risk of progression of ILA.

Desquamative interstitial pneumonia (DIP) is a rare subtype of ILD. Although DIP is usually associated with exposure to tobacco smoke, some cases have been associated with autoimmune rheumatic diseases such as RA. Tomographic features of DIP[20] include ground-glass opacities with mild reticulation, basal and peripheral predominance, and, less frequently, cystic lesions (Figure 5).

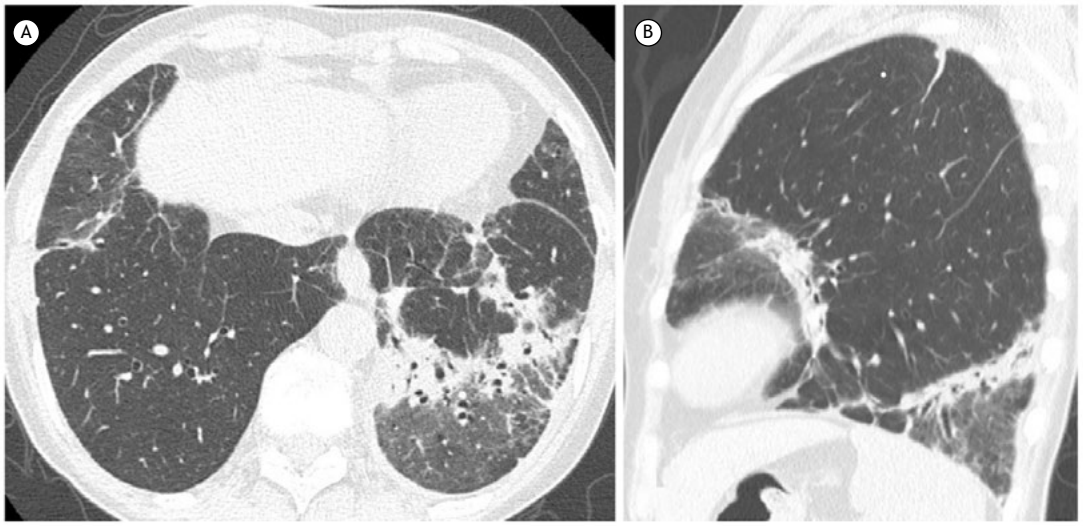

Figure 3. CT scans in axial (in A) and sagittal (in B) reconstructions of a male patient with rheumatoid arthritis. The scans demonstrate peripheral and peribronchovascular consolidations, which is compatible with organizing pneumonia.

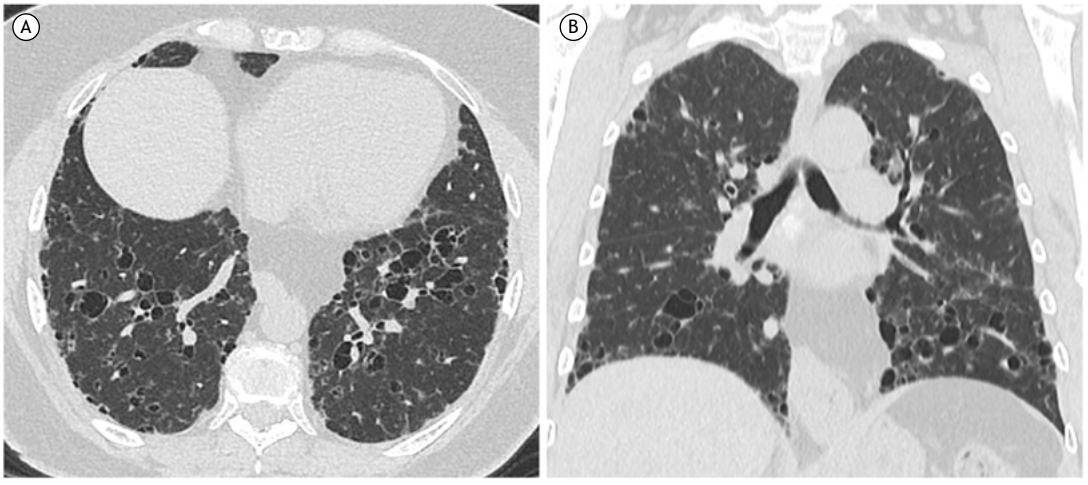

Figure 4. CT scans of a 60-year-old female patient with rheumatoid arthritis and lymphocytic interstitial pneumonia. Axial (in A) and coronal (in B) reconstructions show thin-walled cysts with variable sizes and discrete ground-glass opacities, predominating in the lower lobes and along the peribronchovascular bundle.

PLEURAL MANIFESTATIONS

Pleural disease is considered the most common thoracic manifestation in patients with RA and was identified in 73% of patients in a postmortem study.[21] However, most patients are asymptomatic, and few present with chest pain or dyspnea.[1,21] The most common pleural manifestations are effusions and pleurisy, with a prevalence of approximately 3% and 20%, respectively.[4]

Pleural effusion can occur due to pleural inflammation (Figure 6), infections, or RA-associated cardiac disease in patients with RA. Pleural effusions secondary to cardiac failure are usually bilateral, which is different from those secondary to pleural inflammation or infections, which are usually unilateral and present with small volume. Pleural effusion associated with inflammation is usually exudative with low glucose levels (≤ 25 mg/dL), low pH levels (< 7.3), high LDH levels (> 700 IU/L), high rheumatoid factor titers, and low total complement activity levels, as well as low C3 and C4 levels. Chronic pleural inflammation may result in pleural involvement with thickening of both parietal and visceral pleurae, which is quite similar to empyema. Pleural involvement can also be nodular, mimicking neoplasms.[4]

Pleural effusion may be transient, persistent, or relapsing, and when untreated or recurrent, pleuritis can lead to pleural fibrosis, trapped lung, and lung restriction.[1] Bronchopleural fistulae and pneumothorax are other less common findings that are usually associated with the rupture of rheumatoid lung nodules. Bronchopleural fistulae, immunosuppression, and chronic pleural disease fistulae increase the risk of empyema.[1,4]

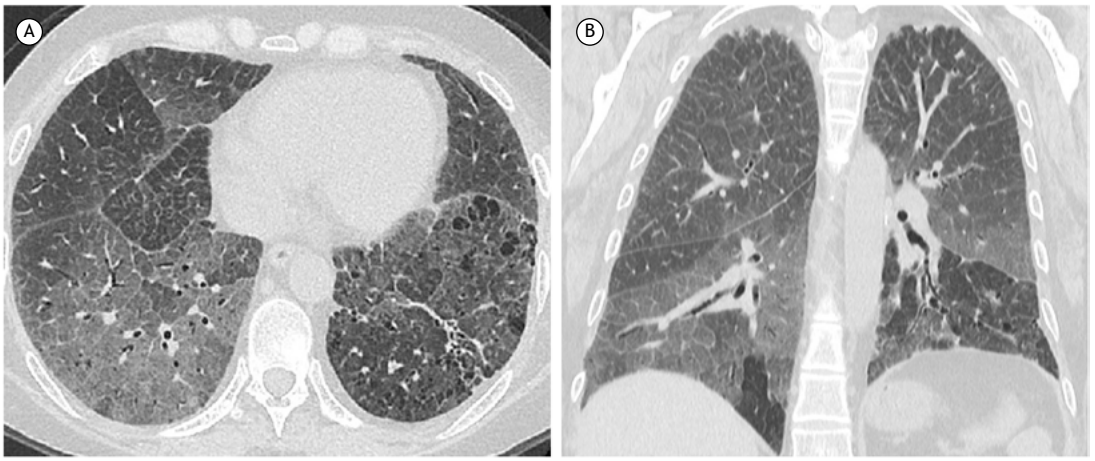

Figure 5. CT scans of a 45-year-old female patient with rheumatoid arthritis and desquamative interstitial pneumonia. Axial (in A) and coronal (in B) reconstructions demonstrate diffuse ground-glass opacities, interlobular septal thickening, and cysts, predominating in the lower lobes.

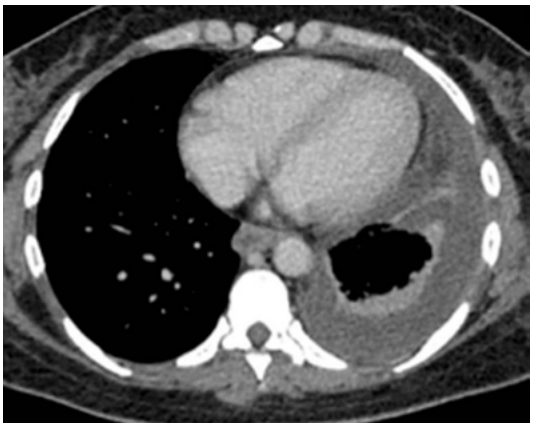

Figure 6. Axial reconstruction of a CT scan of a female patient with a left pleural effusion secondary to rheumatoid arthritis.

PAH

In patients with RA, PAH may be seen in isolation or in association with ILD. It is rare as an isolated finding in RA and is more common in older patients with long-standing ILD. PAH can lead to chronic respiratory failure and right heart failure, and it rarely occurs secondary to RA vasculitis.[1,4,22]

Direct CT findings of PAH are enlarged pulmonary arteries, main pulmonary artery diameter to ascending aorta diameter ratio > 1, dilatation of right-sided cardiac chambers, and right ventricular hypertrophy. Indirect signs in the lungs may be identified, such as mosaic attenuation, indicating regional differences in pulmonary perfusion.[1,4]

RHEUMATOID LUNG NODULES

Rheumatoid lung nodules or necrobiotic lung nodules are described in up to 20% of RA patients and are usually associated with subcutaneous nodules. Patients are frequently asymptomatic but may develop symptoms if nodules cavitate to the pleural space. Rheumatoid lung nodules are characterized on CT scans as round opacities, from few millimeters to several centimeters in size, typically located in the subpleural region, and are usually multiple and cavitated (Figure 7A).[23,24]

Because rheumatoid lung nodules have radiological characteristics quite similar to those of granulomatous and neoplastic diseases, they may represent a diagnostic challenge. Imaging features more commonly associated with rheumatoid lung nodules as compared to malignancy include multiplicity, smooth border, cavitation, satellite nodules, and pleural contact.[4,23] Histologically, rheumatoid nodules are composed of central fibrinoid necrosis surrounded by palisading epithelioid histiocytes and peripheral, chronic inflammatory cells.

The risk of malignancy in RA, such as primary lung cancer and lymphoproliferative disorders, particularly diffuse B-cell lymphoma, is overall 10% higher in comparison with that observed in the general population. Higher rates of malignancy may be explained by RA host factors, such as immune-mediated mechanisms, inflammation, viruses, and genetic predispositions, and non-RA risk factors, such as smoking, chronic lung inflammation, and pulmonary fibrosis.[4] Adenocarcinoma is the most common histopathological pattern of lung cancer in patients with RA,[23] followed by squamous cell carcinoma and small cell carcinoma (Figures 7B and 7C).

Caplan syndrome

Caplan syndrome (rheumatoid pneumoconiosis) was first described in a large cohort of coal miners with RA in 1953,[24] and it can be associated with exposure to coal, asbestos, or silica. The prevalence is less than 1% in the USA in autopsy series[25] and is more common in patients with silicosis. The disease is

characterized by the presence of multiple peripheral rheumatoid lung nodules and may precede the onset of arthritis by more than ten years. Radiographically, nodules tend to form rapidly and persist over years, approximately 10% of which developing cavitations or calcifications.[7] The nodules vary from 0.5 to 5 cm and may coalesce (Figure 7D).[4]

Most patients with Caplan syndrome are asymptomatic, and there is no impact on their pulmonary function test results.[3] Although a causal link between RA and dust exposure has not been completely established, it has been hypothesized that exposure to foreign particles leads to chronic immune activity that might facilitate the formation of autoantibodies, promoting the occurrence of RA. Indeed, pneumoconiosis may be associated with increased formation of immune complexes and increased rheumatoid factor levels, even without a definitive autoimmune diagnosis. The question of individual susceptibility remains unanswered.[2,26]

AIRWAY DISEASE

Bronchiectasis

Previous studies described bronchiectasis in 30-40% of RA patients.[4,27] Since bronchiectasis may be clinically silent, the real prevalence may be even greater (Figure 8). Chronic suppurative infections, treatment with disease modifying anti-rheumatic drugs, and genetic predisposition are some of the hypotheses associated with the development of bronchiectasis. Of note, a higher mortality rate was described in patients with RA and bronchiectasis than in those with either condition alone.[27]

Bronchiolitis

Constrictive and follicular bronchiolitis may occur in patients with RA. Constrictive bronchiolitis, also known as obliterative bronchiolitis, is characterized by bronchiolar inflammation with submucosal peribronchial fibrosis associated with luminal stenosis and occlusion. Although uncommon, it is a severe and

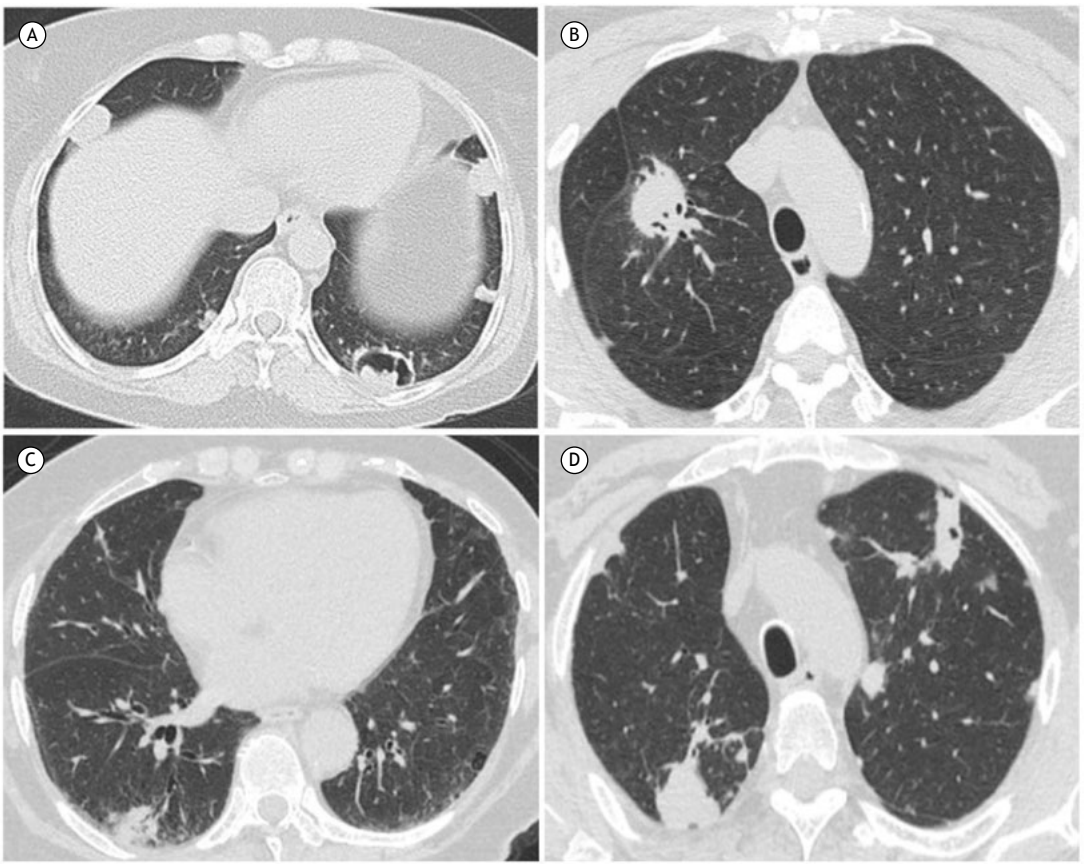

Figure 7. In A, a CT scan in axial reconstruction of a 50-year-old female patient with rheumatoid arthritis shows multiple bilateral subpleural nodules, the largest one being cavitated in the left lower lobe, which is compatible with rheumatoid nodules. In B, a CT scan in axial reconstruction of a patient with rheumatoid arthritis demonstrates a pulmonary nodule in the upper right lobe. Histopathological analysis was compatible with lung adenocarcinoma. In C, a CT scan in axial reconstruction of a patient with rheumatoid arthritis shows a pulmonary nodule in the lower right lobe. Histopathological analysis was compatible with lung adenocarcinoma. In D, a CT scan in axial reconstruction of a 68-year-old male patient with rheumatoid arthritis and Caplan syndrome demonstrates subpleural nodules predominantly in the upper lobes, one with central cavitation.

potentially fatal condition. Constrictive bronchiolitis in RA is more common in females and in those with positive rheumatoid factor results and long-standing untreated disease, but it may also occur secondary to use of medications, including sulfasalazine.[2,27] Patients usually develop progressive dyspnea, cough, and bronchorrhea, and it may occur in the absence of other systemic symptoms.[27] Pulmonary function tests usually show airflow obstruction and air trapping. Tomographic findings include bronchial wall thickening, bronchiectasis, and a mosaic attenuation pattern, with areas of decreased lung attenuation representing air trapping (Figure 9A). Additional expiratory CT images are helpful in this setting to confirm the presence of air trapping.[4]

Follicular bronchiolitis is characterized by reactive hyperplasia of bronchus-associated lymphoid tissue. It is usually secondary to autoimmune rheumatic diseases, mainly RA and SS, and has good prognosis. Tomographic features of follicular bronchiolitis include small centrilobular nodules with branching structures (tree-in-bud sign), corresponding to bronchial dilation, wall thickening, and mucoid impaction (Figure 9B). Air trapping and peribronchovascular and septal thickening may also be seen and correspond to proliferative lymphatic tissue.[4,27]

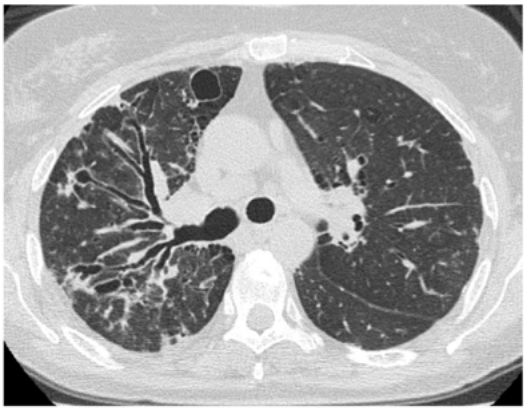

Figure 8. A CT scan in axial reconstruction of a 54-year-old female patient with rheumatoid arthritis demonstrates cylindrical, varicose, and cystic bronchiectasis in the right lung.

Lymphadenopathy

Axillary and mediastinal lymph node enlargement may occur in 20-70% of patients with RA, especially in those with RA-ILD.[4,28] The biology underpinning this enlargement remains unclear. However, migration of immune cells from the peripheral circulation through mediastinal lymph nodes to the lungs has been suggested to contribute to pulmonary fibrosis.[29] Furthermore, patients with either mediastinal or axillary lymphadenopathy showed significantly higher simple disease activity index than did those with no lymphadenopathy, which is a valid and sensitive tool to assess disease activity in patients with RA. Therefore, lymphadenopathy may be associated with signs of inflammatory activity in RA and is usually mild (Figure 10). Although lymphadenopathy in RA patients is mostly part of an inflammatory process, it is essential to exclude the presence of a malignant process or sarcoid reaction in those using TNF-α inhibitors.[4,30]

DILD

DILD in patients with RA can occur by immune-mediated reactions related to the mechanism of action of the drug or due to its direct toxicity and is usually associated with use of disease-modifying antirheumatic drugs and nonsteroidal anti-inflammatory agents.[1,4] The onset of DILD can be within days or years after treatment initiation with the suspected drug, but symptoms are nonspecific. The most common radiologic patterns of drug toxicity are: hypersensitivity reaction, resembling hypersensitivity pneumonitis,

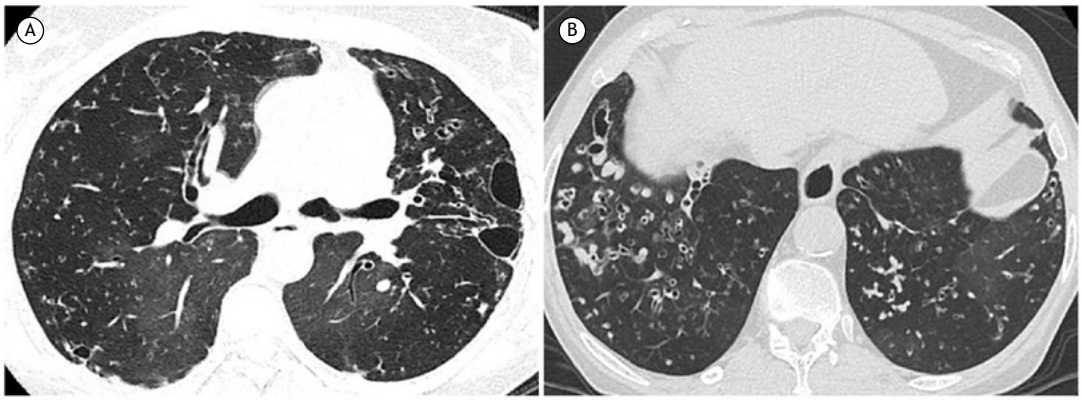

Figure 9. In A, a CT scan in axial reconstruction of a 60-year-old female patient with rheumatoid arthritis and constrictive bronchiolitis demonstrates bronchial wall thickening, bilateral centrilobular opacities, bronchiectasis, and mosaic attenuation pattern, compatible with air trapping. In B, a CT scan in axial reconstruction of a 50-year-old female patient with rheumatoid arthritis and follicular bronchiolitis shows diffuse small centrilobular nodules, tree-in-bud opacities, some bronchiolectasis, and bronchiolar wall thickening, predominating in the lower lung zones.

eosinophilic pneumonia, pulmonary edema, OP, and DAD. The diagnosis is based on clinical and imaging findings, as well as the time between treatment initiation and drug discontinuation and, less frequently, on histopathological findings. The main differential diagnoses include RA-ILD progression or exacerbation, infection, and cardiogenic pulmonary edema.[4]

Methotrexate-induced lung disease is the archetype of drug-induced pulmonary toxicity in patients with RA, usually occurring early with the beginning of therapy. The most common CT and histologic findings of methotrexate-induced lung disease are similar to those of hypersensitivity pneumonitis (Figures 11A and 11B). Other patterns include OP and DAD. Symptoms usually improve with drug discontinuation.[4] In a case-control study[31] with discovery and international replication samples, the association of methotrexate exposure with ILD was evaluated in 410 patients with chronic fibrotic ILD associated with RA (RA-ILD), and 673 patients with RA without ILD. The results suggested that methotrexate use was not associated with an increased risk of RA-ILD in patients with RA and that ILD was often detected later in methotrexate-treated patients.[31]

The use of TNF-α inhibitors is frequently associated with infectious and noninfectious granulomatous lung disease, DAD, and, less often, pulmonary fibrosis. Sarcoidosis-like disease in patients with RA is more common in those that received etanercept. Tomographic features are similar to the typical findings of sarcoidosis, including micronodules and lymphadenopathy (Figures 11C and 11D). Another pattern that can occur is OP, associated with DAD or as a distinct DILD. Rituximab is used in patients with an inadequate TNF-α inhibitor response and can also lead to DAD and OP.[4]

Leflunomide can lead to ILD exacerbation, accelerated formation of pulmonary rheumatoid nodules, and diffuse alveolar hemorrhage. Nonsteroidal anti-inflammatory drugs, including ibuprofen, aspirin, and acetaminophen, have been reported as potential etiologies for DILD and may present as allergic-type reactions, such as eosinophilic pneumonia and pulmonary edema.[1,4]

FINAL CONSIDERATIONS

It is essential to evaluate the presence of respiratory symptoms and objective pleuropulmonary involvement regularly in patients with RA due to the high prevalence of pleuropulmonary manifestations and their potential to increase morbidity and mortality. ILD is associated with worse prognosis, mainly the UIP pattern.

CT is an indispensable tool to evaluate the several potential pleuropulmonary manifestations that may occur in patients with RA and often allows the establishment of a diagnosis without the need of histopathological analysis. The widespread use of CT increased the identification of such manifestations, although the differential diagnoses are variable and often challenging, including infections, DILD, and neoplasms.

AUTHOR CONTRIBUTIONS

GPB and MVYS: study design; data collection; data analysis; and drafting and review of the manuscript. MW: data collection; data analysis; and drafting and review of the manuscript. LVSS: data collection; and drafting and review of the manuscript. RAK and LKD: data analysis; and drafting and review of the manuscript. BGB: guarantor of the study; study design; data collection; data analysis; and drafting and review of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

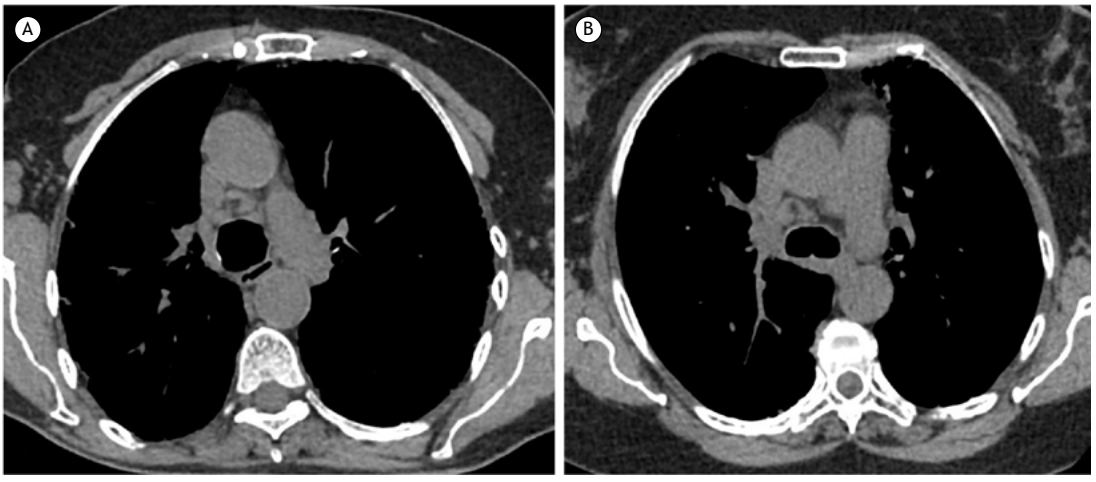

Figure 10. CT scans in axial reconstructions of a 64-year-old female patient with rheumatoid arthritis show mediastinal lymph node enlargement.

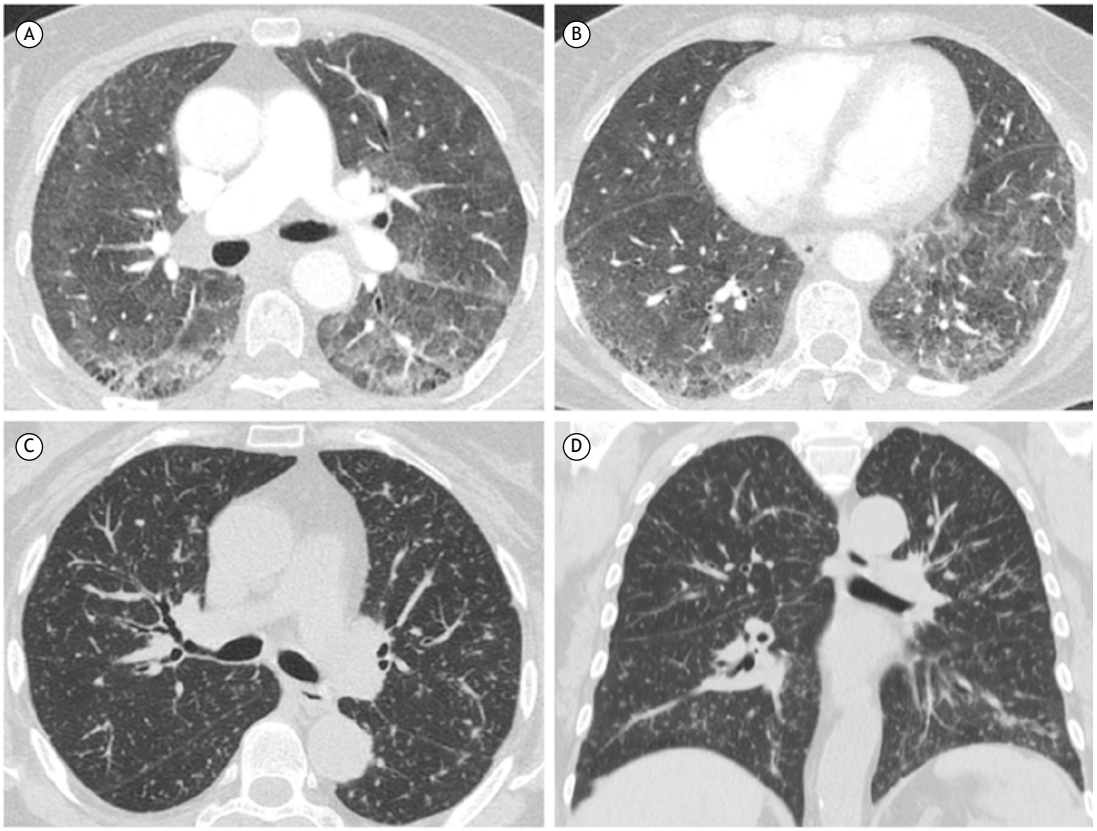

Figure 11. Drug-induced lung disease. In A and B, CT scans in axial reconstructions of a patient with rheumatoid arthritis and lung toxicity associated with the use of methotrexate demonstrate diffuse ground-glass opacities, compatible with hypersensitivity reaction. In C and D, CT scans in axial reconstructions of a patient with rheumatoid arthritis and sarcoid-like reaction associated with the use of TNF-α inhibitor demonstrate diffuse, predominantly perilymphatic, micronodules.

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