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Review Article

Rheumatoid Arthritis Associated Lung Complications

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Abstract

Rheumatoid arthritis is the most common rheumatological disease worldwide with many articular and extra-articular complications, associated with comorbidities and mortality. Cardiac and pulmonary complications contribute the most towards morbidity, mortality and pose a great difficulty in the RA management. Many of the rheumatoid related lung complications can mimic other diseases such as infections and malignancies. Though the advancement in treatment of rheumatoid arthritis has improved many articular complications, but it has also increased risk of many pulmonary complications such as infections and drug related toxicities. Also, some of the very effective treatment options can't be used in the presence of these rheumatoid related lung issues. It's important to understand these respiratory complications for the management of patients with rheumatoid arthritis which are seen by almost every doctor. The purpose of this review article is to provide insight into these pulmonary issues associated with rheumatoid arthritis and their management in the light of recent evidence.

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease mainly causing synovitis and deforming arthritis. Extra-articular complications (EAC) are defined as the pathologies not directly related to joint disease. RA has extra-articular complications (EAC), especially cardiovascular and respiratory, which increase morbidity, and mortality.[1] EAC of RA occurs in approximately 40-50% of cases and needs aggressive treatment.[2] These are often complications due to vasculitis, chronic inflammatory process, and nodules, often more in severe RA and are most directly related to RA factor titer.[3] EAC can involve many organs, especially skin, cardiovascular, lungs, peripheral nervous system, ocular, and haematological. However, CNS, kidneys and GIT involvement due to RA per se are less common but these organs are often involved due to RA related medications or amyloidosis or systemic vasculitis.[4] The prevalence of most EAC in RA patients has decreased due to more effective therapies such as Disease Modifying Anti Rheumatoid Drugs (DMARDs). However, the incidence of RA related lung disease has not declined, and this could be due to increased diagnostic skills and increased survival of the RA patients.[2]

This review will mainly focus on RA related lung diseases and their clinical significance **(Table-1)**. In some patients, lung involvement can start before articular manifestations in 10-20% of

cases[5]. Hence, it's essential to keep in mind RA as one possible cause of lung involvement of unclear cause. Lung involvement in RA can be any of the following alone or in variable combinations; interstitial lung diseases, pleural disease, pulmonary capillary disease, pulmonary hypertension, nodules, and airway disease. Drug-related lung toxicities and increase risk of infections are also common.[6] Most of these complications occur in the severe disease.[7]

Rheumatoid Associated- Interstitial Lung Diseases (RA-ILD).

Pathophysiology of RA-ILD:

Possible mechanisms of initiation of RA-ILD includes many hypotheses. Citrullination of lung proteins promotes increased binding to HLA-DRB1 and increases immunogenicity[8]. Smoking can cause Citrullination and hence increase the risk of RA-ILD[9]. Lung infections can lead to the Citrullination of lung proteins. Those with abnormal HL-DRB1 also have a high risk of RA. Bronchus-associated lymphoid tissue (BALT) found in RA patients' lung tissues can produce cytokines and anti-CCP. These mechanisms may explain why some patients have positive anti-CCP and lung disease only or why 10-20% of cases have lung involvement before articular manifestations[10]. These patients with de novo lung disease without any symptoms or signs of rheumatoid arthritis should have rheumatoid arthritis excluded. These patients often present with chronic dyspnoea and dry cough and may have fine end inspiratory crackles at lung bases. RA-ILD patients often have high titre of RA factor and / or anti-CCP in the blood[10,11].

Epidemiological factors for RA-ILD:

RA-ILD is more common in men in the 50- 60s, smokers, high titer of RA factor, longstanding RA and elevated anti-CCP antibodies' titer. Male to female ratio for RA-ILD is 2:1, although the prevalence of RA is more common in females. Age is an important and consistent risk factor for RA-ILD[12]. RA-ILD is the most common lung manifestation of RA, and approximately 30% of RA patients have ILD on HRCT[13]. However, the prevalence rate varies from 4% to 68% depending on the population studied (country, symptomatic, asymptomatic or autopsy) and the methodology used for diagnosis (HRCT, Chest X-ray or lung function tests).

HRCT Chest & Lung Function Tests:

Infections can mimic many of the radiological changes of RA related lung disease, so it's prudent to exclude infections and other aetiologies as clinically appropriate. Lung function tests will show a restrictive pattern with reduced lung volumes, FVC, and KCO[13]. Usual interstitial pneumonitis is the most common (40-62%) pattern of RA-ILD seen in RA, unlike other autoimmune diseases affecting lungs where non-specific interstitial pneumonitis (NSIP) is more common ILD **(Fig-1).** UIP is sub pleural, predominantly basal, reticular shadowing with honeycombing and no ground-glass opacities. The second common (32%) ILD pattern in RA is NSIP, basal ground glass opacities without honeycombing.[14] Third common patterns of RA-ILD includes cryptogenic organizing pneumonia (COP) which shows areas of non-infective consolidations. Other less common patterns include lymphocytic interstitial pneumonitis (LIP), desquamative interstitial pneumonitis (DIP), damaging alveolar disease (DAD), or combined pulmonary fibrosis with centrilobular emphysema (CPFE).[15]

There is an excellent correlation between radiological and histopathological finding in cases with IPF and similar correlation exist for RA-ILD[16]. This is why radiological findings are sufficient for diagnosis in majority of the cases suspected to have RA-ILD and surgical biopsy is needed only when radiological findings are non-diagnostic. UIP has poor response to immunosuppressive drugs and hence poor prognosis. NSIP and COP has good response to steroids and better prognosis. Hence radiological or tissue certainty is very important.

Histological assessment of RA-ILD:

BAL (Broncho-alveolar lavage) helps diagnosis of ILD and also helps in therapeutic in cases such as LIP and DIP[17]. BAL fluid has higher concentration of cytokines and inflammatory mediators such as platelet derived growth factors, interferon and transforming growth factors in cases with NSIP pattern when compared to those with UIP pattern. Also, majority of the smokers have UIP pattern[18]. Studies have shown a smaller from patients with RA-UIP when compared with number of fibroblasts and increased CD4

lymphocytes in histopathological specimen IPF. This may be the reason why RA-UIP or CTD-UIP may have better prognosis than IPF. However, study conducted by Park et al. didn't find any statistically significant difference in survival among UIP pattern of any cause (related to RA or IPF).[19]

Treatment and prognosis of RA-ILD:

RA-ILD is treated with the use of immuno-suppressants regardless of the underlying ILD pattern, smoking cessation, treatment for GORD, Oxygen supplementation, rehabilitation for lung diseases, and preventative vaccines. The mainstay for immunosuppressive therapy is corticosteroids. Other immunosuppressants such as Cyclophosphamide Rheu (Cyc), Azathioprine (AZA), Cyclosporine (CS), or Mycophenolate (MMF) are used, and response is better in cases with NSIP or COP.[20] Methotrexate (MTX) is not proven to worsen preexisting RA-ILD. Similarly, it's not clear whether TNF inhibitors or Rituximab worsen or improve RA-ILD. A lung transplant may be considered in young patients, especially those with UIP whose lung disease doesn't respond to drug therapy.[21] UIP has a poor prognosis like IPF. Risk factors for poor prognosis are male gender, old age, the extent of fibrosis, and reduction in KCO[13]. Many studies have demonstrated poor survival in patients with UIP and spontaneous or treatment related resolution in patients with NSIP.[19]

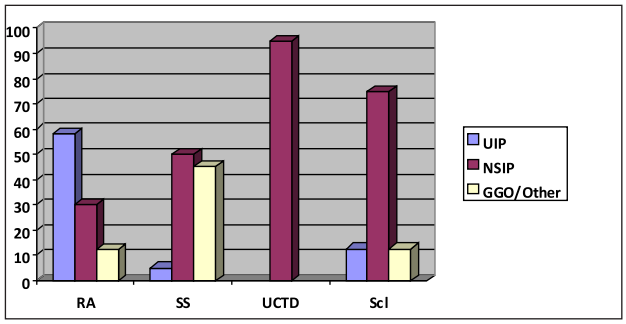

Fig-1: Comparison of various patterns of ILD in different connective tissue disorders:

Abbreviations: GGO (Ground glass opacities), NSIP (Non-specific interstitial pneumonitis), RA (Rheumatoid arthritis), SS (Sjogren's syndrome), UCTD (Undifferentiated connective tissue diseases), UIP (Usual interstitial pneumonitis). Prevalence quoted from the article by Eunice JK et al.[22]

Suggested screening for RA-ILD:

Although there are no clear guidelines for ILD screening in asymptomatic RA patients, however, some studies do suggest screening by symptoms (dry cough dyspnoea), examination (fine end inspiratory basal crackles, clubbing) and chest x-ray at the initial diagnosis and then every year. Any patient with suspected ILD should get HRCT chest and lung function tests. This may help detect these patients at early stage and prevent the progression. If HRCT shows RA-ILD but is unequivocal about the pattern, such patients may need surgical biopsy if not contra-indicated. Those with UIP pattern should be counselled about poor prognosis and may be referred for assessment related to possible lung transplant when clinically practical.[22] These suggestions may need further exploration with regard to cost effectiveness.

Rheumatoid Lung Nodules

Clinical & radiological presentations:

Prevalence of RA nodules vary from 0.4% in radiological studies up to 32% in autopsies studies of RA patients. Mostly there are no symptoms and no specific treatment is needed.

Nodules, like subcutaneous nodule have fibrinoid necrosis, vasculitis and macrophages. These are rounded nodules mostly located in sub pleural part of the middle or upper lobe. Size can vary from single to multiple and a few mm to several centimetres (up to 7cm). These can cavitate due to necrosis and cause pleural effusion, pneum-othorax, hydro pneumothorax, bronchopleural fistula, or superadded infection[23].

Predisposing factors and treatment:

These are more common in those with subcutaneous RA nodules. Similarly, patients may have nodules in myocardium and /or cardiac valves as well. Other risk factors are RA factor's high titer, male patients and smokers. Methotrexate and TNF inhibitors can increase the nodule size. These nodules have no relation with the disease activity in the joints.[6]

Diagnostic considerations:

Chronic infections such as TB and fungus are common in immunocompromised rheumatoid arthritis patients and can mimic these nodules with cavitation. Wegner's granulomatosis or

Churg Strauss Vasculitis can also have similar pictures. Infections often have constitutional symptoms, air-bronchogram, tree in bud opacities and mediastinal lymphadenopathy. Irregular margins with sharp projections, spiculated appearance, and rapid growth in size may also point toward malignancies[24]. Malignancy is an important differential, especially if the patient is a smoker. A follow-up interval CT scan may help monitor any change in the size or shape. PET scan can also help characterize and differentiate from malignant cause. RA nodules classically have low uptake due to necrosis and fibrosis unless there is active inflammation. When the diagnosis is equivocal, biopsy may be needed.[25,26] RA nodules with occupational (asbestosis, coal, or silica exposure) pneumoconiosis are called Kaplan syndrome. Prognosis is generally god in these patients.[27]

Rheumatoid Associated Pulmonary Vascular Disease

Primary or secondary pulmonary hypertension:

High risk of venous thromboembolism (VTE) & pulmonary emboli (PE), vasculitic changes in pulmonary capillaries, RA-ILD and airway diseases & rheumatoid related heart disease causes pulmonary hypertension (PHTN) in RA patients.[28] However, a significant number (21%) of RA patients have isolated pulmonary hypertension without having lung or heart or VTE related factors.[29] These patients may be less symptomatic due to limited mobility unless the disease is advanced. An echocardiogram is the first tool used, and patients may need the right heart catheterization in some cases. Pulmonary artery systolic pressure of more than 30 mmHg by Doppler Echocardiography is defined as pulmonary hypertension. RA related PHTN cases can be treated similar to other such cases due to connective tissue diseases.[6]

Rheumatoid Associated Pleural Disease

Pleural effusions and pleuritis:

Pleural inflammation, impaired fluid resorption by pleura, and rupture of nodules are the primary mechanism for exudative pleural effusion. Pleurisy and pleural thickening are common in RA. Pneumothorax is rare, but pleural effusion can coexist with pericardial effusion. Pleural effusion is often unilateral and more in old age.

Diagnostic imaging:

CT or Chest X-ray or ultrasound can be used to detect pleural effusions. CT helps better as it can elaborate pleural nodules, bronchopleural fistula, or underlying parenchymal disease as well.[6] Pleural fluid aspiration and analysis is essential. Sometimes video-assisted thoracoscopy and pleural biopsy are also needed, especially to exclude other causes such as TB or malignancies.[30]

Pleural fluid analysis:

Exudate effusion in rheumatoid arthritis usually has a high RA factor titer low glucose level is due to reduced crossing ability caused by the pleural thickening and increased glucose consumption by inflammatory cells.[31] Chronic effusion has more drop in glucose, which can be low or normal in acute effusion. Chronic effusion also causes cholesterol crystals (pseudo-chylous effusion) without high Triglycerides or chylomicrons. Acute can have neutrophils, whereas chronic is mainly lymphocytic. Eosinophils can also be present in the fluid. Multinucleated giant cell with intracellular inclusions of IgG &/or RA factors) are classic but not always present.[32]

Treatment:

Pleural effusion treatment is treated with therapeutic aspiration if they are large. Otherwise, treatment is that of the underlying cause, and effusions often resolve slowly over periods of months. The risk of pleural fibrosis and trapped lung is an important factor to consider when deciding to wait and watch policy. Surgical decorticating is needed for trapped lungs.[6]

Rheumatoid Related Airway Disease

The upper airway Disease:

Laryngeal involvement can occur due to arthritic changes of the cricoarytenoid joint, dislocation of the joint, nodule formation on the vocal cord, or vasculitis affecting recurrent laryngeal nerve or vagus nerve. Vocal cord examination with laryngoscopes will help diagnose; however, HRCT will help detect the cricoarytenoid joint synovitis or deformities. Treatment is airway support for acute obstruction or otherwise that of the underlying RA.[33]

Lower airways disease:

Bronchioles can have follicular bronchiolitis

(FB), obliterative bronchiolitis (OB), bronchial hyperresponsiveness or bronchiectasis. FB is BALT hyperplasia causing thickened bronchial walls and restrictive or obstructive lung function test. HRCT shows branching peri bronchial small (<3mm) nodules.[34] OB is fibrosing/constricting bronchiolitis with the rapidly progressive obstructive disease more common in females with long standing seropositive RA. Penicillamine, gold salts, and sulfasalazine can also cause OB. HRCT is non-specific emphysema, bronchiectasis, and wall thickening.[6]

Treatment:

Follicular bronchiolitis needs standard treatment for RA PLUS may need corticosteroids and Macrolides. Treatment for OB is difficult and needs strong immunosuppressive drugs, which may or may not work. A lung transplant may berequired.[35]

Rheumatoid Drug Related Lung Toxicities

Methotrexate (MTX):

MTX can cause acute pneumonitis, a hypersensitivityresponse, more within the first year, with histologically having eosinophils and non-necrotizing granuloma but non-specific HRCT findings. It improves chronic fibrosing interstitial lung disease with fibrosis by stopping the drug and adding corticosteroids if needed. Also, MTX can cause worsening of rheumatoid nodules. Risk factors include old age, other extra-articular complications, diabetes, low albumin, genetic predisposition to drug sensitivity, and prior use of other DMARDs.[36]

Leflunomide & Other DMARDs:

It can cause epithelial-mesenchymal transition, hence promoting fibrotic ILD, ten times more in Asians (1%) as compared to the Western.[37] Gold salt, penicillamine, and sulfasalazine can cause bronchiolitis obliterated. Biological and immunosuppressive drugs do increase the risk of infections.

TNF inhibitors & Rituximab:

There is no clear cause-effect relationship documented. However, various small studies suggested these drugs may rarely exacerbate ILD, but the risk is very low and inconsistent. TNF inhibitors increase the risk of reactivation of TB.[38]

Discussion & Conclusion

Pulmonary complications associated with rheumatoid arthritis play a vital role in decision making for RA patients' management. Firstly, many drugs used to treat RA, such as methotrexate, leflunomide, sulfasalazine, gold salt, penicillamine, and possibly biological drugs, can also affect the lungs directly as a side effect or indirectly by promoting infections. Secondly, infections and other medical illnesses such as malignancies can also mimic many of the RA-associated lung pathologies and are more common in RA patients than among the general population. This leads to a considerable delay in the early recognition of the RA related complications and hence increase morbidity and mortality. Thirdly, RA-related lung pathologies are common in severe and chronic RA, smokers, and the older population which affects the patient's ability to cope with the intensive nature of the treatment needed. Fourthly, RA related lung disease are the second common contributing factor for increased mortality (next only to cardiac complications).[2,4,5-7]

Most lung complications are insidious in onset, often subclinical, or present with non-specific symptoms that may not surface due to reduced mobility of RA patients. Hence, when they present clinically, it may already have progressed. This is especially true about ILD. Also, unlike other connective tissue disorders that present more with NSIP, RA mostly has UIP which is the most poorly responding variety of ILD and the prognosis is poorer. A significant proportion of RA patients (10- 20%) can present just with the pulmonary disease without articular disease at the onset.[7,9,12,13] We should have an aggressive approach with a high index of suspicion about lung complications in rheumatoid patients to detect and adequately manage RA associated systemic diseases. Though not a part of guidelines, however, thorough history, lung auscultation, and routine chest X-ray at regular intervals may help raise suspicion. HRCT and lung function tests should be done when there is any clue regarding rheumatoid related lung issues. HRCT often gives a diagnosis. Rheumatoid arthritis patients may need further testing, such as bronchoalveolar lavage (BAL), surgical lung biopsy, pleural biopsy, transthoracic echocardiography, and right heart catheterization depending on the clinical indication.[22] Once

diagnosed, RA related lung disease (s) should be managed by multimodality approach including adequate control of disease (s) by immunosu- immunosuppression, smoking cessation, oxygen therapy, pulmonary immunosuppression, smoking cessation, oxygen therapy, pulmonary rehabilitation, cardiac risk assessment, and management. Specific treatment related to the complications (as discussed earlier) should also be added to the regimen. Early evaluation for lung transplant should be done for suitable transplant patients whose pulmonary disease is poorly controlled despite adequate medical therapy such as obliterative bronchiolitis or advanced ILD due to UIP.[19,21,35] Due to the multifactorial impact of rheumatoid related extra-articular complications on manage- ment, morbidity, and mortality the team treating such patients should be vigilant for early detection and treatment of complications.

Table-1: Summary of the rheumatoid related lung issues.

RA Related	Subtypes	Diagnontic Modalities	Treatment Options
H.D	UIP NSIP DIP / LIP DAD CPFE	X-ray Chest HRCT Chest Lung Functions (FVC, KCO) BAL Surgical biopsy	Immunosuppression Smoking cessation Oxygen Rehabilitation. Lung transplant
Pleural Disease	Effusion Pleuritis Pneumothorax Bronchopleural fistula Hydropneumothorax Hemopneumothorax Pleural fibrosis	Xray Chest CT chest Ultrasound Pleural fluid analysis VAT and pleural biopsy	Standard treatment for RA. Pleural aspiration Surgical decorticectomy
Upper Airways	Cricoarytenoid disease RLN or vagal nerve palsy Laryngeal obstruction Vocal cord nodules	Laryngoscopy with or without biopsy HRCT Larynx	Airway support if needed Treat RA. Corticosteroids
Lower Airways	Bronchiolitis (FB, OB) Bronchiectasis Bronchial Hyperresponsiveness	CTPA or V/Q scan TTE Right heart catheterization	Treat RA Corticosteroids, Macrolides Lung transplant
Pulmonary Vascular	PE Pulmonary hypertension	CTPA or V/Q scan TTE Right heart catheterization	Anticoagulation Oxygen Drugs for PHTN.
Nodules	Nodules	HRCT Chest Biopsy	Treat RA Monitor
Drug related	ILD / OB Worsening of nodules	Exclude other causes	Stop the offending drug Corticosteroids

Abbreviations: BAL (Broncho-alveolar lavage), CPFE (Combined pulmonary fibrosis & emphysema), CTPA (CT pulmonary angiogram), DIP (Desquamative interstitial pneumonitis), DAD (Diffuse alveolar damage), FB (Follicular bronchiolitis), FBC (Forced vital capacity), HRCT (High resolution CT), ILD (interstitial lung disease), KCO (Corrected carbon mono-oxide diffusion), LIP (Lymphocytic interstitial pneumonitis), NSIP (Nonspecific interstitial pneumonitis), OB (Obstructive bronchiolitis), PE (Pulmonary embolism), RA (Rheumatoid arthritis), RLN (Recurrent laryngeal nerve), UIP (Usual interstitial pneumonitis), VAT (Video assisted thoracoscopy), V/Q (Ventilation perfusion scan).

References

1. Bongartz T, Cantaert T, Atkins SR, et al. Citrullination in extra-articular manif- estations of RA. Rheumatol (Oxford) 2007:46(1);70-5.
2. Young A, Koduri G. Extra-articular manifestations and complications of RA. Best Pract Res Clin Rheumatol 2007: 21(5);907-27.
3. Turesson C. Extra-articular rheumatoid arthritis. Curr Opin Rheumatol 2013: 25(3);360-6.
4. Mielants H, Van Den Bosch F. Extra-articular manifestations. Clin Exp Rheumatol. 2009:27(S55): S56-61.
5.O'DwyerDN, Armstrong ME, Cooke G. rheumatoid arthritis associated ILD. Eur J Intern Med.2013;24(7);597-603.
6.Megan S, Bridget F, Lawrence A.Ho. Rheumatoid arthritis-associated lung disease. European Respiratory Review.2015:24 (135);1-16.
7. Marigliano B, Soriano A, Marriotta D. Lung involvement in connective tissues diseases: a comprehensive review and a focus on rheumatoid arthritis. Autoimmune Rev 2013; DOI: 10.1016/j.autrev.2013.05.001.
8. Hill JA, Southwood S, Sette A. Cutting edge, conversion of arginine to citrulline allows for a high-affinity peptide interaction with rheumatoid arthritis associated HLA-DRB1 0401 MHC class II molecule. J Immunol 2003;171(2):538-41.
9. Klareskog L, Stolt P, Lundberg K. A new model for rheumatoid arthritis's aetiology: smoking may trigger HLA-DR (shared epitomes)-a restricted immune reaction to autoantigens modified by Citrullination. Arthritis Rheum 2006: DOI: 10.1002/art. 21575.
10. Rangel-Moreno J, Hartson L, Navaro C. Inducible bronchus-associated lymphoid tissue in patients with pulmonary complications of rheumatoid arthritis. J Clin Invest 2006;116(12):3183-94.
11. Fischer A, Solomon JJ, du Bois RL. Lung disease with anti-CCP antibodies but no RA or connective tissue disease. Respir Med 2012;106(7):1040-7.
12. Turesson C, McClelland RL, Christianson T, et al. Clustering of extra-articular manifestations in rheumatoid arthritis patients. J Rheumatol.2008: 35(1);179-180.
13. Cavagna L, Monti S, Grosso V. The multi-faceted aspects of interstitial lung disease in rheumatoid arthritis. Biomed Res Int. 2013; DOI: 10.1155/2013/759760.
14. Flaherty KR,Thwaite EL, Kazerooni EA. Radiological vs . histological diagnosis in UIP and NSIP: survival implications. Thorax 2003;58(2):143-8.
15. Cottin V, Cordier JF. CPFE in connective tissue disease. CurrOpinPulm Med 2012;18 (5):418-27.
16. Raghu G, Mageto YN, Lockhart D. Accuracy of clinical diagnosis of new onset IPF and other ILD: A perspective study. Chest. 1999;116(5):1168-74.
17. Hunninghake GW, Zimmerman MB, Schwartz DA, et al. Utility of lung biopsy for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2001;164(2):193-6.
18. Gochuico BR, Avilla NA, Chow CK, et al. Progressive preclinical ILD in rheumatoid arthritis. Arch Intern Med 2008;168(2):159-66.
19. Park JH, Kim DS, Park IN. Prognosis of fibrotic ILD: idiopathic vs. collagen vascular disease related subtypes. Am J RespirCrit Care Med. 2007;175(7);705-11.
20. Fischer A, Brown KK, Du Bois RM, et al. mycophenolate improves lung functions in connective tissue disease-associated ILD. J Rheumatol 2013; DOI: 10.3899/ jrheum. 121043
21. Yazdani A, Singer LG, Strand V. Survival and quality of life in RA associated ILD after lung transplant. J Heart Lung Transplant 2014:33(5);514-20.
22. Eunice JK, Harold RC, Talmadge EK. Rheumatoid arthritis -ILD: prevalence of histopathologic and radiographic pattern. Chest 2009: 136(5);1397-1405.
23. Alpay KN, Celik S, Yilmaz OS. Cavitary pulmonary nodules in rheumatoid arthritis: case reports and review of the literature. Eur J Rheumatol 2018; DOI: 10.5152/eurjrheum.. 2017.16106.
24. Zwirewich CV, Vedal S, Miller RR. Solitary pulmonary nodules: HRCT and radiologic-pathologic correlation. Radiology 1991:179(2); 469-76.
5.Gupta P, Ponzo F, Kramer EL. FDG uptake in pulmonary rheumatoid arthritis nodules. ClinRheumatol 2005: 24(4);402-5.
26.Chhakchhuak CL, Khosravi M, Lohr KM.

Role of FDG-PET scan in rheumatoid arthritis lung nodules: case report and literature review. Rheumatol 2013; DOI: 10.1155/ 2013/621340.
27. Scheiber J, Koschel D, Kekow J. Rheumatoid Eur J Intern Med 2010;21(3):168-72.
28. Shahane A. Pulmonary hypertension in rheumatic diseases: epidemiology and pathogenesis. RheumatolInt 2013:33 (7);1655-67.
29. Dawson JK, Goodson NG. Raised pulmonary artery pressure with Doppler echocardio-graphy in rheumatoid arthritis patients. Rheu-matology (Oxford). 2000;39(12):1320-25.
30. Avnon LS, Abu-Shakra M, Flusser D. Pleural effusions in rheumatoid arthritis: what cell predominance to anticipate? RheumatolInt 2007:27(10);919-25.
31. Balbir-Gurman A, Yigla M, Nahir AM. Rheumatoid pleural effusions. Semin Arthritis Rheum 2006; 35(6): 368-78.
32. Corcoran JP, Ahmad M, Mukherjee R. Pleuropulmonary complications of rheumatoid arthritis. Respir Care 2014:59(4): e55-9.
33. Feraco P, Bazzocchi A, Righi S. Involvement of cricoarytenoid joints in rheumatoid arthritis. J ClinRheumatol 2009;15(5):264.
34. Mori S, Koga Y, Sugimoto M, et al. Small airway obstruction in rheumatoid arthritis. Mod Rheumatol 2011;21(2):164-173.
35. Lynch JP, Weight SS, DerHovanessian A. Obliterative bronchiolitis. SeminRespirCrit Care Med 2012;33(5):509-32.
36. Roubille S, Haraoui B. ILD induced or exacerbated by DMARDs and biologic agents in rheumatoid arthritis: a systematic review. Semin Arthritis Rheum 2014;43(5):613-26.
37. Namba T, Tanaka KI, Ito Y. Induction of EMT-like phenotype by an active metabolite of leflunomide and its contribution to pulmonary fibrosis. Cell Death Differ 2010;17(12):1882-95.
38. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C. ILD induced or exacerbated by TNF inhibitors: analysis of 122 cases. Semin Arthritis Rheum 2011: 41(2);256-64.