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Pulmonary abnormalities on high-resolution computed tomography in patients with long standing rheumatoid arthritis

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ABSTRACT

Background. Rheumatoid arthritis (RA) is a systemic inflammatory disease, associated with a number of extra-articular organ manifestations. Pulmonary involvement is a frequent and severe extraarticular manifestations of rheumatoid arthritis. RA can affect lung parenchyma, airways and pleura.
Objectives. To identify RA-related lung disease on chest computed tomography (CT).
Material and methods. We performed high-resolution computed tomography (HRCT) on a total of 92 patients with longstanding RA.
Results. The subjects were predominantely female (79.3%), the age at entry was 63.77 ±11.56 years, and 42.9% had a history of smoking. Disease duration was 15.00±11.55 years. Pulmonary CT abnormalities were found in 71 of the 92 patients (77.2%). The most common HRCT anomalies were: linear attenuation (reticulation) (52.11%), bronchiectasis andbronchial wall thickening (45%), nodular attenuation (39.43%) and pleural involvement (pleural effusion or thickening) (39.43%).
Conclusions. We conclude that RA-related lung disease was commonly detected on chest CT imaging in longstanding RA patients.

Keywords: rheumatoid arthritis, interstitial lung disease, imaging

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease. Its main feature is persistent, symmetrical, erosive synovitis, but a large number of extraarticular manifestations can occur in virtually any organ leading to cutaneous, ocular, hematological, cardiovascular and pulmonary lesions (1).

Pulmonary involvement occurs in 60-80% of patients with RA and can affect any component of the lung. The spectrum of rheumatoid arthritis-associated respiratory disease includes a wide range of pulmonary abnormalities: interstitial lung disease (ILD), airway disease (AD), nodules, pleural disease and vascular disease (2-4).

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Prevalence rates of pulmonary abnormalities in RA reported in the literature vary widely, depending on the criteria used to define disease, methods used to detect pulmonary involvementand patient populations examined. It has been reported that RA-associated lung disease is seen more frequently in men with longstanding rheumatoid disease, in the presence of high rheumatoid factor titers and in the setting of more severe joint involvement. However, it is a subject of debate. High resolution computed tomography (HRCT) has been proven to be useful for the detection and characterization of morphological changes in the lungs of RA patients (1).

OBJECTIVE

Our aim was to investigate the prevalence and types of pulmonary involvement in patients with longstanding rheumatoid arthritis using high-resolution computed tomography scan (HRCT).

MATERIAL AND METHODS

Our study included 92 RA patients. They were diagnosed according to the ACR/EULAR 2010 criteria. All patients were recruited from "Sf. Apostol Andrei" Emergency Clinica County Hospital of Constanța from June 2017 to June 2019. Data collected were: patients' characteristics, including age, sex and smoking history, history regarding respiratory symptoms (cough, dyspnea, sputum production), serum levels of anti-citrullinated protein antibody and rheumatoid factor (RF), disease activity as assessed by the Disease Activity Score-28/Erythrocyte sedimentation rate (DAS28-ESR),medication for RA(diseasemodif yingantirheumaticdrugs). All patients underwent plain radiograph chest P/A and chest HRCT. HRCT images were evaluated independently by a radiologist, rheumatologist and a pulmonologist. HRCT abnormalities included the following findings: (1) bronchial dilatation (bronchiectasis), (2) bronchial wall thickening, (3) airspace consolidation, (4) nodular attenuation (including parenchymal micronodules, nodules and subpleural micronodules), (5) ground-glass attenuation, (6) linear attenuation (reticulation), (7) honeycombing, (8) architectural distortion, (9) emphysematous lesions, (10) enlarged lymph nod, (11) pleural abnormalities (pleural thickening, pleural calcification, pleural effusion) (5-7).

Pulmonary abnormalities described above were classified into four main domains: interstitial lung disease (ILD) (ground-glass opacity, reticular pattern, honeycombing, consolidation), airway disease (AD) (bronchiolitis, bronchial wall thickening, bronchiectasis, cystic bronchiectasis), nodular lesions (including parenchymal micronodules, nodules, and subpleural micronodules) and others (pleural thickening, pleural calcification, pleural effusion, lymph node enlargement, emphysematous lesions -low attenuation area/LAA- and atelectasis (5,6,8).

Tuberculosis (TB) sequelae, definedas apical nodules associated with fibrotic changes, were excluded.

Statistical analysis was performed using SPSS 20.0 software. Numerical variables, analysed using Student t test, were expressed as mean ± SD. Categorical variables, evaluated using Chi-square test or exact Fisher test, were expressed as frequencies and percentages.

RESULTS

Study cohort characteristics

The subjects were predominantely female, 73 (79.3%), the mean age at entry was 63.77 ±11.56 years and 39 patients (42.9%) had a history of smoking, with a mean of 18.19±17.26 pack-years. Mean age at RA onset was 50.7 ±15.25 years and disease duration was 15.00±11.55 years. All patients had long standing disease. Anti-CCP antibody and RF were positive in 81.5% and 90.2% of the subjects, respectively. Metothrexate was the cDMARD used in 50 of our subjects (53.8%). Erosive disease was identified in 70 subjects (76.1%). Most patients were overweight or obese and mean BMI was of 29.53±28.07. Respiratory symptoms were present in 65 patients (70.7%), with exertional dyspnea being the main complaint in 59 of the cases(64.1%), followed by non productive cough in 46 patients (50%) and productive cough in 15 cases (16.3%). The X-ray abnormalities were present in 46 of cases (50%) and 71 patients (77.2%) had abnormal chest CTs (Table 1).

Pulmonary CT anomalies were correlated with respiratory symptoms and chest X-ray changes. There were no significant correlations between the presence of HRCT pulmonary lesions and the patients' demographic characteristics (age, sex, smoking history) or the RA features (disease duration, RF seropositivity, disease activity, the severity of joint involvement, methotrexate therapy) (Table 2).

The most prevalent chest HRCT abnormalities are identified in the pulmonary parenchyma, linear attenuation, groundglass opacity, airspace consolidation, honeycombing and archytectural dystortion being the structural anomalies characteristic of interstitial lung disease (ILD) (9) (Table 3, Table 4).

TABLE 1. *Study cohort characteristics*

Variable (n=92)	Patients (%)	Mean and standard deviation
Women	73 (79.3%)	
Age	-	63.77 ±11.56 years
BMI (kg/m²)		27,19± 5.17
History of smoking	39(42.9%)	
Disease duration	-	15.00±11.55 years
Positive RF	83 (90.2%)	
Anti CCP antibodies	75 (81.5%)	
Active disease (DAS28-ESR)	69 (75.1%)	
MTX	50 (53.8%)	
TB sequelae	14 (15.2%)	
Respiratory symptoms	65 (70.7%)	
X-ray pulmonary anomalies	46 (50%)	
Chest HRCT anomalies	71(77.2%)	

TABLE 2. *Main features of the patients presenting with CT changes.*

	CT (+) (n = 71)	CT (-) (n = 21)	P
Women	55 (77.5%)	18 (85.7%)	0.547
Age	64±11.43	63±12.24	0.73
Smoking history	31 (43,7%)	8 (38.1%)	0.776
Disease duration	13.8±9.88	19.00±15.59	0.071
Positive RF	65 (91.7%)	18 (85.7%)	0.42
Active disease (moderate/ high disease activity)	44(62%)	12 (57.1%)	0.69
Erosions	54 (76.1%)	16 (76.2%)	0.9
Methotrexate	40 (56.3%)	10 (47.6%)	0.481
Respiratory symptoms	59 (83.1%)	6(28.6%)	**<0.001**
Chest Xray abnormalityes	44 (62.0%)	2 (9.5%)	**<0.001**

They are seconded by the CT abnormalities suggestive for airway disease (AD) (bronchial dilatation and bronchial wall thickening). Pleural changes were identified in 28 patients (39.43%): 21 cases had pleural thickening, 2 patients had an isolated pleural effusion and in 5 cases these changes coexisted. Positive high-resolution computed tomography findings are presented in the table below (Table 3).

TABLE 3. *Main pulmonary lesion types among patients*

Lesion type (%)	N = 71
Linear attenuation (reticulation)	52%
Nodular attenuation	39.43%
Bronchial dilatation (bronchiectasis)	33.8%
Bronchial wall thickening	11.26%
Pleural abnormalities	39.43%
Enlarged lymph nodes	29.57%
Emphyzema	28.16%
Ground-glass attenuation	9.85%
Airspace consolidation	8.45%
Honeycombing	7.04%
Archytectural distortion	5.63%
Air trapping	-

TABLE 4. *Main causes of pulmonary lesions (N = 71)*

ILD	Groundglass opacity	9.85%
	Reticular pattern	52%
	Honeycombing	7.04%
	Consolidation	8.45%
	Archytectural dystortion	5.63%
AIRWAY DISEASE	Bronchiectasia	33.8%
	Bronchial wall thickening	11.26%
NODULAR LESION	Nodular pattern	39.43%
OTHER	Pleural thickening	36.6%
	Pleural effusion	9.8%
	Emphysematous lesions	28.16
	Enlarged lymph node	29.57%

DISCUSSIONS

Even though cardiovascular disease is the most common cause of RA-related death, pulmonary manifestations contribute significantly to morbidity, leading to a mortality of 10-20% in RA patients (3).

Our study showed that RA patients had considerable changes on chest HRCT, with higher or similar rates when compared to other studies investigating pulmonary HRCT features in patients with long-standing RA (Table 5) (2,8,10-12).

TABLE 5. *Clinical and demographic features of RA patients with CT abnormalities*

	Remy-Jardin, 1994	**Cortet, 1997**	**Youssef, 2012**	**Shawky, 2020**	**Tanaka, 2020**	**Andronache, 2021**
Patients who underwent chest HRCT	77	68	36	82	208	92
Age (years)	57±9	58.8 ± 10.6	48,5 (median)	59.43±3.68	59.25±13.16	63.77±11.56
Disease dura-tion (years)	12±8	12 ± 9.2	8 (median)	6.01±2.02	7.94±9.31	15.00±11.55
FR (+)	NA	52 (76.5%)	28 (77.8%)	64 (78.8%)	175 (84.1%)	83 (90.2%)
Smoking his-tory	8 (10.38%)	16 (23.5 %)	none	16 (19.5%)	97 (46.8%)	39 (42.9%)
Respiratory symptoms	27 (35.06%)	-	NA	35 (42.7%)	21 (10.1%)	65 (70.7%)
CT findings	38 (49%)	55 (80.9%)	17 (47.2%)	47 (57.3%)	146 (70.2%)	71 (77.2%)

TABLE 6. *Chest CT anomalies in RA patients*

Lesion type (%)	**Remy-Jardinet 1994 (n = 77)**	**Cortet 1997 (n = 68)**	**Tanaka 2004 (n = 63**	**Mori 2008 (n = 61)**	**Youssef 2012 (n = 36)**	**Shawky 2020 (n = 82)**	**Tanaka 2020 (n = 146)**	**Andronache 2021 (n = 71)**
Bronchial dilatation (bronchiectasis)	30%	30.5 %	75%	49.2%	36.1%	12.2%	41.3%	33.8%
Bronchial wall thickening				18%		17.1%		11.26%
Nodular attenuation	22%	28%	49%	47. 5%	11.1%	29.2%	21,6%	39.43%
Linear attenuation (reticulation)	18%	-	98%	13.1%	22.2%	-	20.2%	52%
Ground-glass attenuation	14%	17.1%	90%	26.2%	11.1%	24.2%	6.3%	9.85%
Honeycombing	10%	2.9%	60%	9.8%	5.6%	12.2%	6.7%	7.04%
Airspace consolidation	6%	-	35%	4.9%	-	8.5%	7.7%	8.45%
Archytectural dystortion	6%	-	62%	0	-	-	-	5.63%
Emphyzema	5%		24%	-	5.6%	-	-	28.16%
Air trapping	-	25%	43%	-	-	-	-	-
Enlarged lymph node	9%	-	20%	-	-	-	-	29.57%
Pleural abnormalities	16%	1.5%	29%	-	5.6%	-	-	39.43%

The prevalence and type of pulmonary abnormalities identified on chest HRCT vary among different studies and reasons for that are: different definitions, aims and heterogeneous patient populations (Table 6) (1,2,6,8,10-12). Lack of a unitary classification leads to dissipated data. However, the lesions suggestive for airway disease (bronchial dilatation and bronchial wall thickening) are constantly present in at least 30% of the cases (30-75%). In our study, linear attenuation (reticulation), as asign of ILD, is the most frequent CT finding (52%).

The Remy-Jardinet et al. 1994 cohort included 84 patients (65.47% women), with a mean disease duration of 12±8 years). Thirty eight (49%) patients had abnormal CT scans. Abnormalities identified were: bronchiectasis (30%), pulmonary nodules (22%), ground glass attenuation (14%) and honeycombing (10%) (10).

In 1997, Cortet et al. compared the results of pulmonary function tests (PFTs) and lung HRCT in rheumatoid arthritis (RA) patients. This study included 68 patients, (79.41% women) with a mean age of 58.8 years (range: 35-82) and a mean disease duration of 12 years (range: 5-16). Rheumatoid factor was positive in 52 patients (76.5%). Fifty two patients (76.5%) were lifelong non-smokers. Fifty-five patients displayed an abnormal HRCT pattern. The most frequent HRCT findings were: bronchiectasis (30.5%), pulmonary nodules (28%), and air trapping (25%). Ground glass attenuation and honeycombing were present in 17.1%, respectively 2.9% of the patients(2).

Akira et al. studied 29 RA patients (22 of them – 75.86% with CT changes) and they identified three major patterns on CT: reticulation with or without honey combing (86.36%), centrilobular branching lines with or without bronchial dilatation (22.72%) and consolidation (22.72%) (13).

The advent of lung HRCT lead to the possibility of a more detailed assessment of lung involvement: Youssef et al., in 2012, in a series comprising non-smokers, 34 females (94.4%) and 2 males (5.6%), with median age of 48.5 years and median disease duration of 8 years, 77.8% positive for RF, and nearly two-thirds (28/36) of the patients with one or more pulmonary symptom such as dyspnea, cough, wheezing or phlegm, yielded the following results: based on the HRCT findings, abnormalities were detected in 17 patients (47.2%). In regards to the type of pulmonary involvement detected, interstitial lung disease was the commonest as it was detected in 14 patients (38.9%). Eight patients (22.2%) had reticular opacities, while two (5.6%) had honeycombing and 4 (11.1%) had ground-glass opacity. Bronchial abnormalities were detected in 13 patients (36.1%), emphysema in 2(5.6%), rheumatoid pulmonary nodules in 4 patients (11.1%), and pleural effusion in 2 (5.6%) (11).

Sabri et al., in 2015, evaluated HRCT findings in patients with pulmonary complications of RA. The study involved 20 patients, 70% women, aged 16-64 years (average 48 years). All patients were known cases of RA presenting with dyspnea and cough. All of them had HRCT changes: 9 cases (45%) showed signs of interstitial disease (bilateral sub-pleural predominantly basal ground glass opacification, bilateral sub-pleural predominantly basal reticulation with traction bronchiolectasis, diffuse ground glass), 9 cases (45%) airway disease (hyperinflation, bronchial wall thickening, mild bronchiectasis , mosaic perfusion, beading of the bronchial wall – suggesting follicular bronchiolitis) and findings of both entities in 2 cases (10%) (14).

Recently, in 2020, Shawky et al. presented data from their cohort: eighty-two longstanding RA patients (the mean duration was 72.15±24.03 months), 57 females and 25 males, mean age 59.43±3.68 years, 16 smokers (19.5%), 35 patients complaining of respiratory symptoms (42.7%); abnormal CT findings were detected in 47 patients (57.3%): ground glass appearance in 24,4%, bronchial wall thickening in 17.1%, micronodules in 29.2% (parenchymal 14.6% and subpleural 14.6%), honeycomb appearance in 12.2%, bronchial dilatation in 12.2%. (12).

CONCLUSIONS

Pulmonary involvement evaluated via chest HRCT is present in a high percentage of RA patients, even in those with no chest X-ray findings or respiratory complaints. We identified interstitial lung disease as the main cause of pulmonary lesions, followed by airway disease.While there is a high proportion of pleural abnormalities, some may be secondary to previous TB infection.

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