

THE RIGHT UPPER LOBE BRONCHUS ANGLE: A TOOL FOR DIFFERENTIATING FIBROTIC AND NON-FIBROTIC SARCOIDOSIS

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ABSTRACT. *Purpose:* To evaluate the Right Upper Lobe Bronchus Angle (RUL-BA) on chest CT in patients with Stage 4 sarcoidosis and compare to others with non-fibrotic sarcoidosis. *Methods:* IRB approval was obtained for review of all chest CT scans performed from January 2015 through December 2017 that contained the word sarcoidosis using the computer program Montage. The most recent CT scans of 633 people were reviewed. The patients' age and sex at the time of their most recent CT scan were recorded. The radiographic diagnosis and the Right Upper Lobe Bronchus Angle (RUL-BA) were determined by a chest radiologist with 20 years of experience. *Results:* The RUL-BA increased with Stage 4 sarcoidosis, measuring on average 104 degrees, compared to the average angle of 88 degrees for those without fibrotic sarcoid. More often men's CT scans exhibited the earlier stages of sarcoidosis, and a higher number of women's scans showed fibrotic sarcoidosis. As would be expected, scans with advanced disease were typically from older patients; however, there was no correlation between age and degree of fibrosis as measured by increasing RUL-BA. *Conclusion:* The RUL-BA assists radiologists in differentiating fibrotic sarcoidosis from non-fibrotic sarcoidosis. Further research will determine if the RUL-BA measurement can help differentiate fibrotic sarcoid from other fibrotic lung diseases and if the angle can be used to follow disease progression. (*Sarcoidosis Vasc Diffuse Lung Dis* 2020; 37 (2): 99-103)

KEY WORDS: pulmonary fibrosis, chest CT scan, sarcoid

INTRODUCTION

Sarcoidosis was first described by Hutchinson in 1869 (1). The exact cause of Sarcoidosis remains unknown, but an unidentified inhaled antigen is suspected because of the cell-mediated response (2) and lung involvement in 90% of patients (1). The prevalence of sarcoidosis in the United States is reported as 50 per 100,000 among Caucasians and 141 per

100,000 among African Americans. The fibrotic form of the disease has a 16% 10-year mortality rate and is associated with significant morbidity caused by concomitant aspergillosis, pulmonary artery hypertension and respiratory exacerbations (2).

Classically the Scadding Staging System (SSS) has been used to group Sarcoidosis into 5 stages based on chest x-ray findings. Stage 0 is normal lung, Stage 1 demonstrates hilar lymphadenopathy, Stage 2 has parenchymal nodules and hilar lymphadenopathy, Stage 3 has parenchymal nodules alone and Stage 4 has fibrotic lung disease (3). The Scadding Staging System can be applied to findings on cross sectional imaging, which is more sensitive and parallels findings on pathology including perilymphatic distribution of parenchymal abnormalities (4).

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Stage 4 Sarcoidosis occurs in 20-25% of patients affected with the disease. It is irreversible and may require lung transplant as anti-inflammatory medications are usually ineffective at this stage. Stage 4 Sarcoidosis may cause a diagnostic challenge to differentiate from other types of fibrosis. Posterior displacement of the upper lobe bronchus due to volume loss is a known feature of the fibrotic stage (5). We suggest a method to quantify the amount of posterior bronchial displacement, which could potentially follow disease progression.

METHODS

IRB approval was obtained for review of all chest CT scans that contained the word sarcoidosis (using the computer program *Montage*), performed from January 2015 through December 2017. The most recent CT scans of these 633 patients were reviewed by an experienced chest radiologist (MMS with 20 years of experience) and a radiology resident using lung window settings (W 1600, L -600). The patients' age and gender were recorded. Patients with a pattern of fibrosis inconsistent with sarcoidosis were excluded.

Sarcoidosis on CT was graded as follows:

Grade 0: No CT evidence of thoracic disease

Grade 1: Mediastinal and/or hilar lymphadenopathy without pulmonary nodules

Grade 2: Mediastinal and/or hilar lymphadenopathy and perilymphatic pulmonary nodules

Grade 3: Pulmonary nodules in a perilymphatic distribution without lymphadenopathy

Grade 4: Sarcoidosis with pulmonary fibrosis

Grade 4 was considered the fibrotic group, while Grades 0 through 3 represented the non-fibrotic group. The angle between a line traversing the right upper lobe bronchus and a sagittal line connecting the sternum to the vertebral body and tangential to the most medial aspect of bronchus was measured and recorded, as drawn below. The angle is called the Right Upper Lobe Bronchus Angle (RUL-BA) (Figure 1 and Figure 2).

The association between having fibrotic sarcoidosis and the RUL-BA was examined via logistic regression models. The full model compared the likelihood of having Stage 4 Sarcoidosis based on RUL-BA, adjusting for age and gender. A stepwise variable selection procedure was employed to find best model fit, as judged by Akaike Information Criterion (AIC). The best model fit for fibrotic sarcoid was found with RUL-BA, adjusting for age. Furthermore, ROC curves were examined to evaluate balance between sensitivity and specificity

RESULTS

Our initial study population consisted of 640 chest CT scans. 7 of these scans were excluded because the patients' right upper lobe had been resected, 69 were excluded because the radiographic diagnosis was not consistent with patterns of sarcoid

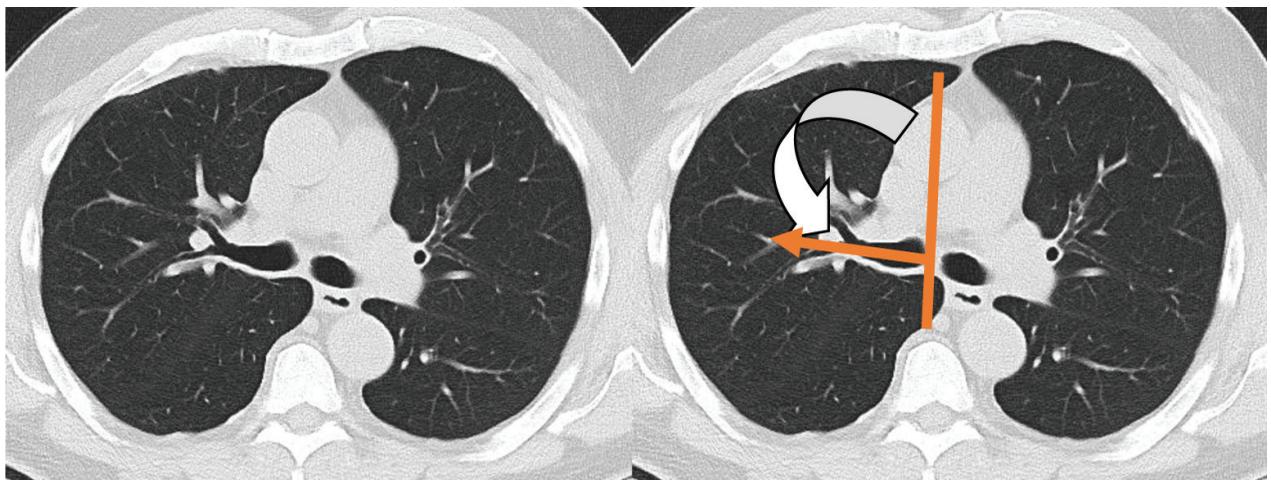


Fig. 1. Normal Right Upper Lobe Bronchial Angle (RUL-BA) measuring 88 degrees

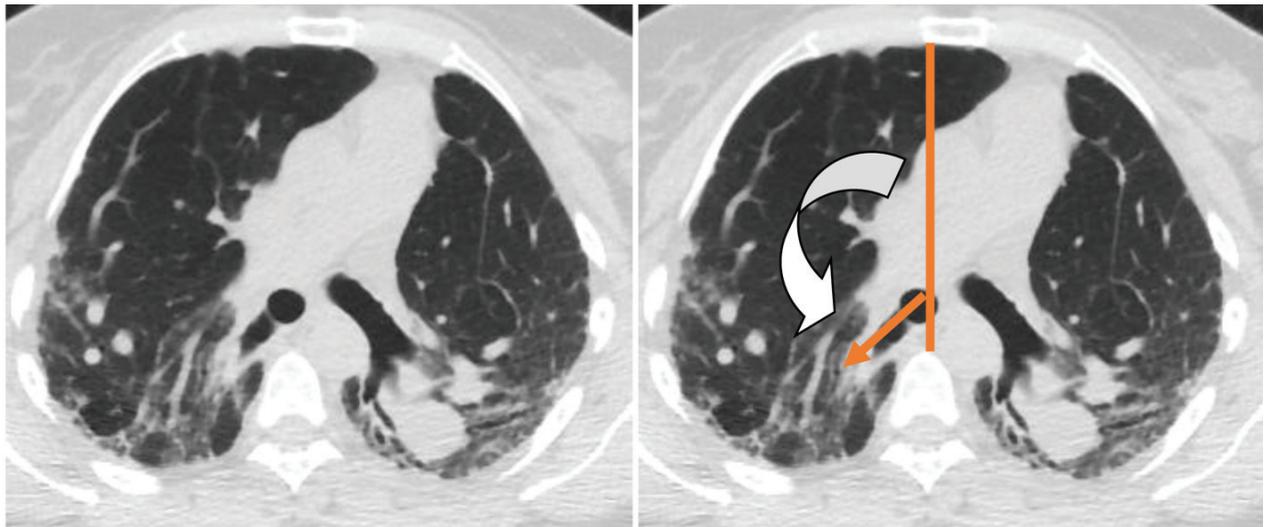


Fig. 2. Right upper lobe posterior predominant fibrosis causing retraction of the right upper lobe bronchus and increase in the Right Upper Lobe Bronchial Angle (RUL-BA) measuring 145 degrees

described in methods section, leaving 564 patients in our study population. The RUL-BA increased with Stage 4 Sarcoidosis, with an average angle of 104 degrees, compared to an average angle of 88 degrees for those without fibrotic sarcoid. As would be expected, scans with the later stage of disease were typically from older patients; however, there was no correlation between age and degree of fibrosis as measured by increasing RUL-BA (Table 1).

The logistic regression analysis resulted in a McFadden Pseudo-R² of .39, indicating fair fit. RUL-BA was a significant predictor in the model, with a p value well under $\alpha = .05$ (Table 2).

While holding age constant, for every one-degree increase in RUL-BA above 90 degrees, the odds of having fibrosis were 1.249 times higher. ROC Curve exploration resulted in an 88% in discriminatory ability (Figure 3).

Table 1. Results found on most recent chest CT scan of studied patients

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
# of patients	148	103	107	45	161
Average age	54 (19-91)	57 (27-90)	55 (30-86)	56 (31-81)	59 (29-94)
% male	58/148 (39%)	52/103 (50%)	60/103 (58%)	24/45 (53%)	70/162 (43%)
Average RULBA	88	87	89	87	104
Range RULBA	73-105	70-104	74-120	67-95	74-145

Table 2. Logistic Regression Analysis Results of Fibrosis based on RULBA and adjusted by age

Predictor	Coefficient (β)	Odds Ratio	95% Confidence Interval	p-value
Intercept	-22.633	1.481×10^{-12}	$1.182 \times 10^{-12} - 9.423 \times 10^{-9}$	< 0.0001
RULBA	0.222	1.249	1.954 - 1.314	< 0.0001
Age	0.019	1.02	1.0 - 1.04	0.049

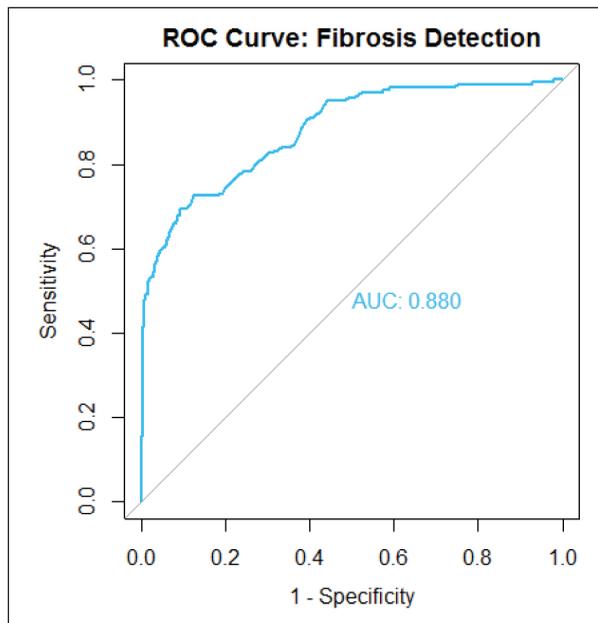


Fig. 3. ROC Curve exploration resulted in a discriminatory ability of 88%

DISCUSSION

The diagnosis of sarcoidosis is made when a patient presents with expected clinical and radiographic findings and pathology showing noncaseating granulomas in a typical peri-lymphatic distribution. Chest x-ray has been used for staging disease with Scadding's Staging System (3). Increasingly, chest CT is used to better define parenchymal abnormalities. In addition, Gallium studies and PET scans are used to determine disease activity and determine if anti-inflammatory medications might be beneficial. The RUL-BA is an ancillary CT tool that can act like an imaging biomarker when it is positive.

Sarcoid is believed to be caused by an unidentified environmental agent as it effects the skin, eyes and lungs. In sarcoid, there is accumulation of granulomas consisting of centrally located macrophages and epithelioid cells surrounded by lymphocytes. The role of the granuloma is to limit inflammation and protect the body. Stage 4 sarcoid occurs when there is an increase in matrix metalloproteinases and a relative decrease in their inhibitors. There is increased fibronectin and CCL18 that increases collagen deposition (6).

Sarcoid is an upper lobe predominant disease along with tuberculosis and hypersensitivity pneumonitis and they all cause the formation of granu-

lomas. The upper lobe to lower lobe lung ventilation ratio is 3:1 whereas the lung lower lobe to upper lobe perfusion ratio is 6:1. Big particles are removed from the trachea by mucociliary clearance, but small particles can get to the alveoli and need to be removed by lymphatics whose function is related to perfusion. The lymphatics work less well in the lung apices, likely the reason why granulomas have an upper lobe predilection (7). Hypersensitivity pneumonitis is caused by an inhaled antigen, so it is not surprising that there is an upper lobe predominant disease. Tuberculosis is inhaled as well, and it also has an upper lobe predilection – but more specifically in the posterior aspects of the upper lobes. Sarcoidosis has the same distribution and in fact, serum samples of patients with sarcoid contain mycobacterial antigen antibodies, supporting the idea that sarcoid is an immune response to environmental pathogen (8).

Lung fibrosis is an end stage disease, but we must differentiate the various types of end stage fibrosis because it will potentially lead to better outcomes as new treatments are developed. Currently, glucocorticosteroids or second-line drugs (methotrexate or azathioprine) are still recommended, monoclonal antibodies have a limited application in patients with sarcoidosis; anti-fibrotics are currently in clinical trials. Preliminary results using mesenchymal cells obtained from umbilical cord blood show promise for treating sarcoidosis (9). Although there are limited options for treatment of end-stage fibrosis, as treatments are developed the importance of a simple and specific diagnostic test will increase. The use of the RUL-BA can help differentiate patients with fibrotic versus non-fibrotic sarcoid which is important because the treatments and prognosis is different.

Our study has limitations. The use of Montage to identify patients with the word sarcoid in their report has potentially caused selection bias, additional research will be needed in patients with a clinical diagnosis of sarcoid, which was staged with chest x-ray to see if the angle can be used as a tool to differentiate fibrotic from nonfibrotic disease on cross sectional imaging.

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