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# COVID-19 infections in sarcoidosis: a prospective single center study of 886 sarcoidosis patients

*Robert P. Baughman, Elyse E. Lower*
Department of Medicine, University of Cincinnati Medical Center, Cincinnati, OH, USA

## Introduction

Sarcoidosis patients, especially those receiving immunosuppressive therapy (1), may have an increased risk for opportunistic infections including fungal infections and mycobacteria (1-3). Recent reports have suggested an increased rate of coronavirus disease 2019 (COVID-19) infection in sarcoidosis patients (4-7). These studies were usually retrospective and/or self-reported cases. We report the results of a prospective study performed in our sarcoidosis clinic comparing the rate of COVID-19 infection in sarcoidosis to cancer patients.

## Methods

All patients with a diagnosis of sarcoidosis (8) seen at the University of Cincinnati Sarcoidosis Clinic between July 1 and December 31, 2020 were eligible for study. In addition, all breast cancer patients seen by EEL during this time were studied. Patients with symptoms consistent with COVID-19 infection and confirmed by PCR were included in the study. Additionally, we recorded herpes zoster, fungal, or mycobacterial infections occurring after the diagnosis of sarcoidosis or breast cancer. The protocol has been approved by the University of Cincinnati Institutional Review Board and registered on ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02356445). Comparisons between proportion of various infections between groups was performed with Chi square analysis except in those cases where there were less than 5 cases in any of the outcomes. In those cases, Fisher's exact test was performed.

## Results

During the study time, 886 sarcoidosis patients were seen. Of these 77 (8.9%) had documented COVID-19 infection and 19 (24.7%) required hospitalization and one patient died of COVID-19 infection. During the same time period, 1118 breast cancer patients were seen. For the cancer patients, only 42 (3.8%) had documented COVID-19 and only one required hospitalization. Of the cancer patients, six of the 186 (3.2%) on active chemotherapy had COVID-19 infection versus 20 of 581 (3.4%) previously on chemotherapy and 16 of 351 (4.6%) never receiving chemotherapy. There was no significant difference in rate of COVID-19 infection between the three cancer groups (Chi square=0.928, $p>0.05$). The overall rate of COVID-19 infection was significantly higher for sarcoidosis patients (Chi square=22.31, $p<0.0001$) as was the rate of hospitalization (Chi square=9.58, $p=0.0020$). Table 1 summarizes the rate and outcome of COVID-19 in sarcoidosis patients in this study compared to other reports (4-7).

A total of 77 (8.9%) sarcoidosis patients and 101 (9.2%) cancer patients reported one or more episodes of herpes zoster infection after respective disease diagnosis. The rate was not significantly different between sarcoidosis and cancer patients (Chi square=0.06, $p>0.05$).

We also examined the rate of COVID-19 infection versus age, race, current therapy, lung, neu-

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Correspondence:
Robert P. Baughman MD,
200 Albert Sabin Way, Room 1001, Cincinnati, OH 45267, USA

**Table 1.** Rate and outcome of COVID-19 infection in sarcoidosis patients

| | Current Study | Manansala [6] | Baughman ¶ [7] | Morgenthau [4] | Jeny [5] |
|---|---|---|---|---|---|
| Sarcoidosis | | | | | |
| Total number | 866 | 236 | 4216 | NR | NR § |
| COVID-19 | 77 (8.9%) * | 5 (2.1%) | 101 (2.4%) | 37 | 36 † |
| Treated at home | 58 (75.3%) | 3 (1.3%) | 87 (84.5%) | 15 (40.5%) | NR |
| Hospitalized | 19 (24.7%) | 2 (0.8%) | 14 (13.6%) | 22 (50.5%) | 36 |
| Hospitalized and treated in ICU | 6 (31.6%) | 2 (100%) | 3 (21.4%) | NR | 13 (36.1%) |
| Vent | 3 (3.9%) | NR | NR | 9 | 4 (11.1%) |
| Death from COVID-19 infection | 1 (1.3%) | 1 (20%) | NA | 12 (32.4%) | 5 (13.9%) |

*Mean (percent); ¶Only those centers with outcome of COVID-19 infection reported; †Reported on hospitalized patients only; § NR: Not reported; ICU: intensive care unit

rologic, or cardiac involvement, and other history of fungal and mycobacterial infections. Table 2 summarizes our findings. There were no significant differences in these features for sarcoidosis patients with or without COVID-19 infection. No individual immunosuppressive therapy was associated with an increased risk for COVID-19 infection. A total of 23 of 159 (14.5%) sarcoidosis patients receiving one or more third line therapy (infliximab, adalimumab, rituximab, or repository corticotropin injection) developed COVID-19 infection versus 54 of 620 (8.7%) who were not receiving a third line therapy (Chi square=4.700, $p<0.05$). Nineteen (24.7%) COVID-19 infected sarcoidosis patients were hospitalized. Of 33 COVID-19 infected patients treated with prednisone, ten (30.3%) were hospitalized, which was not significantly different from 9 of 44 (20.5%) not receiving prednisone who required hospitalization (Ch square=0.971, $p>0.05$). Of the six COVID infected patients treated with rituximab, four (67%) were hospitalized, which was a significantly higher rate than than those not treated with rituximab (Fisher's exact test, $p<0.025$). Of the ten COVID infected patients treated with infliximab, none required hospitalization (Fisher's exact test, $p=0.0595$). Only 6 of 23 (26.1%) receiving any third line therapy required hospitalization versus 13 of 54 (24.1%) not on third line therapy (Chi square=0.0347, $p>0.05$).

## Discussion

In this prospective study, the rate of COVID-19 infection was more than twice as high for sarcoidosis patients (8.9%) than cancer patients (3.8%). These rates were higher than previously reported in studies performed at an earlier time in the COVID-19 pandemic (Table 1) (6,7). The higher rate in the current study mirrors a surge of cases seen in our area of the United States, especially in November and December of 2020. The rate of herpes zoster infection was no different between those with sarcoidosis and cancer. This suggests that the increased rate of COVID-19 in sarcoidosis was related to the virus and not increased risk to viral infections in general. This study did not include asymptomatic patients or those who had symptoms consistent with COVID-19 infection with negative or no culture performed. While this may underestimate the rate of COVID-19 infection, the same criteria for diagnosis was used for both groups.

Three previous studies reported a rate of hospitalization for COVID-19 infection in sarcoidosis patients ranging from one to fifty percent (Table 1) (4,6,7). In the current study, a quarter of our sarcoidosis patients were hospitalized for their COVID-19 infection, which was significantly higher than the rate for COVID-19 infected cancer patients. Three of the prior reports noted the percentage of hospitalized patients requiring intensive care unit admission (5-7). An average of 30% of hospitalized patients required ICU time, including 32% of the patients in this study (Table 1). In our study, hospitalization rate was unrelated to age, race, sex, or major organ involvement. Patients receiving infliximab were less likely to require hospitalization. A large study of COVID-19 infected rheumatoid arthritis patients found a lower rate of hospitalization for those on infliximab (9) but an increased rate of hospitalization for those on prednisone but not on other immunosuppressants. In the current study, we found

**Table 2.** Rate of COVID-19 infection based on race, gender, underlying treatment and other infections*

| | COVID-19 infected | Not COVID-19 infected | Total |
|---|---|---|---|
| Total Number | 77 | 779 | 866 |
| Age years (Median, range) | 56 (26-76) | 58 (21-93) | 58 (21-93) |
| Female:Male | 52:25 | 545:234 | 597:259 |
| Black:White:Asian:Middle east | 28:48:0:0 | 327:452:7:3 | |
| **Current therapy** | | | |
| Prednisone | 32 (41.6%) | 313 (40.2%) | 345 (39.8%) |
| Methotrexate | 17 (22.1%) | 161 (20.67%) | 178 (20.6%) |
| Azathioprine | 4 (5.2% | 39 (5.0%) | 43 (5.0%) |
| Leflunomide | 1 (1.3% | 27 (3.5%) | 28 (3.2%) |
| Mycophenolate | 2 (2.6%) | 29 (3.7%) | 31 (3.6%) |
| Hydroxychloroquine | 9 (11.7%) | 103 (13.2%) | 112 (12.9%) |
| Infliximab | 10 (13.0%) | 84 (10.8%) | 94 (10.8%) |
| Adalimumab | 5 (6.5%) | 10 (1.3%) | 15 (1.7%) |
| Rituximab | 6 (7.8%) | 41 (5.3%) | 47 (5.4%) |
| RCI | 2 (2.6%) | 24 (3.1%) | 26 (3.0%) |
| None | 0 (0%) | 6 (0.8%) | 6 (0.7%) |
| **Organ involvement** | | | |
| Lung | 63 (81.8%) | 637 (81.2%) | 700 (80.8%) |
| Heart | 4 (5.2% | 88 (11.3%) | 92 (10.6%) |
| Neurologic | 16 (20.8%) | 138 (17.7%) | 154 (17.8%) |
| **Infection since diagnosis of sarcoidosis** | | | |
| Herpes zoster | 4 (5.2%) | 73 (9.4%) | 77 (8.9%) |
| Pneumocystis | 0 (0%) | 1 (0.1%) | 1 (0.1%) |
| Histoplasmosis | 1 (1.3%) | 8 (1.0%) | 9 (1.0%) |
| Cryptococcus | 0 (0%) | 2 (0.3%) | 2 (0.2%) |
| Blastomycosis | 0 (0%) | 0 (0%) | 0 (0%) |
| Coccidiomycosis | 0 (0%) | 1 (0.1%) | 1 (0.1%) |
| Aspergillus | 0 (0%) | 8 (1.0%) | 8 (0.9%) |
| Any fungus | 1 (1.3%) | 20 (2.6%) | 21 (2.4%) |
| *Mycobacterium tuberculosis* | 0 (0%) | 0 (0%) | 0 (0%) |
| *Mycobacterium kansasii* | 0 (0%) | 2 (0.3%) | 2 (0.2%) |
| M. avium complex | 0 (0%) | 4 (0.5%) | 4 (0.5%) |
| Other mycobacterium | 0 (0%) | 2 (0.3%) | 2 (0.2%) |
| Any mycobacteria | 0 (0%) | 8 (1.0%) | 8 (0.9%) |
| Any fungus or mycobacteria | 2 (2.6%) | 56 (7.2%) | 58 (6.7%) |

*No significant difference in rates between any of the groups

a borderline reduction in the rate of hospitalization for those receiving infliximab but no increased rate of hospitalization for patients receiving prednisone. We observed that patients treated with rituximab were more likely to be hospitalized. In a prior study, we found rituximab therapy associated with increased rate of infection, but not hospitalization. Treatment with rituximab has been associated with increased risk for severe viral infections in non-sarcoidosis conditions (10).

In a retrospective analysis of COVID-19 infected patients in New York, Morgenthau et al reported that a third of COVID-19 infected sarcoidosis patients died and those with moderate to severe pulmonary disease experienced a seven fold increase in mortality (4). In that study, patients with underlying malignancy did not have an increased risk of death from COVID-19 infection. Other studies have reported a lower rate of mortality from COVID-19 infection (Table 1) (5,6) One self-reported study of COVID-19 infection (7), did not capture mortality. In the remaining four studies shown in Table 1, 19 of 155 (12.3%) COVID-19 infected sarcoidosis patients died from COVID-19 infection.

We investigated potential risk factors for COVID-19 infection in sarcoidosis patients. We found no increased risk associated with age, sex, race, current therapy, or major organ involvement (Table 2). We also investigated whether prior opportunistic infections rendered the patient more likely to acquire COVID-19 infection. Our rates of fungal and mycobacterial infection were similar to those previously reported in sarcoidosis patients (1-3). However, we did not find a history of prior opportunistic infection a risk for subsequent COVID-19 infection. While no individual immunosuppressive therapy was associated with an increased risk for COVID-19 infection, sarcoidosis patients receiving one or more third line therapy (infliximab, adalimumab, rituximab, or repository corticotropin injection) developed COVID-19 infection at a higher rate than those not receiving a third line therapy.

As more studies are reported, a better understanding of the risk for COVID-19 infection in sarcoidosis is emerging. The overall risk for COVID-19 infection in sarcoidosis appears increased. To date, about a quarter of COVID-19 infected sarcoidosis patients required hospitalization and a third of those hospitalized required intensive care unit admission. The mortality from COVID-19 infection in sarcoidosis exceeded ten percent. As vaccination appears to reduce risk for hospitalization and death from COVID-19 infection, aggressive implementation of vaccination in sarcoidosis patients is imperative.

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