



Pulmonary Findings in Rheumatic Diseases

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Abstract

Introduction: One of the affected systems in rheumatic diseases is the respiratory system. This study was carried out to investigate the pulmonary involvement findings and the respiratory function tests in rheumatic diseases.

Methods: Rheumatic patients, who were requested consultation by the Bağcılar Training and Research Hospital Training and Research Hospital Department of Chest Diseases between 2015 and 2017, have been included in the study. A total of 110 patients; 64 rheumatoid arthritis, 43 ankylosing spondylitis, two psoriatic arthritis, and one Behçet were included in the study. Pulmonary involvement findings, respiratory examination findings, and pulmonary function tests (RFT) in chest X-ray and high-resolution computed tomography (HRCT) were examined.

Results: About 33.64% normal and 66.36% abnormal findings were observed in HRCT findings. Abnormal HRCT findings were found in 70% of RA patients (n=45) and in 58% of patients with AS (n=25). When RFTs were examined, 50.0% normal, 32.7% restrictive type respiratory disorder, 15.5% mixed type respiratory disorder, and 1.8% obstructive respiratory disorder were observed.

Discussion and Conclusion: Pulmonary involvement with rheumatic diseases can be seen in different ways. HRCT and RFT provide information on the prevalence and grade of pulmonary disease. It leads to correct diagnosis and treatment.

Keywords: Rheumatic disease; lung; respiratory function test; high resolution computed tomography.

One of the targets of autoimmunity damage in rheumatic diseases is the lung. Pulmonary involvement is one of the major causes determining the morbidity and mortality of the rheumatic diseases. At the same time, the incidence, prevalence, clinical course, and type of lung involvement show significant heterogeneity due to underlying rheumatic disease^[1]. In pulmonary involvement, besides pleura, pulmonary parenchyma, and airways; respiratory muscles, pulmonary veins, interstitium, and bone structures may be affected as well. In rheumatic diseases, concomitant lung involvement may be present

or sometimes lung involvement may be seen before the typical appearance of the disease^[2]. As well as being affected by the disease itself, the treatments used may also cause lung disease due to toxicity. The most common lung condition in these cases is pneumonitis which appears in all the histopathological patterns of idiopathic interstitial pneumonia. Moreover, connective tissue diseases (in themselves and especially due to the immunosuppression produced by the drugs used in their treatment) have an increased prevalence of infections, especially respiratory system infections, mainly with the new biological

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Submitted Date (Başvuru Tarihi): 15.04.2019 **Accepted Date (Kabul Tarihi):** 26.06.2019

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treatments used today. These have also been related with the development of pneumonitis, this condition may be fatal in some cases^[3].

The classic clinical finding in rheumatoid arthritis (RA) is the chronic symmetrical polyarthritis caused by persistent inflammatory synovitis. Respiratory system involvement is seen in 30–40% of patients. Pulmonary involvement is often developed by the progression of the disease. Pleural thickening is the common finding, which is mostly observed, and is seen more frequent than the pleural effusion^[4]. Interstitium and airways are also frequently affected. Among the interstitial lung disease forms, usual interstitial pneumonia and nonspecific interstitial pneumonia are the most common forms and seen 40–60% and 11–30%, respectively^[5]. Rheumatoid nodules can be in size from a few millimeters to a few centimeters^[6]. Pulmonary arterial hypertension is a rare condition. It is usually seen in elderly patients with long-term disease. Studies on pulmonary vasculitis have shown that the prevalence of rheumatoid vasculitis progressively decreases due to better control of the disease and earlier diagnosis^[7]. Diffuse alveolar hemorrhage (DAH) is a rare condition in patients with RA, but it is very important to consider DAH for two reasons. The first one is an emergency case and is often fatal. The second one can be explained with the relationship between specific drugs such as leflunomide^[8].

Ankylosing spondylitis (AS) is a chronic inflammatory multisystem disorder which affects mainly the axial skeleton and peripheral joints. The lung involvement is rare and seen in the advanced stages of the disease. Upper lobe fibrillary disease, interstitial lung disease, pleural thickening, pleural effusion, and mycetoma formation are the most common forms^[9]. Pneumothorax may be seen more rarely, and chest wall restriction, which can be caused by fusion of costovertebral joints, may also be observed^[10].

Behcet's disease is a multisystemic disease characterized by oral, genital ulcers, and eye involvement. Pulmonary involvement is about 1–16% and it is one of the complications with the highest mortality. Arterial and venous thrombosis, pulmonary fibrosis, pulmonary vasculitis, and pulmonary aneurysm can be seen^[11]. Psoriatic arthritis (PsA) is inflammatory arthritis, usually associated with psoriasis, in which rheumatoid factor is negative. Studies on pulmonary involvement in PsA are inadequate. Lung involvement in PsA is rarely seen as apical fibrosis and pleural thickening^[12]. In addition, comorbidities including chronic obstructive pulmonary disease and sarcoidosis were observed in 70% of these patients^[13].

Materials and Methods

The study included rheumatic patients who were followed up by the Department of Physical Medicine and Rehabilitation of Bağcılar Training and Research Hospital between 2015 and 2017 and who were requested consultation by the Department of Chest Diseases. Patient files were examined retrospectively. Ethical approval for this study was obtained from Bağcılar Training and Research Hospital ethical committee. Pulmonary involvement was evaluated in chest X-ray and high-resolution computed tomography (HRCT). Respiratory examination findings and respiratory function tests (RFTs) were evaluated. Smoking history was examined. HRCT findings were evaluated in terms of pulmonary nodules, bronchiectasis, pleural effusion and pleural thickening, air trapping, ground-glass appearance, atelectasis, sequelae findings, mosaic pattern, reticulonodular pattern, mediastinal lymphadenopathy (LAP), infiltration, and emphysema findings. The distribution of pulmonary nodules according to lung lobes was determined. C-reactive protein (CRP), hemoglobin, hematocrit, erythrocyte sedimentation rate, and drug therapies were recorded.

Statistical Analysis

In this study, statistical analysis has been performed by Number Cruncher Statistical System 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods (mean, standard deviation), independent t-test has been used for comparison of binary groups with normal distribution variables, Mann–Whitney U-test has been used for comparison of binary groups of non-normally distributed variables, and Chi-square test has been used for the comparison of qualitative data. The weighted Kappa test has been used to determine the compliance with HRTC and chest X-ray. The results have been evaluated as $p < 0.05$ significance level.

Results

A total of 110 patients were included in the study (72 females and 38 males). The mean age of the patients was 47.57 (22–79). When the smoking habit was examined; 53 (48%) patients had never smoked, 19 (17%) had stopped smoking, and 38 (35%) were smoking. While the respiratory examination was normal in 93% of the patients, roncus was observed in auscultation in 7% (Table 1). Sixty-four patients were being followed for RA, 43 for AS, two for PsA, and one for Behcet's disease (Table 1). The sedimentation values of the patients in the laboratory tests were 21.64 ± 17.13 mm/h, the hemoglobin values were 13.29 ± 2.12 g/dl, the

Table 1. Demographic features, clinical findings, and diagnosis

	n	%
Diagnosis		
Rheumatoid arthritis	64	58.18
Ankylosing spondylitis	43	39.09
Psoriatic arthritis	2	1.82
Behcet	1	0.91
Gender		
Male	38	34.55
Woman	72	65.45
Cigarette		
Ex-smoker	19	17.27
Smoker	38	34.55
No	53	48.18
Respiratory examination		
Normal	103	93.64
Rhonchus	7	2.73
Respiratory function test		
Normal	55	50.0
Restrictive type disorder	36	32.7
Mixed type disorder	17	15.5
Obstructive type disorder	2	1.8

n: Number of cases; %: Percent.

hematocrit values were $39.81 \pm 5.90\%$, and the CRP values were found as 9.04 ± 10.67 mg.

The mean of hemoglobin and hematocrit values of RA group has been found statistically significantly lower than the AS group ($p=0.0001$ and $p=0.032$). The mean sedimentation rate of RA group has been found statistically significantly higher than the AS group ($p=0.001$), whereas no statistically significant difference has been found between the mean values of CRP ($p=0.687$).

When RFTs were examined, 50.0% normal, 32.7% restrictive type respiratory disorder, 15.5% mixed type respiratory disorder, and 1.8% obstructive type respiratory disorder were observed (Table 1). When the patients with chest (PA) X-ray were examined, 62.2% normal and 37.8% abnormal X-ray findings were determined. In HRCT findings, 33.64% normal and 66.36% abnormal findings were observed (Table 2). Abnormal HRCT findings were found in 70.3% ($n=45$) of RA patients and in 58% of patients with AS ($n=25$). The abnormal radiological findings of HRCT were as follows: Pulmonary nodules, sequelae findings, pleural effusion or thickening, atelectasis, air trapping, emphysema, mediastinal LAP, mosaic pattern, ground glass, reticulonodular pattern, and infiltration (Table 3). According to the distribution of pulmonary nodules were

Table 2. HRCT and chest X-ray findings

	n	%
Chest X-ray		
Normal	51	62.20
Abnormal	31	37.80
HRCT		
Normal	37	33.64
Abnormal	73	66.36

n: Number of cases; %: Percent; HRCT: High-resolution computed tomography.

Table 3. High-resolution computed tomography radiological findings

	n	%
Pulmonary nodule	39	35.45
Sequelae findings	28	25.45
Pleural effusion/thickening	11	10.00
Bronchiectasis	10	9.09
Atelectasis	8	7.27
Air trapping	7	6.36
Emphysema	6	5.45
Mediastinal LAP	5	4.55
Mosaic pattern	4	3.64
Ground glass	3	2.73
Reticulonodular pattern	2	1.82
Infiltration	1	0.91

n: Number of cases; %: Percent; LAP: Lymphadenopathy.

seen as 12.73% bilateral, 11.82% in the right lung, 11.82% in the left lung.

In this study, RA, AS, PsA, and Behçet's patients were using various medications due to their diseases. In RA, disease modifying antirheumatic drugs (DMARD) and biological agents can be used with nonsteroidal anti-inflammatory drugs (NSAIDs). DMARDs used in RA are sulfasalazine, methotrexate (MTX), and leflunomide. In AS, NSAIDs and anti-tumor necrosis factor (TNF) drugs can be used in axial involvement and sulfasalazine and methotrexate may be used in peripheral involvement. The anti-TNF drugs used were adalimumab, etanercept, infliximab, and golimumab. The drugs used in the treatment and are shown in Table 4. When HRCT findings were examined according to the treatment protocols of the patients, abnormal HRCT findings were found as 42.47% who have received MTX and its combinations, 27.40% who have received anti-TNF drugs and their combinations, 2.73% who have received MTX and anti-TNF, and 27.40% in the subjects who have received other drugs (Table 4).

Table 4. Drugs used in treatment and HRCT findings

	Normal HRCT		Abnormal HRCT	
	n	%	n	%
MTX and /or DMARDs	13	35.14	31	42.47
Anti-TNF and /or NSAIDs	6	16.22	20	27.40
MTX and anti-TNF	3	8.11	2	2.73
Other	15	40.54	20	27.40

n: Number of cases; %: Percentage; HRCT: High-resolution computed tomography; MTX: Methotrexate; TNF: Tumor necrosis factor; DMARD: Disease-modifying antirheumatic drugs; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Discussion

Pulmonary involvement is one of the extra-articular manifestations of rheumatic diseases. Pulmonary disease can develop as a result of restrictive changes caused by musculoskeletal disease and changes in lung.

Especially in AS, limitation of the chest expansions caused by ankylosis of the costovertebral and costosternal joints, leads to restrictive type function disorder. Although pulmonary compliance, diffusion capacity, and arterial blood gases are normal in these patients, there is a restriction in RFT^[14].

Ayhan-Ardic et al.^[15] investigated pulmonary involvement with RFT and HRCT methods in 40 patients with asymptomatic AS and RA who had no history of smoking. Abnormal HRCT findings were found in 70% of patients with RA (n=14) and 50% of patients with AS (n=10). No correlation has been found among HRCT and the activity markers and RFTs of the disease. Similarly in our study, 70% of patients with RA (n=45) and 58% of patients with AS (n=25) have been determined with abnormal HRCT findings. No significant correlation was found among HRCT findings and sedimentation and CRP of activity markers of the disease. In the study of Ardic et al., restrictive pattern has been seen in 5% of RA patients and 20% of AS patients. In our study, while the restrictive type respiratory disorder was found as 32.7% in all rheumatic disease groups, it was determined as 44.2% in AS and 23.4% in RA. This difference may be due to differences in our inclusion criteria. All patients who were smokers, non-smokers, and ex-smokers have been included in the study. In the study of Ardic et al., only non-smokers have been included in the study.

In a study carried out by Altin et al.,^[16] abnormal HRCT finding has been observed in 73% of 38 AS patients; mosaic patterns, nodules, parenchymal bands, bronchial wall thickening, ground-glass appearance, and interlobular septal thickening. In our study, the most common radiolog-

ical findings were nodules, sequelae findings, air trapping, bronchiectasis, emphysema, atelectasis, and pleural effusion-thickening. In our study, parenchymal bands and apical fibrosis findings were considered as sequelae findings. Hence, the most common radiological findings in these two studies are similar to our findings.

Abnormal HRCT findings have been found in 59% of 78 patients with AS by Hasiloğlu et al.,^[17] the most common radiological findings were parenchymal bands, interlobular septal thickening, emphysema, and apical fibrosis, respectively. In our study, abnormal HRCT findings were found in 58% of the patients, the most common radiological findings were nodules, sequelae, air trapping, and bronchiectasis, respectively. We found different radiological findings from the findings of the study of Hasiloglu et al. This may be due to older age population in our study.

Maghraoui et al.^[18] have found abnormal HRCT findings in 61% of the patients in their review in which they aimed to determine the prevalence of abnormal HRCT findings in AS. The most common abnormalities have been pleural thickening, parenchymal bands, and interlobular septal thickening, respectively. In our study, similarly, abnormal HRCT findings have been detected in 58% of the patients. The most common abnormal findings in our study were nodules, sequelae findings, and air trapping. Pleural thickening is relatively lower rate than Maghraoui's study.

In the study of Skare et al.,^[19] abnormal HRCT findings have been determined in 55% of 71 patients with RA. In our study, 70% of the patients have had abnormal HRCT findings. The higher HRCT findings in our patients may be due to the fact that our patient mean age is 10 years older compared to the study of Skare et al. The most common HRCT findings in this study were ground glass, parenchymal bands, bronchiectasis, and pulmonary nodules. In our cases, the most common radiological abnormalities were nodules, sequelae, pleural effusion-thickening, bronchiectasis, atelectasis, and emphysema, respectively.

The chest X-ray has advantages such as low cost, lower radiation value, and easier access compared to HRCT. However, HRCT is more useful in determining the specific diagnosis of the lung disease, in determining its severity, and in the follow-up of its treatment^[20].

Kawassaki et al.^[21] have determined abnormal chest X-ray in 45% and abnormal RFT values in 30% of 246 RA patients with an average age of 56 years. In our study, we found abnormal chest X-ray in 36% and abnormal PFT values in 45% of the RA group. The mean age and the smoking history of both studies were similar. Although the mean age and

smoking history of both studies were similar, abnormal PFT values were higher rate and abnormal chest X-ray findings were lower rate compared to Kawasaki's study. The number of patients who had chest X-ray in our study was fewer than Kawasaki's study. This may be the reason of different findings.

Şendur et al.^[22] have investigated the superiority of HRCT compared to the chest X-ray in detecting pulmonary findings in patients with AS. While the chest radiographs of all patients included in the study are normal, abnormal findings have been determined in 7 (29%) patients in the HRCT. In our study, 10 patients (31%) in the AS group were found to have abnormalities in their HRCT while their chest radiography was found normal. In the RA and AS group, abnormal findings were observed in 55% of 51 patients with normal chest X-ray.

The most common radiological abnormalities in our patients with RA were nodules, sequelae findings, pleural effusion-thickening, bronchiectasis, atelectasis, emphysema, air trapping, mosaic pattern, and mediastinal lymphadenomegaly.

Pulmonary nodules were the most common HRCT findings in our patients with a rate of 35.4%. This rate was 37% in RA patients whereas 32% in AS patients.

It is important to remember that lung nodules are frequently observed in normal population. The prevalence of pulmonary nodules in screening studies for lung cancers among smokers changes between 17% and 51%^[23,24].

In patients, pulmonary involvement may also develop due to the drugs used in the treatment^[25]. MTX is one of the drugs used in both RA and AS, MTX toxicity is seen in 5% of patients. In patients with MTX toxicity, PA chest X-ray shows bilateral diffuse interstitial and alveolar infiltrations^[26]. In our study, a 54-year-old female patient with RA was found to have infiltration in the right upper and middle zones, and bilateral hilar fullness on her X-ray based on the use of MTX. Since peribronchovascular thickening, micronodular infiltrations, and septal thickening were observed in HRCT mediastinal multiple LAPs, MTX was discontinued. After 3 months of follow-up, complete recovery of the radiology was observed.

In our study, no significant difference was found among MTX and other DMARDs, TNF and NSAID, MTX and TNF, other drug groups, and abnormal HRCT findings ($p=0.064$).

The number of patients with Behcet and PsA was very few, in HRCT of Behcet's patient, nodule, mediastinal LAP in one of the PsA, and apical pleural thickening were seen in the other. Mixed type respiratory disorders were observed in RFTs.

Conclusion

The lung involvement spectrum associated with rheumatic diseases is quite broad. HRCT provides us insight into the activity, width, and shape of pulmonary disease and helps to treat it properly.

Since pulmonary involvement is the second most common cause of death in RA, it is important to detect pulmonary involvement in early stage RA^[27]. Therefore, both RA and AS should be evaluated with PA X-ray at the beginning of treatment and the cases which are considered necessary should be evaluated with HRCT.

Randomized prospective studies are required to reveal the findings of pulmonary involvement in rheumatic diseases.

Ethics Committee Approval: The Bağcılar Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 21.12.2018, number: 2018.12.2.04.113.r1.126).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: G.Ö.; I.Ü. Design: G.Ö.; I.Ü.; Supervision: G.Ö.; Fundings: I.Ü.; Materials: G.Ö.; I.Ü.; Data Collection or Processing: G.Ö.; I.Ü.; Analysis or Interpretation: G.Ö.; I.Ü.; Literature Search: I.Ü.; Writing: G.Ö.; I.Ü.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

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