



Coccidioidomycosis and COVID-19 Infection. An Analysis from a Single Medical Center Within the Coccidioidal Endemic Area

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Abstract At a single medical center, we identified 60 cases of coccidioidomycosis that were coincident with COVID-19 infection. Among these, seven patients developed new or clinically progressive coccidioidomycosis. Receipt of dexamethasone for COVID-19 infection was the only significant risk factor for the progression or development of clinically active coccidioidomycosis in this cohort. All patients survived and none developed disseminated coccidioidomycosis.

Keywords Coccidioidomycosis · Fungal infections · COVID-19 · SARS-CoV-2

Introduction

Infection with SARS-CoV-2 results in COVID-19, a respiratory illness of varying severity. In progressive cases involving the lower respiratory tract, infection

may result in multiple pulmonary infiltrates and respiratory failure. Treatment often requires immunosuppressive medications, including corticosteroids. Because of these issues, patients with COVID-19 may be at risk for opportunistic respiratory infections, including those due to fungi [1].

Coccidioidomycosis is a fungal infection endemic to specific areas of the western and southwestern United States [2]. Infection is almost always due to inhalation of arthroconidia from the environment into the respiratory tree. It has been postulated that the COVID-19 pandemic might affect the presentation of coccidioidomycosis, including causing cases of reactivation of clinically quiescent coccidioidomycosis and association with more severe coccidioidal disease [3]. To date, there have been multiple case reports of progressive or worsening coccidioidomycosis in association with COVID-19 [4–8], but no case series or analysis of the risk of the interaction of these two respiratory infections. In this report, we examine coincident cases of coccidioidomycosis and COVID-19 from a single medical center located in the coccidioidal endemic region. Our goals were to describe such cases, determine if there were instances of progression of coccidioidomycosis, and, if so, to detail their management and outcome.

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Materials and Methods

A retrospective review was conducted of the electronic health records for patients with both coccidioidomycosis and COVID-19 between January 1 and December 31, 2020 at Mayo Clinic in Arizona. Cases were identified using a search for ICD-10 codes for both infections (B38.0 – B38.9 for coccidioidomycosis; U07.1 for COVID-19).

Inclusion criteria for COVID-19 required a positive antigen or PCR test. Inclusion criteria for coccidioidomycosis required a patient to have proven or probable coccidioidomycosis, or coccidioidal seropositivity in an immunosuppressed host treated with ongoing antifungal suppression. We defined proven coccidioidomycosis as patients with a positive culture confirmed by the Hologic AccuProbe *Coccidioides Immitis* Culture Identification Test (Marlborough, Massachusetts), pathology or polymerase chain reaction for *Coccidioides* species. Probable coccidioidomycosis was defined as the presence of a positive coccidioidal serology, appropriate symptoms and typical radiographic manifestations.

Progressive coccidioidomycosis in association with COVID-19 infection was defined as coccidioidal disease deterioration manifested by an increase in the previously identified coccidioidal complement fixation (CF) titer or by progression of radiographic changes previously attributed to coccidioidomycosis.

We included patients with coccidioidomycosis prior to COVID-19, concurrent with COVID-19, and after COVID-19. Patients whose coccidioidomycosis preceded their COVID-19 were included only if the patient still had active symptoms, serology or radiographic abnormalities. We defined coccidioidomycosis as concurrent with COVID-19 when the symptoms, radiographs and serologic abnormalities of coccidioidomycosis were encountered at the time of diagnosis of COVID-19. Coccidioidomycosis after COVID-19 was defined as being diagnosed within 6 weeks after the diagnosis of COVID-19. The outcome of interest was either progression of already diagnosed coccidioidomycosis or development of clinically active coccidioidomycosis at the time or soon after COVID-19.

Statistical analysis was performed using Stata 17 (Stata Corp.). A p -value ≤ 0.05 was considered to be significant. The Mann–Whitney rank sum test was

used for the analysis of age. All categorical variables were analyzed using the Chi-square test.

Results

A total of 3323 patients with coccidioidomycosis and 5959 with COVID-19 were identified during the period of study. Among these, 60 patients met the criteria of having coccidioidomycosis either prior, concurrently, or within 6 weeks after COVID-19 infection. The median age of the patients was 56 years (range 17–82) and 37 were male. One was African-American, one was Filipino, and five identified as Hispanic. Two declined to provide information on their race or ethnicity. Coccidioidomycosis involved the lungs in 54 subjects or manifested a positive antibody test in an immunosuppressed host in 3 subjects. Two had coccidioidal meningitis and one had non-meningeal disseminated coccidioidomycosis. Twenty-three patients with coccidioidomycosis were on antifungal therapy at the time of their diagnosis of COVID-19.

Clinically active coccidioidomycosis progressed or developed among seven individuals during COVID-19 infection. Patients who progressed did not differ by underlying illnesses, including tobacco use, diabetes mellitus, cancer, or pulmonary or cardiovascular disease (data not shown). Other characteristics comparing patients who progressed or developed coccidioidomycosis to those who did not are displayed in Table 1. As shown, there were no differences in age, sex, ethnicity, whether the coccidioidomycosis was prior, concurrent or after COVID-19, whether they were on antifungal therapy at the time of COVID-19 diagnosis, whether they were receiving immunosuppressive medication or were solid organ transplant (SOT) recipients. Moreover, coccidioidomycosis was no more likely to progress in those hospitalized or in those who received remdesivir or plasma or monoclonal antibody therapy. No patients received anti-cytokine therapy. However, patients who received dexamethasone as part of their COVID-19 treatment were significantly more likely to have progressive or newly diagnosed clinical coccidioidomycosis ($P = 0.042$).

Details regarding the seven patients whose coccidioidomycosis progressed or developed during COVID-19 infection are displayed in Table 2. Four

Table 1 Summary description of the cohort of patients with coccidioidomycosis and COVID-19 infection

Characteristic	Stable (53)	Progressed (7)	P-value
Age (median, range)	55 (17–82)	63.5 (23–81)	0.185
<i>Sex</i>			
Male	31	6	
Female	22	1	0.164
<i>Ethnicity (n = 58)</i>			
Non-Hispanic	47	5	
Hispanic or Filipino	4	2	0.091
<i>Occurrence of coccidioidomycosis in relation to COVID-19</i>			
Prior	40	4	
Concurrent or after	13	3	0.303
<i>Type of coccidioidomycosis</i>			
Antibody only	2	1	
Pulmonary	48	6	
Disseminated	3	0	0.999
<i>Antifungals prior to COVID-19</i>			
No	31	6	
Yes**	22	1	0.164
<i>Immunosuppressive Therapy</i>			
No	35	5	
Yes	18	2	0.776
<i>Solid organ transplant</i>			
No	41	6	
Yes	12	1	0.614
<i>Hospitalized</i>			
No	30	2	
Yes	23	5	0.162
<i>Dexamethasone</i>			
No	36	2	
Yes	17	5	0.042
<i>Remdesivir</i>			
No	46	5	
Yes	7	2	0.285
<i>Plasma or monoclonal antibody</i>			
No	45	6	
Yes	8	1	0.955

**Among the 25 patients on antifungal treatment at the time of COVID-19, 19 were receiving fluconazole, and 3 posaconazole. The patient whose coccidioidomycosis progressed despite antifungal treatment received isavuconazole

patients had a diagnosis of coccidioidomycosis prior to COVID-19 infection, one was diagnosed during infection, and two developed pulmonary

coccidioidomycosis after COVID-19 infection. Two patients were on immunosuppression and one was an SOT recipient (liver). Six were not on antifungal therapy at the time of development of COVID-19. Five patients were hospitalized for COVID-19 and five received dexamethasone treatment, one as an outpatient.

Six patients developed increasing lung masses and rising coccidioidal complement-fixation (CF) titers while one developed a coccidioidal CF titer to 1:128 without a definable pulmonary focus. Figure 1 demonstrates the second subject in Table 1, who manifested increasing pulmonary infiltrates at the site of prior pulmonary coccidioidomycosis with typical findings of COVID-19 in other parts of the pulmonary parenchyma. All patients survived and no patient developed extrathoracic dissemination.

Discussion

These results indicate that coccidioidomycosis is not an uncommon coincident condition among patients with COVID-19 infection who reside in the coccidioidal endemic region. Because coccidioidomycosis and COVID-19 have many overlapping symptoms, we relied on objective markers of serologic CF titers and or distinctive radiographic progression to identify coccidioidal outcomes. While in the majority of patients, coccidioidomycosis did not worsen during COVID-19, it did progress or develop either during or soon after COVID-19 in seven of the 60 patients identified. In most cases, progression appeared to be related to those with severe COVID-19 requiring hospitalization and the use of dexamethasone. No patients manifested new extrathoracic dissemination or died and all improved with antifungal therapy once coccidioidomycosis was diagnosed.

Our findings suggest that within the coccidioidal endemic region, clinicians should be alert to the possibility of progressive pulmonary coccidioidomycosis during management of COVID-19, particularly during hospitalization or when dexamethasone or other corticosteroids are used. If found, it would be prudent to initiate antifungal therapy, as recommended in the Infectious Diseases Society of America guidelines for immunocompromised patients [9]. Although we did not find that any patients in this cohort who developed extrathoracic coccidioidomycosis in

Table 2 Description of cases of coccidioidomycosis that progressed in association with COVID-19 infection

Diagnosis*	Age	Sex	Race, ethnicity	Underlying illnesses	Coccidioidal presentation prior to COVID-19	Antifungal therapy prior to COVID-19	COVID-19 severity	COVID-19 course	Details of coccidioidal worsening	Management
1	Prior	81	Male	White, non-hispanic	Coronary artery disease, melanoma	Stable pulmonary nodules, coccidioidal CF titer 1:2	None	Hospitalized 11 days; received dexamethasone and remdesivir	Enlarging pulmonary nodules; coccidioidal CF increased to 1:256	Fluconazole started and patient improved
2	Prior	65	Male	White, non-hispanic	Spondylitis with prednisone and TNF- α inhibitor therapy	Stable pulmonary nodule, negative coccidioidal CF titer	None	Hospitalized 8 days; received dexamethasone, remdesivir and convalescent plasma	Pulmonary infiltrate enlarged; coccidioidal CF titer increased to 1:256	Fluconazole started and patient improved
3	Prior	62	Female	White, non-hispanic	Diabetes mellitus	Pulmonary cavity with coccidioidal CF titer 1:2	Isavuconazole	No hospitalization; no ancillary therapy	Pulmonary cavity enlarged	Patient improved after resection and continued isavuconazole
4	Prior	65	Male	White, non-hispanic	Liver transplant	Positive coccidioidal EIA IgG only	None	Hospitalized; received no ancillary therapy	New lung mass with positive coccidioidal serology	Fluconazole started and patient improved
5	After	67	Male	Filipino	Prostate cancer, non-alcoholic steatohepatitis	None	None	Hospitalized for 4 days; received dexamethasone	New pulmonary nodules and cavities with CF 1:128 two months after COVID-19	Fluconazole started, improved
6	After	35	Male	White, non-hispanic	None	None	None	No hospitalization but received dexamethasone	Developed worsening dyspnea and CF titer 1:32 within one month after COVID-19	Fluconazole started and patient improved
7	Concurrent	45	Male	White, hispanic	Diabetes mellitus, tobacco use	None	None	Hospitalized and received dexamethasone	Developed CF titer to 1:128	Fluconazole started and CF declined

*Relation of diagnosis of coccidioidomycosis to COVID19 infection

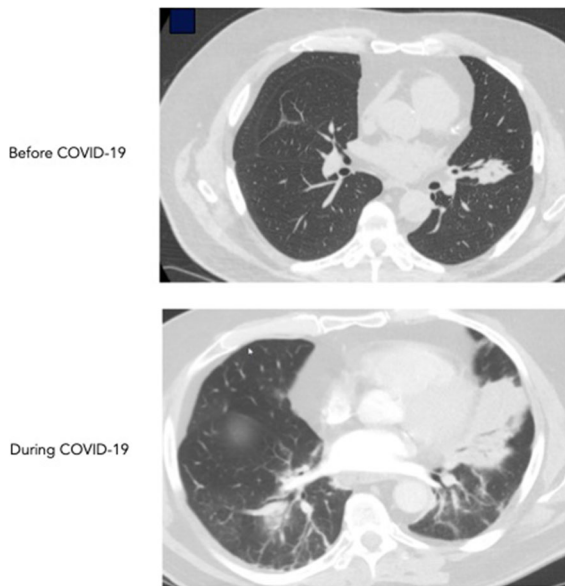


Fig. 1 CT scans from subject with progressive pulmonary coccidioidomycosis (subject 2, Table 2) obtained prior to and during COVID-19 infection after the patient had received a course of dexamethasone

association with COVID-19, two case reports have reported this occurrence [6, 7]. In addition, other case reports noted that coccidioidomycosis was not initially recognized during COVID-19 [10, 11]. Our results and these case reports suggest that clinicians in the coccidioid endemic area be aware of coccidioidomycosis as an acute pulmonary illness even in the midst of the COVID-19 pandemic.

This study has several limitations. The data were accrued early during the COVID-19 pandemic and before the emergence of both the delta and omicron variants of SARS-CoV-2. Because of this, results could be different today either because of infection with the newer viral variants or because of changes in therapy for COVID-19. In addition, the study was retrospective in nature and may have contained hidden and uncontrollable biases. No patients in this cohort received anti-cytokine therapy, so we cannot comment on the effect of these agents on the development of coccidioidomycosis. Finally, because the study was performed at a single medical center, results might vary with a larger and more diverse cohort.

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analysis and wrote further drafts and revisions; Janis E. Blair provided conceptualization, methodology, data curation, and wrote an original draft.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Informed Consent This is an observational study. It was approved by the Mayo Clinic Institutional Review Board, and written informed consent was waived. The subject whose radiographic image is shown in Fig. 1 gave consent for its use.

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