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Frequency of acute worsening events in fibrotic pulmonary sarcoidosis patients

Robert P. Baughman*, **Elyse E. Lower**

Department of Medicine, University of Cincinnati Medical Center, Cincinnati, OH, USA

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Summary
Patients with fibrotic sarcoidosis can develop worsening of pulmonary symptoms for various reasons. We studied acute worsening events defined as episodes treated with limited courses of either antibiotics and or increased corticosteroid doses which resolved within four weeks. The prevalence of acute worsening events in patients with fibrotic sarcoidosis was investigated. Of 740 sarcoidosis patients seen in our clinic over a four month period, 129 (17%) had fibrotic sarcoidosis. We noted the age, race, gender, computer tomography (CT) results, and pulmonary function as measured by forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and the FEV_1/FVC ratio. In a retrospective manner, the fibrotic sarcoidosis patients reported a median of three acute worsening events (range zero to eight) in the prior year. Bronchiectasis was noted on CT imaging in 63 of 129 (49%) of the fibrotic sarcoidosis patients. Fibrotic sarcoidosis patients reported a higher frequency of acute worsening events (3 (0–6)) than those without bronchiectasis (2 (0–8), $p = 0.0001$). Sixteen patients receiving anti-tumor necrosis factor antibodies reported a higher frequency of acute worsening events compared to those not receiving anti-tumor necrosis factor antibodies ($p = 0.0297$). There was no relationship between the number of acute worsening events and race, gender, smoking history, or FVC, FEV_1, or FEV_1/FVC ratio. We conclude that acute worsening events are frequent in patients with fibrotic sarcoidosis patients and are more common in patients with bronchiectasis and those receiving anti-tumor necrosis factor antibody therapies.

* Corresponding author. 1001 Holmes, Eden Ave, Cincinnati, OH 45267, USA.
E-mail addresses: bob.baughman@uc.edu, baughmrp@ucmail.uc.edu (R.P. Baughman).

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Introduction

Pulmonary sarcoidosis patients can develop episodes of acute worsening of pulmonary symptoms. While this can occur in all stages of pulmonary sarcoidosis, an acute worsening in fibrotic sarcoidosis patients can result in significant pulmonary morbidity. There are several causes of acute worsening of pulmonary sarcoidosis, including worsening of the underlying sarcoidosis, infection, acute bronchospasm, or extra-pulmonary causes [1].

Relapse of sarcoidosis can occur during reduction or withdrawal of corticosteroids and/or other systemic therapy for pulmonary sarcoidosis [2,3]. This event has been termed an acute pulmonary exacerbation of sarcoidosis [1]. Patients with acute pulmonary exacerbation of sarcoidosis will often respond to reinstitution or an increase in corticosteroid dosage [4]. Patients relapsing during corticosteroid withdrawal are usually maintained on long term immunosuppressive therapy to prevent further relapses [2,3,5].

Acute pulmonary worsening can also occur in patients receiving stable doses of treatment. These episodes are often related to infection, and patients may respond to a short course of corticosteroids and broad spectrum antibiotics. Because resolution usually occurs in less than 4 weeks, these episodes are considered unique from acute pulmonary exacerbations of sarcoidosis [1]. In addition to infection, patients can also develop airway reactivity that responds to short courses of corticosteroid therapy [6].

Disease worsening can cause significant morbidity in patients with fibrotic sarcoidosis. In order to better understand the frequency and associated features of acute worsening of fibrotic sarcoidosis, we studied patients seen at the University of Cincinnati Sarcoidosis Clinic.

Methods

Patients were recruited from those seen at the University of Cincinnati Interstitial Lung Disease and Sarcoidosis Clinic. Patients with sarcoidosis based on ATS/ERS/WASOG criteria who had chest imaging consistent with pulmonary fibrosis were eligible for evaluation. This retrospective study was part of an ongoing investigation of pulmonary infections in sarcoidosis and it was approved by the University of Cincinnati Institutional Review Board. This study examined a subset of sarcoidosis patients with pulmonary fibrosis seen during a four month period in our clinic. The presence of pulmonary fibrosis was decided by the radiologist who made the official interpretation of prior chest X-ray and high resolution CT (HRCT) scan which were performed as part of routine evaluation of the patient's sarcoidosis. Although we reviewed these films, we chose to use the radiologist interpretation. All patients had both a routine chest X-ray and HRCT scan to review.

Acute worsening was defined as an episode in which the patient was either prescribed an antibiotic for 5—21 days and/or a short increase in systemic glucocorticoids for increased cough and/or dyspnea. Although some patients underwent chest roentgenograms during these episodes, an abnormal imaging was not required.

During a four month period, each fibrotic sarcoidosis patient was asked to estimate the number of acute worsening events that had occurred during the prior twelve months. When possible, this number was verified by chart review.

In addition to the number of episodes, additional demographic information including age, gender, self-declared race, smoking history, and sarcoidosis duration and organ involvement was recorded from the chart review. Chest imaging was reviewed for the presence or absence of bronchiectasis along with the most recent pulmonary function tests including FEV_1, FVC, and FEV_1/FVC ratio and the predicted values [7]. Current and past systemic sarcoidosis medications were categorized as glucocorticoids, cytotoxic drugs such as methotrexate, leflunomide, and azathioprine, and anti-tumor necrosis factor (TNF) monoclonal antibodies infliximab and adalimumab. Since the dosage of prednisone varied over the course of the year of study for most patients, we were not able to calculate an average dose of prednisone.

Statistics: The distribution of acute worsening events was not normally distributed and therefore the Mann Whitney *U* test, Spearman Rank, and other non-parametric tests were used. A p value of less than 0.05 was considered significant.

Results

During the four month period of the study from May to September 2012, 740 patients with sarcoidosis were seen in the Interstitial Lung Disease and Sarcoidosis Clinic. A total of 129 (17%) sarcoidosis patients with pulmonary fibrosis were studied. Of these, 63 (49%) had bronchiectasis identified on chest imaging, usually high resolution computer tomography (HRCT). Table 1 summarizes the demographics of the patients enrolled in the study, including age, race, gender, disease duration, pulmonary function studies,

Table 1 Demographics of fibrotic sarcoidosis patients studied.

	Total
Number	129
Female:Male	92/37
Black:White	78/51
Age years	57 (35—87)[a]
Disease duration, years	13 (1—42)
FVC, l	2.57 (1.11—5.43)
FVC % predicted	79 (33—131)%
FEV_1, l	1.90 (0.77—3.51)
FEV_1 % predicted	56 (17—106)%
FEV_1/FVC %	73 (35—100)%
DLCO	17.5 (7.68—41.56)
DLCO % predicted	74 (37—128)%
Smoking history	
Current/Prior/Nonsmokers	16/33/80
Bronchiectasis	
Yes/No	63/66
Acute worsening events in prior year	3 (0—8)

[a] Median (Range).