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Ultrasonographic evaluation of lung parenchyma involvement in sarcoidosis

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Abstract. *Purpose:* To use ultrasonography (USG) for the evaluation of lung parenchyma in patients with sarcoidosis, andto compare the USG findings with the results of a high-resolution computerized tomography (HRCT) and pulmonary function test-carbon monoxide diffusion test (PFT-DLCO), which are commonly used methods in the evaluation of parenchymal involvement in sarcoidosis. *Material and Methods:* Patients with sarcoidosis and healthy controls were enrolled in the study between January 2015 and December 2017. The clinical findings, HRCT and PFT-DLCO results of all subjects were recorded, and USG findings and comet tail artifact (CTA) measurements were recorded by another pulmonologist. The USG, HRCT and SFT-DLCO findings were compared between the two groups. Based on the findings of theclinical-radiologic investigations and PFT-DLCO, as the current gold standard in diagnosis, the sensitivity and specificity of USG in demonstrating lung parenchyma involvement in sarcoidosis patients were estimated. *Findings:* The sarcoidosis group consisted of 79 patients and the control group included 34 subjects. The mean number of CTAs in the sarcoidosis and control groups was 33.4 and 25, respectively (p=0.001). In the sarcoidosis group, the number of CTAs in patients with DLCO% <80 and ≥80% was 37.4 and 29.7, respectively (p=0.011), and a negative correlation was identified between the number of CTAs and DLCO% (p=0.019 r=-0.267). The mean number of CTAs in patients with and without parenchymal involvement in HRCT was 36 and 25.5, respectively (p=0.001). The number of CTAs in the patients with sarcoidosis with a normal DLCO% value (≥80%) was higher than in the control group (p=0.014). The diagnostic sensitivity and specificity of thoracic USG were found to be 76% and 53%, respectively. *Conclusion:* The number of CTAs in patients with sarcoidosis was higher than that of the healthy controls. The number of CTAs in patients with sarcoidosis with parenchymal involvement in HRCT and/or a low DLCO (<80%) was also elevated. Thoracic USG has a high sensitivity (76%) in demonstrating parenchymal involvement in patients with sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (2): 130-140)*

Key words: B-lines, lung ultrasonography, sarcoidosis

Introduction

Sarcoidosis is a systemic granulomatous disease with an unclear etiology, which is frequently associated with pulmonary involvement and results in non-caseating granulomatous infiltration. The majority of cases are asymptomatic at the time of diagnosis, and many cases resolve spontaneously without treatment. Approximately 25% of cases are associated with progressive pulmonary disease (1-3), and the pulmonary parenchymal involvement of sarcoidosis is crucial regarding disease staging and the initiation of treatment. Sarcoidosis is classified into five stages based on a lung X-ray findings (4). The disease is considered

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to be at an advanced stage in the presence of a parenchymal reticular appearance and traction bronchiectasis without hilar lymph node involvement, together with honeycomb appearance and reticular opacities. Progressive parenchymal radiologic changes, such as parenchymal cavitary appearance, lung honeycombing and fibrotic changes, also represent indications for treatment (5).

Ultrasonography (USG) transmits high-oscillating sound waves to tissues, and an image is presented on a monitor based on the reflection or refraction of these sound waves as they travel back to the USG probe. Multiple reflections of a sound wave between the tissue and the probe, or between two tissues, is referred to as reverberation artifact (6). Thoracic USG is commonly used for several diagnostic procedures in pulmonology practice, although its use for the assessment of lung parenchyma/interstitium is relatively limited (7). Diseases that involve the interstitium present with interstitial inflammation, fibrosis, thickened interstitial surface, and thickened interlobular septa (8). Healthy lungs are filled with air in the absence of a pathologic condition, as such they are not well-visualized in sonography. Changes due to the involvement of interstitial zones and the thickening of the interlobular septa (ILST) in the presence of interstitial lung diseases (ILD) result in comet tail artifacts (CTAs), as a type of reverberation artifact detected in USG. CTAs develops when a sound beam hits a reflective surface. A dense tail appearance with a gradually decreasing echogenicity appears on the monitor between the subsequent echoes transmitted to the transducer (9) (Figure 1).

When we looked at the literature, we have seen that there is only one study using USG for the assessment of lung parenchymal involvement in sarcoidosis (10). In the present study, the intention was to use USG for the evaluation of lung parenchyma in patients with sarcoidosis, and thento compare the USG findings (CTA) with the results of high-resolution computerized tomography (HRCT) and pulmonary function test-carbon monoxide diffusion tests (PFT-DLCO). We aimed to investigate the use of thoracic USG in the evaluation of lung parenchymal involvement in sarcoidosis, as a simple, easily-accessible, and reproducible imaging method that eliminates radiation exposure.

Material and Methods

Patient population

This prospective, controlled, cross-sectional study was conducted between January 2015 and December 2017 in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee. The study population com-

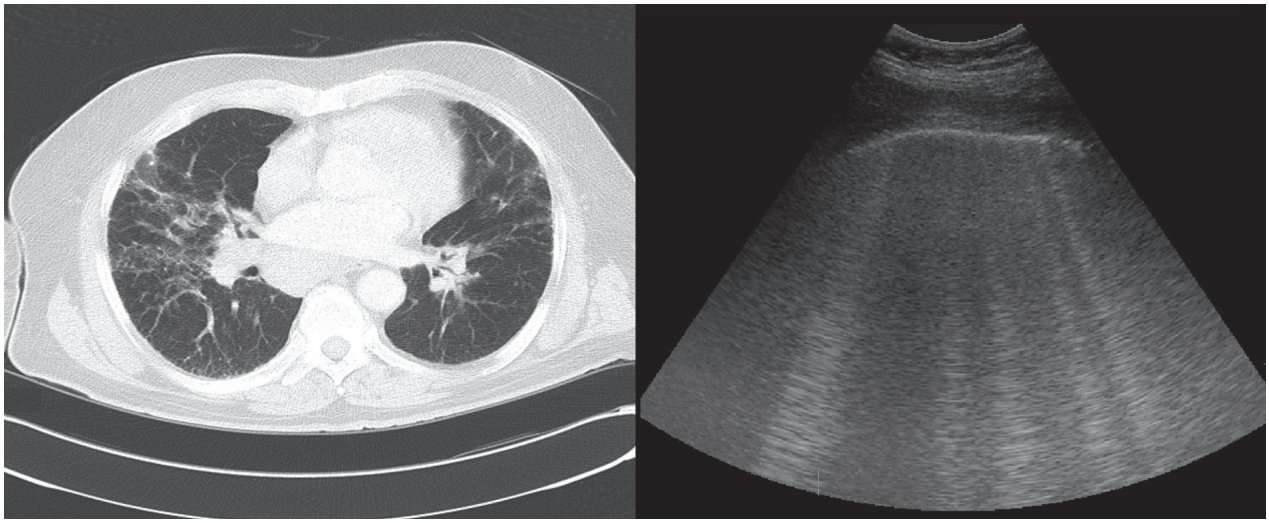

Fig. 1. Bilateral ground-glass densities in HRCT and CTAs detected using thoracic USG (CTAs marked by red arrow on the left) in patients with sarcoidosis. On the monitor, CTAs start with a narrow baseat the visceral pleural region and extend towards the peripheral along the monitor.

prised two groups: patients who had been diagnosed as having sarcoidosis based on clinical, radiologic and histopathologic findings in our pulmonology clinics (sarcoidosis group), and healthy subjects with no clinical or radiologic signs or symptoms suggestive of ILD, and who had a normal HRCT scan (control group).

Patients with other previously diagnosed interstitial lung diseases and patients with congestive heart failure (CHF) were excluded from the study. Clinical inquiry and physical examination (PE) findings, HRCT findings, and pulmonary function test (PFT) and DLCO results of all subjects were collected and recorded by a pulmonologist. Then, a thoracic USG of the subjects was performed by another pulmonologist who had no information on the diagnosis and was blinded to the HRCT and PFT-DLCO findings. The number of CTAs detected at the pre-specified anatomic lines was recorded during the thoracic USG.

Pulmonary function test and carbon monoxide diffusion test

The PFT-DLCO tests of the participants were conducted according to the guidelinesof the American Thoracic Society (ATS) and European Respiration Society (ERS) for the standardization of pulmonary function tests (11-12). The SFT and DLCO measurement tests were performedon a Sensor Medics Vi-Max 22, CareFusion, (San Diego, California) device using the single breath technique. For each lung volume, values of between 80 and 120% of the predicted value were considered normal, and forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and FEV1/FVC parameters were recorded in liters (Lt) and percentages. The DLCO (mL/minute/mmHg/Lt) and DLCO/alveolar ventilation ratios (VA) (DLCO/L, %) were considered normal when values were between 80 and 120% of the predicted value for each lung, and values were recorded in liters and percentages.

High-resolution computerized tomography

HRCTs were obtained after deep inspiration using a high-resolution technique from the axial plane, starting with the apex towards the end of the diaphragm, with 15-mm table movement, at 120 kV, 200 mA, with section thickness of 2 mm, at a 512 × 512 matrix and bone algorithm using a Siemens Medical Solutions-2010 (Forchheim, Germany) device without the use of contrasting agent. Images were obtained with a window width of 1200 Hounsfield units (HU), at window level of 700 HU.

Thoracic ultrasonography

The thoracic USG was performed by a pulmonologist experienced in USG, using a General Electric (GE) Logic 7 device and a 3.5 MHz convex probe in the abdominal mode. The sonographic scanning of the thorax was performed on a total of 12 predefined bilateral anatomic lines, the first line being the linea mid-clavicular, as the vertical line passing through the mid-section of the clavicula at the anterior thorax. The other lines were as follows: linea axillaris anterior, the vertical line passing anterior to the plica axillaris anterior to the lateral thorax; linea axillaris media, the vertical line starting from the axilla apex; and linea axillaris posterior, the line starting from posterior of the linea axillaris. The final lines were the linea scapularis, the vertical line that transverses the angulus inferior scapula at the posterior thorax, and the linea paravertebralis, which progresses parallel to the vertebral column (Figure 2).

Comet tail artifact definition

CTAsare defined as hyperechogenic, adjacent bundle structures that start from the visceral pleura with a narrow base and broadening while running peripherally along the monitor and are observed when the USGprobe is located on an intercostal space (6). Along each of the pre-specified anatomic lines, the regions with the highest number of CTAs were detected while the probe was moved longitudinally along the intercostal spaces while the patient was in the sitting position. The numbers of CTAs in these regions were recorded.

Statistical analysis

The statistical analysis was performed using SPSS 17.0 (IBM Inc. Released 2008. SPSS Statistic for Windows Chicago, US) software. Descriptive statistics are presented as mean±standard deviations for continuous variables, and as percentages for cat-

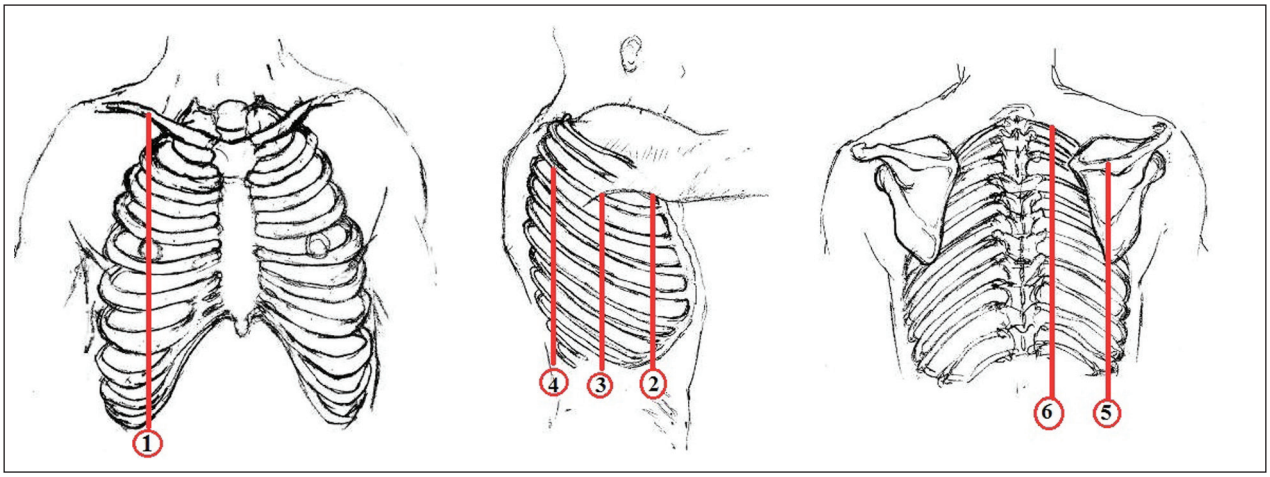

Fig. 2. Pre-specified anatomic lines (1-Linea mid-clavicularis, 2-Linea axillaris anterior, 3-Linea axillaris media, 4-Linea axillaris posterior 5-Linea scapularis 6-Linea para vertebralis).

egorical variables. The Kolmogorov-Smirnov test was used to check for normal distribution of the variables. Chi-square, t-test, Mann-Whitney U, and receiver operating curve (ROC) analysis tests were performed as necessary to compare the data between the two groups. A correlation analysis was performed to assess the relationship between the SFT-DLCO parameters and the CTA numbers of the participants. The correlation coefficient is presented with "r" values, and *p*-values lower than 0.05 were considered statistically significant.

Findings

A total of 113 patients were included in the study, with 79 (67.2%) in the sarcoidosis group and 34 (32.8%) in the control group. After being identified with concomitant CHF, two patients in the sarcoidosis group were excluded from the study. Of the remaining 77 patients with sarcoidosis, 60 (77.9%) were women, and 17 (22.1%) were men, and the mean age of the patient group was 48.1±14.4 years. Of the 34 patients in the control group, 13 (38.2%) were women, and 21 (61.8%) were men, and mean age was 39.7±12.7 years. In the sarcoidosis group, 18 (23.3%) patients had a history of smoking;the remaining 59 (76.7%) patients had no history of smoking. The mean smoking history was 8.2±4.6 pack-years. The mean age of the patient group and the proportion of females were significantly higher than in the control group (p<0.004, p<0.001, respectively) (Table 1).

Among the symptoms of the patients with sarcoidosis, the most frequently reported was exhaustion, reported by 49 (63.6%). The laboratory findings of the patients showed that four (5.1%) had hypercalcemia and four (5.1%) had hypercalciuria. In total, 14 (18.1%) patients had elevated serum ACE levels, and regarding the stage of sarcoidosis, 20 (26%), 30 (39%), 22 (28.6%), and five (6.5%) patients were at stages 0, 1, 2, and 3 of the disease, respectively. No patients were at stage 4.

The HRCT findings showed that 19 patients had normal lung parenchymaand 58 had a lung parenchyma pathology. Twenty-seven (35.1%) patients had bilateral ground-glass opacities, 10 (13%) had bilateral ILST, and 9 (11.7%) had a bilateral reticular appearance (Table 2). The HRCT findings of all patients in the control group were normal. The PFT-DLCO test results of the patients with sarcoidosis showed that the FEV1 Lt, FEV1%, FVC Lt, FVC %, DLCO (mL/dakika/mmHg) and DLCO% values

Table 1. Demographic characteristics of patients with sarcoidosis and the control group

	Sarcoidosis group (n=77)	Control group (n=34)	p value
Age (years ±sd)	48.1±14.4	39.7±12.7	p=0.004
Sex (f/m)	60/17	13/21	p<0.001
Smoking history (yes/no)	18/58	10/24	p=0.643
Smoking (pack-years±sd)	8.2±4.6	10.1±7.2	p=0.475

Table 2. HRCT findings in patients withsarcoidosis

HRCT findings	
Parenchymal abnormal findings (Yes/No)	58/19
Right lung nodule larger than 1 cm	30(39%)
Left lung nodule larger than 1 cm	25(32.5%)
Bilateral ground-glass appearance	27(35.1%)
Left lung sequela band appearance	22(28.6%)
Right lung sequela band appearance	19(24.7%)
Bilateral reticulo-nodular appearance	16(20.8%)
Bilateral peri-lymphatic, broncho-vascular, 1-2 mm nodules located along ILS	10 (13%)
Bilateral ILST	10 (13%)
Bilateral traction bronchiectasis / honeycombing appearance	8 (10.4%)
Bilateral mosaic perfusion appearance	5 (6.5%)
Other	12(15.6%)

ILST: Inter-lobular septal thickening

were significantly lower than those of the controls (p<0.05) (Table 3).

The CTA numbers of patients with sarcoidosis were not significantly different to the those of the controls in the right and left linea axillaris anterior, right linea mid-clavicularis, and left linea axillaris media regions (p>0.05). The CTA numbers in all other scanned regions were significantly higher in patients with sarcoidosis than in the controls (p<0.05). The mean number of CTAs in the patient and control groups was 33.4±13.1 and 25±6.5, respectively (p=0.001) (Table 4).

Analyses of the correlations between the PFT-DLCO parameters and the number of CTAs in the sarcoidosis group showed that DLCO% values were ≤80% and >80% in 37 (48%) and 40 (52%) of the patients, respectively. The mean number of CTAs in patients with DLCO% ≤80% was 37.4±15.8, whereas this figure was 29.7±8.7 in patients with DLCO% >80%, which represents a statistically significant difference (p=0.011) (Table 5). There was no significant relationship between the number of CTAs and FEV1% or FVC% in patients with sarcoidosis (p>0.05) (Table 5). The total number of CTAs was negatively correlated with the DLCO% of patients with sarcoidosis (p=0.019 r=-0.267) (Figure 3). No significant correlations were identified between FEV1 and the number of CTAs, FEV1% and the number of CTAs, FVC, and the number of CTAs, or FVC% and the number of CTAs (p>0.05).

The HRCT findings of the patients in the sarcoidosis group indicated that 58 patients had parenchymal involvement, and the number of CTAs in patients with parenchymal involvement in HRCT was 36±13.5, which was significantly higher than in patients without parenchymal involvement (25.5±7.9) (p=0.001). The mean number of CTAs in 19 (24.6%) patients with sarcoidosis who had a normal HRCT (no parenchymal pathology seen) was 25.5±7.9,

Table 3. PFT-DLCO findings in patients withsarcoidosis and the control group.

PFT-DLCO parameters	Sarcoidosis group (n=77)	Control group (n=34)	p value
FEV1/FVC(Mean±sd)	76.8±7.4	78.4±8.6	p=0.309
FEV1 (Mean±sd)(Lt)	2.53±0.78	3.80±0.8	p<0.001
%FEV1 (Mean±sd)	91.2±17.8	99.6±12.4	p=0.014
FVC (Mean±sd)(Lt)	3.15±0.98	4.35±1	p<0.001
%FVC (Mean±sd)	98.7±17.8	106.2±12.5	p=0.028
DLCO (Mean±sd) (mL/minute/mmHg)	6.61±2.40	9.91±2	p<0.001
%DLCO (Mean±sd)	83.4±18.3	99.7±14.5	p<0.001
DLCO/VA(mL/minute/mmHg /Lt) (Mean/sd)	1.99±1.05	1.76±0.29	p=0.082
%DLCO/VA	101.43±16.9	109.18±16.9	p=0.029

DLCO:Carbonmonoxide diffusion capacity. FVC: Forced vital capacity. FEV1: Forced expiratory volume in one second. VA: Alveolar volume. Mean: Mean SD: Standard deviation

Table 4. Number of CTAs detected on the anatomic lines in patients withsarcoidosis and the control group

Anatomic line	Sarcoidosis group (n=77)	Control group (n=34)	p value
Right linea para-vertebralis (Mean±sd)	2.4±1.4	1.3±0.8	p<0.001
Right linea scapularis (Mean±sd)	3.2±1.9	2±0.8	p<0.001
Right linea axillaris posterior (Mean±sd)	3.78±1.7	2.9±1.1	p=0.011
Right linea axillaris media (Mean±sd)	3.4±1.6	2.9±1	p=0.061
Right linea axillaris anterior (Mean±sd)	2.9±1.9	2.3±1.1	p=0.041
Right linea mid-clavicularis (Mean±sd)	2.3±1.4	1.8±1	p=0.052
Left linea para-vertebralis (Mean±sd)	1.8±1.3	1.3±0.3	p=0.039
Left linea scapularis (Mean±sd)	2.9±1.7	1.9±0.9	p=0.001
Left linea axillaris posterior (Mean±sd)	3.2±1.7	2.5±1.1	p=0.006
Left linea axillaris media (Mean±sd)	2.7±1.5	2.4±1	p=0.228
Left linea axillaris anterior (Mean±sd)	2.3±1.4	1.9±0.9	p=0.095
Left linea mid-clavicularis (Mean±sd)	2.1±1.3	1.5±0.8	p=0.014
Mean number of CTAs (Mean±sd)	33.4±13.1	25±6.5	p=0.001
Number of CTAs per ICS (Mean±sd)	2.7±1	2±0.5	p=0.001

CTA: Comet tail artefact. ICS: Intercostal space Mean: Mean SD: Standard deviation

Table 5. The relation between PFT-DLCO values and number of CTAs in patients with sarcoidosis

PFT-DLCO parameters		Number of patients (n/%)	Number of CTAs (Mean/SD)
	%FEV1<80%	21 (27.2%)	34.6±15.7
%FEV1	%FEV1>80%	56 (72.8%)	32.9±12.2
	p value	-	p=0.868
	%FVC <80%	13 (16.8%)	33.5±14.4
%FVC	%FVC >80%	64 (83.2%)	33.4±13
	p value	-	p=0.962
	%DLCO <80%	37 (48%)	37.4±15.8
%DLCO	%DLCO >80%	40 (52%)	29.7±8.7
	p value	-	**p=0.011**

DLCO:Carbonmonoxide diffusion capacity. FVC: Forced vital capacity. FEV1: Forced expiratory volume in one second. VA: Alveolar volume. Mean: Mean SD: Standard deviation

whereas the mean number of CTAs in the control group was 25±6.5. The difference between the two groups was not statistically significant (p=0.801).

When the relationship between disease stage and the number of CTAs in patients with sarcoidosis was investigated [number of CTAs in patients with stage 0-1-2 and 3 disease; 26.5±10.9, 32.5±10.9, 36.7±11.2, and 51.6±18.5, respectively (Figure 4)], both a one-way ANOVA test and a Bonferroni posthoc test indicated that a significant relationship existed between the disease stage groups and the number of CTAs (p<0.05) (Table 6). No significant

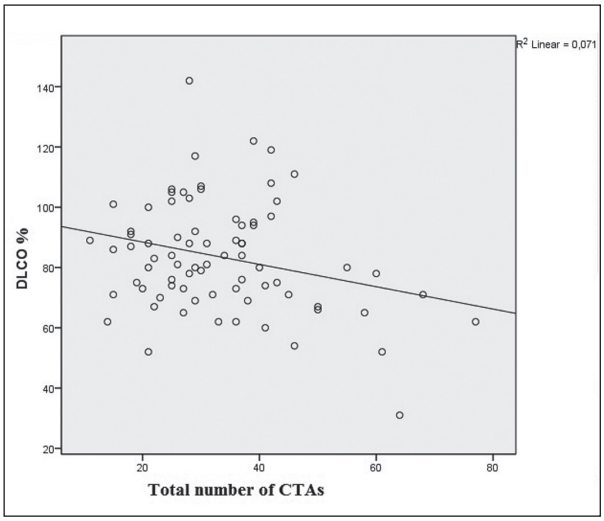

Fig. 3. The line shows the negative correlation between DLCO% value and total number of CTAs in patients with sarcoidosis

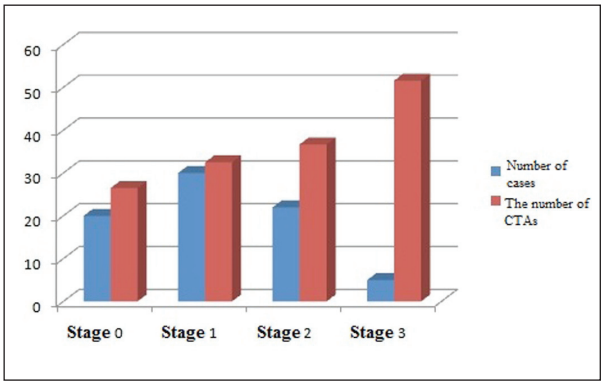

Fig. 4. Graph showing the relationship between disease stage and the number of CTAs in patients with sarcoidosis (Stage 0 number of CTAs 26.5, Stage 1 number of CTAs 32.5, Stage 2 number of CTAs 36.7, Stage 3 number of CTAs 51.6)

relationship was found between disease duration and the number of CTAs (p>0.05).

A total of 40 (51.9%) patients in the sarcoidosis group had a DLCO% of 80 or higher, and the mean number of CTAs in these patients was 29.7±8.7, whereas the mean number of CTAs in the control group was 25±6.5. The mean number of CTAs in patients with sarcoidosis with normal DLCO% values (≥80%) was significantly higher than in the controls (p=0.014).

When HRCT is considered the gold standard, the ROC analysis showed that the cut-off value for the detection of the optimal number of CTAs using USG was 25.5 (AUC:0.725). When the number of CTAs was higher than 25.5, the sensitivity and specificity of USG were estimated as 76% and 53%, respectively (Figure 5).

Table 6. The relation between sarcoidosis stage and number of CTAs in patients with sarcoidosis

Sarcoidosis stage		p value
Stage 0	Stage 1	0.516
Stage 0	Stage 2	0.042
Stage 0	Stage 3	p<0.001
Stage 1	Stage 2	p=0.999
Stage 1	Stage 3	p=0.009
Stage 2	Stage 3	p=0.085

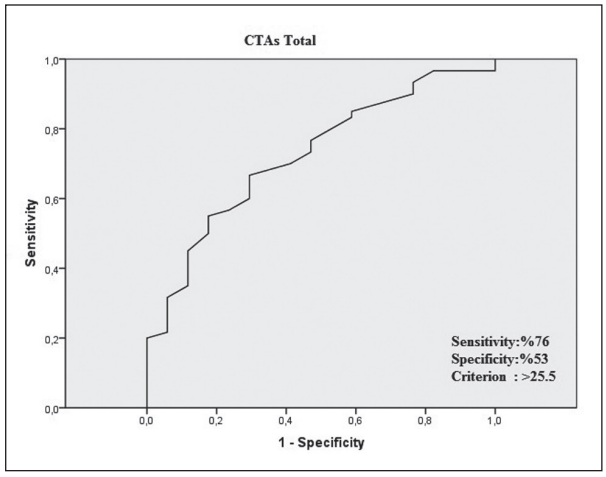

Fig. 5. CTAs evaluation according to high resolution computed tomography involvement

Discussion

The results of the present study show that the number of CTAs in patients with sarcoidosis were significantly elevated when compared to the healthy controls. The number of CTAs detected in a thoracic USG was also elevated in sarcoidosis patients with lung parenchymal involvement in HRCT and decreased DLCO (<80%) levels. The primary, and the most important, outcome of this study is the increased number of CTAs identified in the sarcoido-

sis patients when compared to the healthy controls, while of secondary importance is the correlation found between the thoracic USG findings and the HRCT and DLCO results, as markers of lung parenchyma involvement, in patients with sarcoidosis. The third most important outcome is the significant increase noted in the number of CTAs detected by USG in sarcoidosis patients with normal DLCO% values (DLCO>80%) when compared to the control group. When HRCT findings were considered as the gold standart, the sensitivity and specificity of thoracic USG for demonstrating parenchymal involvement were found to be 76% and 53%, respectively.

Sarcoidosis is a systemic granulomatous disease that most frequently affects the lungs. The rate of disease-related morbidity and mortality depends on the presence of lung involvement (14). Although lung X-ray is the first and the most commonly used method in the identification of lung parenchyma, the most effective radiologic method for this purpose in the present day is HRCT. Large-scale cohort studies have established the superiority of HRCT over other methods in demonstrating lung parenchyma involvement in sarcoidosis (15-17). In addition to such conventional methods as lung radiography, CT and HRCT, previous studies have also drawn attention to magnetic resonance imaging (MR) and radionucleotide methods (Gallium scintigraphy, PET-CT) as potential imaging modalities for sarcoidosis (18). In contrast, there are very few studies that investigated the use of USG as an imaging method in sarcoidosis (10), which remains under-researched. The transmission of sound waves through normal lung parenchyma is weak given that the lungs are filled with air, and this prevents them from being visualized as clearly as other, more solid, organs (19). However, USG may be a good diagnostic tool in the presence of conditions associated with lung edema or in diseases with diffuse involvement of the lung parenchyma, such as ILD. In 1997, Lichtenstein et al. (20) were the first researchers to demonstrate the increased number of CTAs through the use of thoracic USG in patients who had developed diffuse interstitial fibrosis. In the presence of diseases that cause lung fibrosis, mainly in connective tissue disorders, previous studies that compared thoracic USG with HRCT reported that evaluating the number of CTAs in thoracic USG was a valuable method, and several studies confirmed that there were significant increases in the number of CTAs when HRCT showed findings consistent with ILD (21-23). In the present study, the total number of CTAs detected in patients withsarcoidosis (33.4) was significantly higher than in the healthy controls (25) (p=0.001).

Parenchymal abnormalities that can be observed in the presence of sarcoidosis include ground-glass opacities, reticular opacities, interlobular septal thickening, micronodules (1-4 mm), macronodules (>5mm), patched or diffuse consolidations, fibrotic lesions, honeycombing and traction bronchiectasis (9,15,25). In the present study, USG findings were significantly different between subjects with HRCT findings that suggested lung involvement of sarcoidosis and subjects with a normal HRCT. The total number of CTAs in patients with sarcoidosis with parenchymal involvement in HRCT was 36, compared with 25.5 in patients without parenchymal involvement (p=0.001). A prospective, controlled study that investigatedthe diagnostic value of transthoracic USG in diffuse parenchymal lung diseases used thoracic USG to evaluate 53 patients with various ILDs and reported significant differences in the number of CTAs when compared with healthy controls (p<0.001). The authors of the study classified patients based on the number of CTAs as low (≤6/scan) and multiple (>6/scan), with seven patients with sarcoidosis in their ILD group (27);six (85.7%) of these patients had multiple (>6/scan) CTAs. Reissig et al. (26) is one of the few studies that reportedan increased number of CTAs in patients with sarcoidosis when compared with healthy individuals, supporting the findings of the present study. In Reissig et al's study (26) and in similar research (22, 27), the increased number of CTAs was associated with findings of ILD, including interlobular septal thickening and ground-glass densities. Sarcoidosis is a member of the diffuse parenchymal lung diseases family (28), and in the present study, we determinedthat the number of CTAs detected using thoracic USG was significantly elevated in patients with sarcoidosis who had pulmonary involvement, as demonstrated using HRCT.

DLCO is a more valid approach to demonstrating the lung parenchyma involvement of sarcoidosis than simple spirometric tests. In a recent study by Mañá et al. (29) on a very large sarcoidosis case series (640 patients), 30.3% of patients had abnormal DLCOs, although the ratio of patients with abnormal FVC values was only 16.2%. In the presence of

diffuse parenchymal lung diseases, DLCO decreases as a result of disease involvement in the alveolar-capillary membrane. Young et al. (30) demonstrated previously that DLCO was reduced in patients with sarcoidosis with lung parenchyma involvement, and Carrington et al. (31) developed an index they referred to as the "mean interstitial cell index (MICI)," which demonstrates lung involvement in sarcoidosis, and reported a correlation between MICI and DLCO. Interestingly, they also high lighted the additional importance of DLCO by providing evidence that it could decrease by almost 10 to 30 mL/min/mmHg during exercise in patients with sarcoidosis with near-normal MICI values. In another study by Edis et al. (32), who evaluated the effectiveness of thoracic USG in patients with systemic sclerosis (SS), a total of 48 patients were evaluated using thoracic USG and a negative correlation was found between the DLCO values and the number of CTAs of the patient group. In a prospective study, Hassan et al. (33) compared the number of CTAs detected using thoracic USG in patients with ILD and HRCT and PFT findings and found a negative correlation between DLCO values and CTA frequency, concluding that thoracic USG might be a beneficial tool for the evaluation of ILDs. In a study with 33 patients who were diagnosed with systemic sclerosis Gargani et al. (34) classified the patients based on the number of CTAs detected using thoracic USG as patients with >10 and <10 CTAs and found that DLCO% values in patients with above and below 10 CTAs were 66 and 83, respectively ($p<0.05$). In the present study, we identified no significant relation between CTA and FVC ($p=0.718$ $r=-0.042$), whereas the number of CTAs was found to be negatively correlated with DLCO values($p=0.019$ $r=-0.267$). Moreover, the number of CTAs in patients with sarcoidosis with DLCO% <80 was significantly higher (37.4) than inpatients with DLCO% ≥80 (29.7) ($p=0.011$). To our knowledge, no previous studies have evaluated the relationship between CTA and DLCO in patients with sarcoidosis, although there have been several studies related to diseases that involved the lung parenchyma, which reported a negative correlation between CTA and DLCO values (32-36). Our findings are consistent with the literature because sarcoidosis is a component of ILDs (32-36).

A literature review shows that almost all of the studies on assessment of pulmonary interstitium by USG focused on the diagnostic usability of USG (37). We found two case reports investigating the usability of CTAs detectable by thoracic USG in monitoring disease acitivity or evaluating the response to treatment. A study by Buda N et al. (38) demonstrated a reduction in the number of CTAs in a patient with scleroderma following the treatment. The other study by Laria A et al. (39) showed that CTAs disappeared after the therapy in a patient diagnosed with rheumatoid arthritis associated ILD. Considering the significance of pulmonary parenchymal involvement and improvement after treatment, it should be kept in mind that USG can be used in conjunction with HRCT in monitoring the disease activity and evaluating the response to treatment in sarcoidosis. This can be further elucidated by randomized controlled studies demonstrating that number of CTAs detected by thoracic USG are reducable by treatment.

We found that thoracic USG had a sensitivity of 76% and specificity of 53% in demonstrating the parenchymal involvement in patients with sarcoidosis, which showed that we had a lower sensitivity and specificity for thoracic USG in our study. Relatively lower sensitivity may be associated with high number of false negatives. In cases where USG fails to detect any involvement whereas HRCT shows it, false negatives rate may be associated with the type of the parenchymal disease. For example, the number of CTAs may be different in areas of ground glass opacity compared to the micronodular pattern. Lower specificity may be associated with high number of cases with false positives. Although no parenchymal involvement was demonstrated in HRCT, which is considered to be the golden standard, an increased number of CTAs detectable by USG may increase the number of cases with false positives. It can also be explained by higher sensitivity of USG in parenchymal involvements that are not on a macroscopic level to be detected by HRCT. Further studies are required to evaluate whether HRCT is a golden standard in assessment of parenchymal involvement, and the correlation between the type of parenchymal disease and number of CTAs in sarcoidosis.

This study, which represents a starting point for the use of thoracic USG for the evaluation of lung parenchyma in patients with sarcoidosis, has some limitations. Intra-observer and inter-observer variabilities were not calculated for the assessments of

thoracic USG and identification of CTAs, as well as for HRCT findings, which represents the most important limitation of this study. Therefore, while interpreting the study results one should consider that thoracic USG is a highly user-dependent imaging technique. Another limitation is that this study was performed on a relatively low number of patients and reflected the experiences of a single center. Accordingly, the findings of this study cannot be generalized.

In conclusion, this study has shown that statistically significant correlations exist between thoracic USG findings, which represent a novel method for the assessment of lung parenchyma involvement in patients with sarcoidosis, and the findings of HRCT, which is currently considered to be the most sensitive imaging method for the demonstration of lung parenchymal involvement of sarcoidosis, as well as DLCO, currently known to be the most effective test for showing the diffusion of gases through the alveolar-capillary membrane, and therefore, the potential involvement of the alveolar-capillary membrane. We believe that although it may not be the most preferred method for the evaluation of parenchymal involvement in patients with sarcoidosis, thoracic USG may still have an area of use in the regular monitoring and assessment of treatment response in such patients. Further studies are required to investigate methods of early detection of changes in lung parenchyma. We evaluated the use of USG for assessment of sarcoidosis. We believe that, as much as the healthy lung parenchyma cannot be evaluated using USG, it may be effective for the evaluation of lung parenchyma in the presence of such diseases as ILD, which extensively affects the lung parenchyma.

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