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Title: Serum Albumin is a Biomarker of Chronicity of Pulmonary Sarcoidosis

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Abbreviations:

ACE: angiotensin converting enzyme

BMI: body mass index,

BNP: brain natriuretic peptide,

CABG: coronary artery bypass graft,

CKD: chronic kidney disease,

CRP: C-reactive protein,

DLCO: diffusion capacity,

DMARD: disease modifying anti-rheumatic drug,

EF: ejection fraction,

ESR: erythrocyte sedimentation rate,

FVC: forced vital capacity,

LVEF, Left ventricular ejection fraction

NLR: neutrophil-to-lymphocyte ratio,

OSA: obstructive sleep apnea,

PCI: percutaneous coronary intervention,

PASP: pulmonary artery systolic pressure.

PFT: pulmonary function test

PHTN: pulmonary hypertension,

ROC: receiver operating characteristics

SO2: oxygen saturation in room air,

6MWD: 6-minute walk distance,

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Abstract

OBJECTIVE: The duration of sarcoidosis is associated with a higher risk of irreversible pulmonary fibrosis. Sarcoidosis manifests diverse clinical presentations, which, may lead to delayed diagnosis, due to lack of specific diagnostic test. Biomarkers of sarcoidosis duration have not been previously explored.

MATERIAL AND METHODS: A retrospective study was conducted to investigate independent biomarkers of pulmonary sarcoidosis duration.

RESULTS: 108 cases with pulmonary sarcoidosis (mean age 53.4 years, 76.9% females, average duration of sarcoidosis 12 years) were included in the study. We found significant correlation between duration of sarcoidosis and serum albumin levels (r= -0.414, P=0.0001), sedimentation rate (ESR) (r= 0.375, P=0.001), pulmonary artery systolic pressure (PASP) (r= 0.468, P=0.003), diffusion capacity (DLCO%) (r= -0.334, P=0.002) and age (r= 0.492, P=0.0001). Multivariate linear regression analysis revealed that serum albumin levels (β= -5.242, 95% CI -8.372 to -2.112, P=0.001) and age (β= 0.367, 95% CI 0.164 to 0.570, P=0.001) were independent correlates of sarcoidosis duration. ROC curve analysis for prediction of sarcoidosis of >10 years duration gave AUC of 0.722 (95% CI 0.620-0.824, P<0.0001) for serum albumin and an AUC of 0.665 (95% CI 0.561-0.768, P<0.004) for age. An albumin level <2.4 gm/dL yielded 90.5% sensitivity and 98.2% specificity for predicting sarcoidosis of >10 years duration. In comparison, patient age of 51.5 years yielded 70.2% sensitivity and 50% specificity for predicting patients with sarcoidosis for >10 years.

CONCLUSION: Serum albumin level may be a biomarker of pulmonary sarcoidosis duration and chronicity of disease. Further investigations are required to confirm its predictive ability.

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Keyword: Pulmonary sarcoidosis, hypoalbuminemia, serum albumin

INTRODUCTION

Sarcoidosis usually presents in adults younger than 40 years, most frequently between 25 and 40 years of age (1-7). In the United States, chronic disease with the insidious onset of pulmonary symptoms is the commonest mode of presentation especially in African Americans. In contrast, Caucasians are usually affected by acute, self-limited disease (5). Among the factors regulating the clinical presentation of sarcoidosis is the duration of illness (1, 8). For example, patients with chronic sarcoidosis (10-30% of cases) are at high risk of extensive, irreversible pulmonary fibrosis (9). It is important, therefore, to have a robust biomarker that indicates the length of time that a patient has suffered from pulmonary sarcoidosis. Therefore, we aimed to study various biomarkers that may provide information on the duration of disease including patient demographics, clinical characteristics, pulmonary function tests (PFT), echocardiographic findings and serum inflammatory markers.

MATERIALS AND METHODS

This is an observational study of consecutive adult subjects >18 years who were seen with sarcoidosis at the University of xxxx at Chicago between January 2010 and January 2015. The diagnosis of sarcoidosis was made according to the European Respiratory Society (ERS), American Thoracic Society (ATS) and

World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) criteria (1). Sarcoidosis was defined by these societies as

a multisystem disorder of unknown cause that commonly affects young and middle-aged adults who present with characteristic clinico-radiographic findings supported by the presence of noncaseating epithelioid cell granulomas after exclusion of granulomas of unknown causes and local sarcoid reaction. The Institutional Review Board of the University of xxxx at Chicago approved the study and waived the need for patient consent (approval number of 20130195001). The aim of the study is to identify correlates of sarcoidosis duration in a cohort of patients with known pulmonary sarcoidosis. Sarcoidosis duration was measured in years from the onset of initial diagnosis until enrolling in this study. Inflammatory markers examined were the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, ferritin, 25 hydroxy vitamin D and angiotensin converting enzyme (ACE) level.

Continuous variables are expressed as mean ± standard deviation and compared using T-test and categorical variables are described as counts and percentages and compared using Chi-square test. The relationship between sarcoidosis duration and continuous parameters were analyzed by spearman's correlation coefficients because of skewed distribution. To identify independent correlates of sarcoidosis duration, all variables with a P-value <0.05 in univariate analysis were submitted to a stepwise multiple regression analysis. A multivariable model was considered relevant if the variables entered in the model were significant (P<0.05) and had a tolerance measure (equal to the inverse of the variance inflation factor) >0.7. A ROC (receiver operating characteristics) analysis was implemented to detect the ideal cutoff value of serum albumin that yields the highest sensitivity and specificity for

predicting a sarcoidosis duration of >10 years. A P-value <0.05 is considered statistically significant. Data were analyzed using IBM SPSS 21.0 statistical software (IBM SPSS Version 21.0. Armonk, NY).

RESULTS

108 subjects with confirmed pulmonary sarcoidosis were included. The mean age of the study population was 53.4±9.4 years, 76.9% were females, 70% had African descent and the average duration of sarcoidosis was 12 years. The baseline demographics, clinical variables, inflammatory marker values, pulmonary function tests, echocardiographic data, and treatment are summarized in Table 1.

Univariate analysis demonstrated a significant moderate inverse correlation between the duration of sarcoidosis and serum albumin levels (r= -0.414, P=0.0001) (Figure 1a), a significant moderate positive correlation between sarcoidosis duration and erythrocyte sedimentation rate (ESR) (r= 0.375, P=0.001)(Figure 1b) but there was no association between sarcoidosis duration and serum C-reactive protein (CRP) levels (r=0.184, P=0.101) (Figure 1c).

DLCO% had a significant moderate inverse correlation with pulmonary sarcoidosis duration (r= -0.334, P=0.002) (Figure 1d) whilst older patients with sarcoidosis had a longer disease duration (r= 0.492, P=0.0001) (Figure 1e). In addition, a higher pulmonary artery systolic pressure (PASP) as measured by transthoracic echocardiography was associated with longer pulmonary sarcoidosis duration (r= 0.468, P=0.003) (Figure 1f).

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Multivariate analysis revealed that the significant independent correlates of sarcoidosis duration were serum albumin level (β= -5.242, 95% CI -8.372 to -2.112, P=0.001) and the patients' age (β= 0.367, 95% CI 0.164 to 0.570, P=0.001). There was a reasonable correlation (R^2 = 0.377) for the multivariate model.

Receiver operating characteristic (ROC) curve analysis for the prediction of sarcoidosis duration >10 years was performed. Serum albumin levels gave an area under curve (AUC) of 0.722 (95% CI 0.620-0.824, P<0.0001) and an albumin <2.4 gm/dL yielded a 90.5% sensitivity and 98.2% specificity for predicting a sarcoidosis duration >10 years (Figure 2, a). With regards to patients' age, the AUC was 0.665 (95% CI 0.561-0.768, P<0.004) (Figure 2, b). A patients' age of 51.5 years would have a sensitivity of 70.2% and a specificity of 50% for predicting a sarcoidosis duration >10 years.

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DISCUSSION

We have shown in this retrospective analysis that hypoalbuminemia is a main determinant of sarcoidosis duration. Albumin is an acute phase reactant and usually decreased in the setting of inflammation(10, 11). Hypoalbuminemia is observed in acute as well as chronic inflammatory states such as pulmonary sarcoidosis and represents increased albumin degradation due to a high catabolic rate in combination with its transudation into the extravascular space resulting from increased capillary permeability (12, 13). The reduction in serum albumin level with increasing duration of sarcoidosis may be explained by a higher degree of systemic inflammation in patients with a with longer duration of disease(13). A β value of -5.242 for albumin means that for each gram reduction in albumin level would be associated with an increase of 5.242 years of sarcoidosis duration. Because sarcoidosis duration is an important determinant of the clinical presentation and complications in pulmonary sarcoidosis patients, we propose serum albumin measurement could be a simple predictor for the disease duration.

Patients' age is a second determinant of sarcoidosis duration with a β of 0.367, and therefore each 10-year increase in patients' age will be associated with a 3.67 years increase in sarcoidosis duration. Age as a predictor of sarcoidosis duration can be explained by the early onset of disease where 70% of the cases are diagnosed at between 25 and 40 years of age (14, 15) and only 30% are over 50 years of age at onset(8). When including the 81 females in our cohort, patients' age still predicted a duration of sarcoidosis > 10 years (AUC 0.630, 95% CI 0.509 -0.751, P=0.044), but when including only the 24 males, patients age was not associated with a sarcoidosis duration > 10 years (AUC 0.714, 95% CI 0.454-0.975, P=0.105).One of the probable reason might be the number of female patients are significantly higher in our cohort; 4 times the number of male. Thus, Older patients are more likely to have a longer duration

of the disease. Sarcoidosis is a heterogeneous disease with an extreme diversity of clinical presentations, which in addition to the lack of specific diagnostic tests, makes its diagnosis challenging. The ACCESS (A Case Control Etiologic Study of Sarcoidosis) study, a multicenter study from 10 centers in the United States, showed that there was a delay in making the diagnosis of sarcoidosis, even if patients presented with pulmonary symptoms (8). This delay in diagnosis highlights the importance of finding biomarkers of sarcoidosis duration that will indicate disease onset rather than the confirmed pathological diagnosis.

The limitations of the study are mainly those related to non-randomized studies. It is a single center, retrospective with a relatively small cohort. We have used the age of confirmed pathological diagnosis of the disease which is unlikely to be the time of disease onset. In addition, we have not adjusted for confounding factors that may affect ESR and CRP. For example, it is known that sarcoidosis patients with active disease have very high levels of ESR and CRP(16). These inflammatory markers are also significantly elevated in sarcoidosis-associated arthritis (17), concomitant connective tissue disease or simultaneous acute infections. Albumin is a negative acute phase protein whose expression is likely to be modulated by other inflammatory processes and to a lesser extent by the patients' nutritional status. Hepatic function or hepatic involvement of the disease can also influence serum albumin level. We could not discuss the hepatic function or organ involvement pattern due to unavailability of data. Further study is required including patient's liver function.

In conclusion, we show that the serum albumin level is a biomarker of sarcoidosis duration that suggests that following up of its level may predict the real duration of disease. Larger longitudinal follow up

studies are required to confirm these results and to further assess the value of determining sarcoidosis duration and how it affects the clinical course, prognosis and treatment.

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Table 1: Baseline demographics, clinical, laboratory characteristics among 108 sarcoidosis cases.

Baseline demographics and comorbidities	
Age (mean ± SD)	53.4 ± 9.4
Female sex % (n)	76.9% (83)
BMI (mean ±SD)	31.9 ± 8
Duration of sarcoidosis (y, mean ±SD)	12.2 ± 9.1
African American % (n)	70.4% (76)
Diabetes % (n)	31.1% (33)
CKD % (n)	3.7% (4)
PCI or CABG % (n)	1.9% (2)
Atrial fibrillation % (n)	5.6% (6)
CHF % (n)	6.6% (7)
Pulmonary hypertension % (n)	26.2% (28)

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Asthma % (n)	26.2% (28)
OSA % (n)	24.3% (28)
Dyspnea % (n)	52.9% (54)
Pulmonary function tests and echocardiography	
FVC % (mean ±SD)	93.2 ± 20.9
FEV1 % (mean ±SD)	88 ± 24.9
TLC % (mean ±SD)	89.1 ± 15.6
RV % (mean ±SD)	99.4 ± 26.7
DLCO % (mean ±SD)	67 ± 20.3
EF (mean ±SD)	57.8 ± 4.8
Inflammatory markers	
CRP (mg/L, mean ±SD)	2.5 ± 4.2
ESR (mm/hr, mean ±SD)	35.2 ± 33.4
Albumin (g/dL, mean ±SD)	3.6 ± 0.58
Ferritin (ng/mL, mean ±SD)	161.4 ± 602
ACE level (U/L, mean ±SD)	63.2 ± 49.5
25 OH vitamin D (ng/mL, mean ±SD)	16.1 ± 8.5
Treatment	
Oral steroid % (n)	83.5% (86)
DMARD % (n)	43.9% (47)

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Methotrexate % (n)	29.6% (32)
Azathioprine % (n)	4.7% (5)
Lasix % (n)	17.6% (19)
Warfarin % (n)	2.8% (3)
ACE or ARB % (n)	46.7% (50)

Abbreviations: PHTN: pulmonary hypertension, BMI: body mass index, CKD: chronic kidney disease, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, OSA: obstructive sleep apnea, EF: ejection fraction, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DMARD: disease modifying anti-rheumatic drug, ACE: angiotensin converting enzyme, y: year, m: mean, SD: standard deviation.

Table 2: Clinical, laboratory and echocardiographic correlates of sarcoidosis duration.

Clinical correlates of sarcoidosis duration		
Variable	**Sarcoidosis duration (years)**	**P Value**
Age	r= 0.492	0.0001
BMI	r= -0.068	0.495
DLCO%	r= -0.334	0.002

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FVC%	r= -0.249	0.021
FVC%/DLCO%	r= 0.161	0.143
6MWD test	r= 0.074	0.613
SO2 in room air	r= -0.064	0.563
Laboratory correlates of sarcoidosis duration		
ESR	r= 0.375	P=0.001
CRP	r=0.184	P=0.101
Albumin	r= -0.414	P=0.0001
ferritin	r=0.014	P=0.907
ACE	r= -0.118	P=0.342
25 OH vitamin D	r= -0.15	P=0.170
NLR	r=0.048	P=0.639
BNP	r=0.306	P=0.1
Calcium	r= -0.116	P=0.257
Echocardiographic correlates of sarcoidosis duration		

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PASP	r= 0.468	P=0.003
LVEF	r= 0.027	P=0.783

Abbreviations: BMI: body mass index, DLCO: diffusion capacity, FVC: forced vital capacity, 6MWD: 6-minute walk distance, SO2: oxygen saturation in room air, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ACE: angiotensin converting enzyme level, NLR: neutrophyl-to-lumphocyte ratio, BNP: brain natriuretic peptide, PASP: pulmonary artery systolic pressure, LVEF, Left ventricular ejection fraction.

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Figure 1: a-f, Axial (a) and Coronal (b) shows relationship between the duration of sarcoidosis and different clinical biomarkers. The duration of sarcoidosis was correlated with serum (a) erythrocyte sedimentation rate (ESR), (b) serum C-reactive protein (CRP), (c) serum albumin, (d) patients' age at diagnosis, (e) diffusion capacity (DLCO%) and (f) pulmonary artery systolic pressure (PASP). R values and P values are shown in each panel.

Figure 2: a, b Axial (a) -Receiver operating characteristic (ROC) curve for prediction of sarcoidosis duration >10 years according to albumin level(a) and patients' age (b).

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