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NOVEL ID CASES

All That Coughs Is Not COVID-19: A Delayed Diagnosis of Disseminated Coccidioidomycosis Following Severe Acute Respiratory Syndrome Coronavirus 2 Infection

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Coccidioides immitis (and *Coccidioides posadasii*) are endemic fungi of the southwestern United States and northern Mexico. Uncomplicated, symptomatic *Coccidioides* infection most commonly causes a self-limited pneumonia; however, immunocompromised patients can manifest severe pneumonia with an additional risk of dissemination to bone, joints, soft tissues, and in the most severe cases, the central nervous system. In 2020, clinicians were challenged with a previously unseen volume of acute respiratory complaints as a result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. We present a patient with respiratory failure secondary to SARS-CoV-2 who experienced prolonged hypoxia and neurologic deterioration, eventually leading to a diagnosis of occult disseminated coccidiomycosis involving meningitis, miliary-pattern pneumonia, and cutaneous lesions.

Keywords. coccidiodomycosis; coinfection; COVID-19; SARS-CoV-2; valley fever.

Coccidioides is a dimorphic fungus that grows in mycelial form in the laboratory and in the soil, and produces characteristic spherule structures in tissue [1]. Arthroconidia sprouting from mycelial structures in the soil travel on hot, dusty summer winds until they are inhaled by human hosts [1, 2]. The majority of *Coccidioides* infections are subclinical and thus never come to medical attention; however, viable organism may remain as latent granulomas. When symptoms do occur, they are most often indolent and result in respiratory symptoms persisting for weeks to months. Less than 1% of cases progress to disseminated extrapulmonary disease. Patients with immunocompromising conditions such as diabetes, human immunodeficiency virus (HIV), pregnancy, solid organ transplant, and exogeneous immunosuppression (inclusive of long-term corticosteroid use) have an increased risk of reactivation and disseminated disease [2, 3]. Disseminated coccidioidomycosis has an estimated mortality of 50% when occurring in these high-risk patient populations [3].

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a global pandemic and delivered a devastating burden of disease to the United States [4]. We present a case of acute SARS-CoV-2 that was treated with dexamethasone, subsequently precipitating the rapid development of disseminated *Coccidioides* disease. We hypothesize that as the SARS-CoV-2 pandemic continues, additional cases of reactivation of undiagnosed coinfections are likely to be unmasked. An underappreciated role for clinicians in the management of SARS-CoV-2, particularly with increasing utilization of immunomodulator therapies, will be risk stratification of patients in order to appropriately screen for latent disease conditions and guide rapid diagnostics in the case of reactivated disease.

CASE REPORT

A 65-year-old man born in Mexico with a history of poorly controlled insulin-dependent diabetes was diagnosed with SARS-CoV-2 at an outpatient clinic in Los Angeles in July 2020. At the time of this diagnosis, he was without hypoxia and received instructions to self-monitor at home. Over the next 7 days he developed progressive shortness of breath and presented to the emergency department with temperature 36.9°C, heart rate 76 beats per minute, blood pressure 144/91 mm Hg, respiratory rate 25 breaths per minute, and an oxygen saturation of 70%. On physical examination he was awake and tachypneic, with decreased breath sounds bilaterally. Chest radiography showed diffuse, bilateral, patchy infiltrates. Laboratory studies were remarkable for mild lymphopenia (absolute lymphocyte count 1000 cells/mm^3). No fungal diagnostics were obtained. After 5 days of hospitalization, he was discharged in stable condition, afebrile with home oxygen at 2 L per minute and prescription for dexamethasone 6 mg daily to complete a duration of 9 days. Three weeks later he developed fever to 38.3°C and continued to complain of shortness of breath while still requiring home oxygen at 2 L per minute. Computed tomography (CT) of the chest demonstrated diffuse, nodular, ground-glass, and consolidative air space opacities with interlobular septal

Received 9 April 2021; editorial decision 10 May 2021; accepted 18 May 2021.

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Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofab246

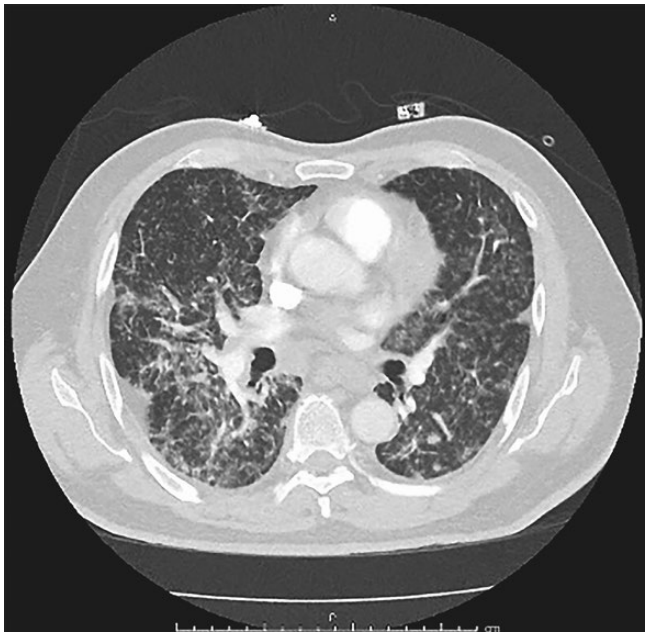

Figure 1. Computed tomography of the chest with pulmonary angiography on the patient's second admission demonstrating diffuse, nodular, ground-glass, and consolidative air space opacities with interlobular septal thickening.

thickening (Figure 1). Mediastinal and bilateral hilar lymphadenopathy was also noted. The radiographic findings were attributed to SARS-CoV-2 despite a negative nasopharyngeal polymerase chain reaction (PCR) result at this time. The patient was hospitalized for 19 days and was treated with broad-spectrum antibiotics for suspected postviral bacterial pneumonia.

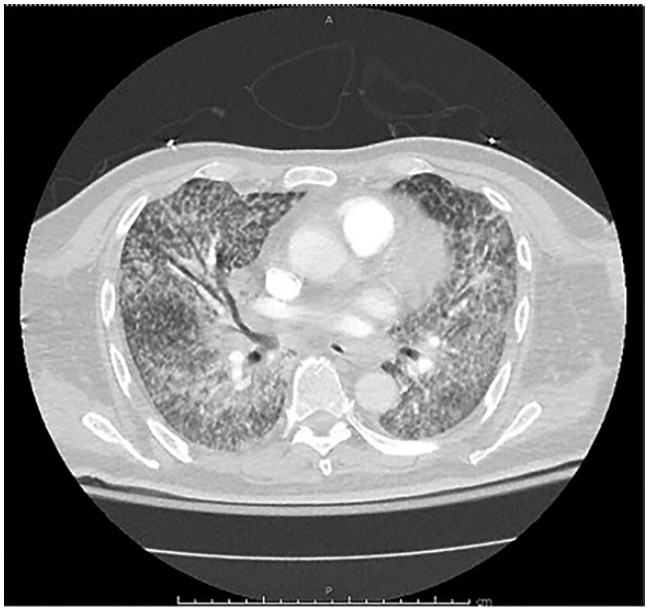

Figure 2. Computed tomography of the chest with pulmonary angiography on the patient's third admission showed an increase in bilateral ground-glass opacities and a miliary pattern of innumerable pulmonary nodules.

Expectorated sputum testing for *Mycobacterium tuberculosis* (MTB) was negative by PCR as well as acid-fast smear and culture. No fungal serologic testing was obtained. The patient was again discharged on home oxygen. Ten days after discharge, the patient returned by ambulance due to altered mental status, recurrent fever, and continued hypoxia. At the time of presentation, the patient had a leukocytosis 18.6×10^3 leukocytes with neutrophil predominance of 87.2%. Additional pertinent laboratory studies included a D-dimer of 6.66 µg/mL and procalcitonin of 0.7 ng/mL. Repeat MTB PCR testing was again negative on 2 expectorated sputum samples. Repeat CT of the chest with pulmonary angiography showed increase in bilateral ground-glass opacities and a miliary pattern with innumerable pulmonary nodules (Figure 2). Despite maximal supportive care and treatment with broad-spectrum antimicrobials, the patient required intubation. Dexamethasone 6 mg intravenous (IV) daily was added on hospital day 7, at the same time infectious disease consultation was sought. Due to altered mental status and persistent fevers, a lumbar puncture was performed with an opening pressure of 13 mm H_2O, 21 nucleated cells (72% neutrophils, 24% lymphocytes, 4% monocytes), glucose 39 mg/dL, protein 70 mg/dL, and 5 red blood cells per mm^3. Serum β-D-glucan returned >500 pg/mL. Empiric IV liposomal amphotericin B was initiated. On hospital day 16, the patient developed 1–3 mm, round, discrete, pink, purpuric macules along the anterior and posterior lower extremities (Figure 3). Two punch biopsy specimens of the skin were obtained for histologic examination and tissue culture. The patient's mental and respiratory status rapidly deteriorated and after discussion with his family, his care transitioned to prioritize comfort-oriented goals. Posthumously, tissue cultures from his punch biopsies isolated *Coccidioides immitis* and *Candida albicans*. Tissue histology revealed mixed inflammation in the upper dermis with many spherules morphologically consistent with coccidioidomycosis (Figure 4). Cerebrospinal fluid *Coccidioides* antibody complement fixation titers returned at 1:16, and a serum *Coccidioides* antigen returned at greater than the upper limit of detection.

DISCUSSION

Each year in respiratory virus season (historically spanning November to April when influenza and respiratory syncytial virus undergo widespread community transmission) pneumonia secondary to *Coccidioides* competes for recognition [5]. The emergence of SARS-CoV-2 creates a new respiratory virus timeline, prompting clinicians to consider it in the differential diagnosis of patients with respiratory symptoms regardless of location or season [4]. Clinician awareness is essential for the diagnosis of invasive *Coccidioides* disease, and the increasing reported prevalence over the past 5 years suggests that awareness is improving [6]. Since 2015, 11 000–15 000 cases of

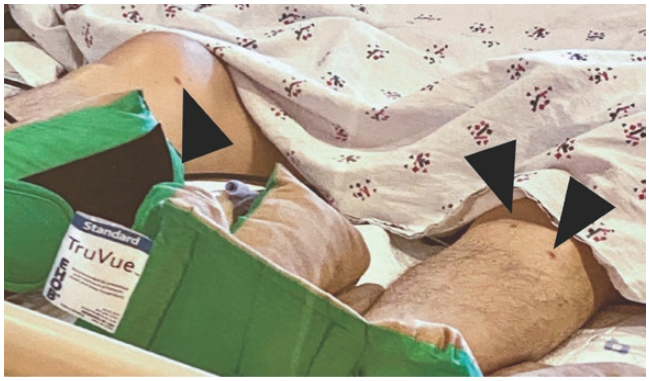

Figure 3. Several 1- to 3-mm round discrete pink-purpuric macules (arrowheads) were observed along the anterior and posterior lower extremities.

invasive coccidioidal disease have been reported annually; the true prevalence is likely underestimated as many are asymptomatic [6]. Superimposed infection, acute coinfection of pulmonary *Coccidioides* and SARS-CoV-2, and disseminated *Coccidioides* temporally related to acute SARS-CoV-2 have all been reported [7–9]. In areas where *Coccidioides* is endemic, and in nonendemic areas for patients with prior exposure, the overlapping signs and symptoms of severe acute or reactivated *Coccidioides* pneumonia and viral pneumonia include fever, shortness of breath, cough, and hypoxia [2, 10]. Due to this overlap in clinical presentations, symptoms of severe pulmonary coccidioidomycosis may be attributed to severe viral pneumonia when SARS-CoV-2 testing is positive.

Our case highlights the challenge facing providers in the era of pandemic SARS-CoV-2 to distinguish respiratory complaints due to acute viral pneumonia and those of underlying more chronic pulmonary disease. As patients delay presentation for chronic symptoms in the context of the ongoing pandemic, concurrent SARS-CoV-2 may become the "tipping point" for patients to seek care [11]. In our case the history of SARS-CoV-2 served as a distractor from his progressive fungal disease as concern for persistent viral pneumonia prevailed; the progressive reticulonodular infiltrates on imaging and his protracted hypoxia, though atypical for a viral pneumonia, failed to alert providers to an alternative disease process. Patients may experience prolonged shortness of breath and cough following acute SARS-CoV-2; clinicians may distinguish patients who require further investigation by the presence of relevant comorbid conditions, which include poorly controlled diabetes, HIV, malignancy, exogeneous immunosuppression, and the presence of radiographic findings inconsistent with resolving viral pneumonia [12]. Short-term glucocorticoids, such as the standard 10-day course of dexamethasone used to treat severe SARS-CoV-2 disease, are not typically regarded as deleterious in *Coccidioides* disease, but without concurrent antifungal therapy the inhibited T-cell function and associated hyperglycemia that accompany high-dose steroids may indeed worsen the disease [13, 14]. Poorly controlled diabetes, as in the case of our patient, is a well-recognized risk factor for disseminated disease; the contribution to development and progression of *Coccidioides* disease by his multiple exposures to high-dose glucocorticoids is difficult to exclude [2, 13]. Our patient did not receive a biologic immunomodulator, but this is a significant concern as the utilization of these agents become widespread in the management of SARS-CoV-2 disease [15, 16].

When considering prolonged exogenous immunosuppression in the context of SARS-CoV-2, recognition of patients at risk for reactivation and dissemination of latent diseases requires careful history taking. Patients with latent disease who develop impaired T-cell immunity, as in poorly controlled diabetes, uncontrolled HIV, recipients of cytotoxic chemotherapy, solid organ transplant recipients, or those receiving high-dose

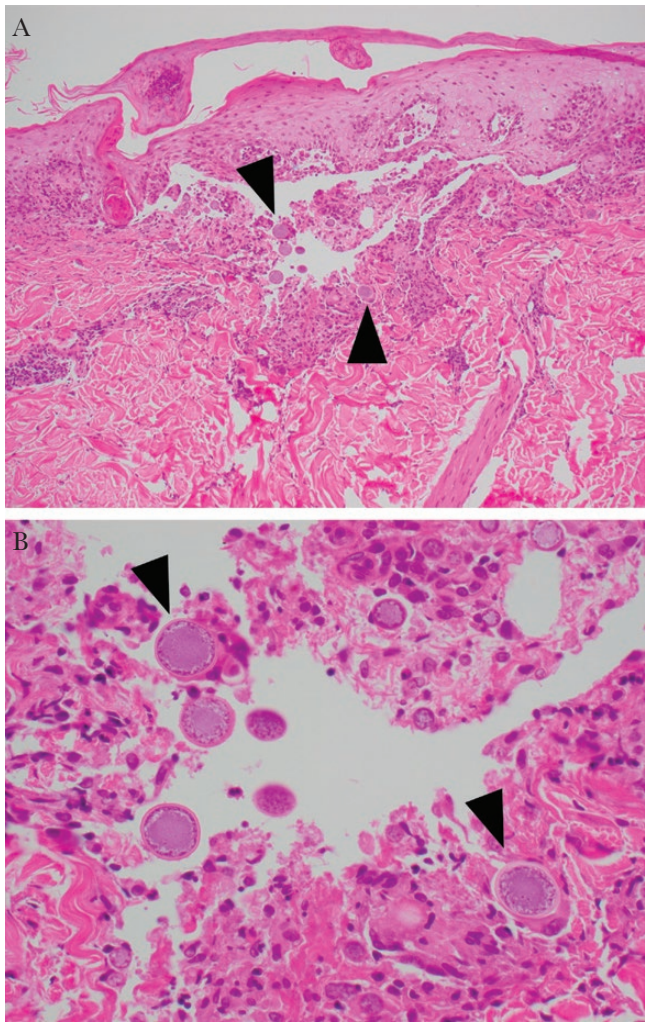

Figure 4. *A*, Hematoxylin and eosin (H&E) stain, ×10 magnification: Reactive epidermal changes with associated mixed inflammation and fungal spherules (arrowheads) were present in the upper dermis, morphologically consistent with coccidioidomycosis. *B*, H&E stain, ×40 magnification: Large fungal spherules (arrowheads) with early endospore formation and associated mixed inflammation were present in the upper dermis.

corticosteroids, carry risk for reactivation and dissemination of granulomatous disease such as *Coccidioides*, *Histoplasma*, *Blastomyces*, and MTB [17, 18]. These patients can be identified by eliciting prior travel and residential history; long-term residence in areas endemic for these pathogens is generally enough to raise the suspicion for latent disease. For patients and providers in nonendemic areas, recognition of prior residency in endemic areas as a risk factor for latent *Coccidioides* disease is essential when considering initiation of immunosuppression. In the case of *Coccidioides* and MTB, screening tests (imperfect as they are) for latent disease are available in the form of antibody testing and the QuantiFERON-Gold assay, respectively. Imaging with evidence of calcified intrathoracic lymph nodes, upper lobe scarring, and evidence of prior granulomatous disease are additional evidence that an individual may harbor viable, latent organisms with potential to reactivate in a setting of immunosuppression. Consideration for latent disease testing, and at minimum vigilance for signs and symptoms of reactivated disease, is advisable when initiating exogenous immunosuppression in these high-risk groups. Patients in these high-risk groups with protracted hypoxic respiratory failure and imaging findings with nodular infiltrates, round consolidations, or cavitating disease may require empiric treatment while diagnostics are pursued.

CONCLUSIONS

In the era of the SARS-CoV-2 pandemic, health care workers are challenged more than ever to rapidly triage and identify the cause of respiratory complaints. Distinguishing uncomplicated acute viral pneumonia from underlying chronic pulmonary disease requires attention to the duration of symptoms, epidemiologic risk for exposure to endemic pathogens with pulmonary involvement, and scrutiny of available imaging for evidence of prior exposure. Identification of patients at elevated risk for reactivation and dissemination of latent granulomatous fungal or mycobacterial disease is achieved with attention to the combination of epidemiologic risk factors and underlying impaired T-cell immunity. Patients who have this combination of risk factors may benefit from screening with serologic testing where reasonably good screening tests exist (ie, *Coccidioides* and MTB), and clinical monitoring for signs and symptoms of reactivation otherwise.

Notes

Acknowledgments. Written informed consent was obtained from the patient's next of kin for publication of this case report and accompanying images.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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