The Brief Case: A Fatal Case of SARS-CoV-2 Coinfection with *Coccidioides* in Texas—Another Challenge We Face

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**CASE**

A 52-year-old Hispanic male who lived in Lynn County, Texas, with obesity (BMI 33) and poorly controlled diabetes mellitus (glycosylated hemoglobin, >12%; range, 4.0 to 5.9%) presented to the emergency room (ER) at an outside hospital with shortness of breath, cough, decreased appetite, and fever for 4 days. He was found with acute hypoxic respiratory failure and was airlifted to one of our satellite hospitals because no hospital beds were available in the patient’s living area. He tested severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive by ID Now COVID-19 assay (Abbott, Abbott Park, IL, USA) and was diagnosed with severe COVID-19 and diabetic ketoacidosis. In the intensive care unit (ICU), he initially required noninvasive positive pressure ventilation with bilevel positive-airway pressure (BiPAP) but decompensated and required escalation to endotracheal intubation and mechanical ventilation by the second hospital day (HD). Chest radiographs were consistent with multifocal pneumonia; bilateral patchy and hazy opacities were seen throughout the lungs and were more prominent on the right side (Fig. 1A). Successive radiographs showed progressive worsening of multifocal opacities and infiltrates throughout the lung fields and developing pleural effusions, culminating in severe bilateral interstitial and alveolar airspace opacities on HD 19 (Fig. 1B).

The patient received dexamethasone 6 mg every 12 h (Q12H) intravenously (i.v.) on HD 1, 20 mg Q24H from HD 3 to 7, continued with 10 mg daily per acute respiratory distress syndrome (ARDS) protocol from HD 8 to 20. He also received a standard 5-day course of remdesivir and 1 unit of convalescent plasma transfusion on HD 1.

Therapeutic anticoagulation with enoxaparin was used. Empiric antibiotics were given throughout his 20-day hospitalization, including cefepime and vancomycin. Despite these efforts, proning, maximum pressure and oxygen requirements, and supportive care, throughout the hospitalization, the patient experienced intermittent fevers as high as 104.9°F and unrelenting respiratory failure with worsening hypoxemia and hypercarbic respiratory failure, to which he eventually succumbed.

Endotracheal aspirates were collected for bacterial culture on HD 2 and 16 and grew normal respiratory flora. Blood cultures obtained on HD 1, 2, and 16 were all negative. Urine *Histoplasma* galactomannan antigen was not detected. On HD 10, due to worsening oxygenation and imaging, bronchoalveolar lavage (BAL) from the right middle lobe was collected for bacterial and fungal cultures. After 5 days of incubation, moist colonies were observed on the brain heart infusion (BHI) agar with blood and inhibitory mold agar (IMA) plates but were too small to identify. Six days later, white fluffy mold on both media (Fig. 2A) was identified as *Coccidioides immitis/Coccidioides posadasii* by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) using the Vitek MS mold kit according to the manufacturer’s instructions (Vitek MS; bioMérieux, Inc., Hazelwood, MO). Unfortunately, the patient...
had expired 1 day earlier on HD 20. The isolate was further identified as *Coccidioides posadasii* by internal transcribed spacer ribosomal DNA (ITS rDNA) sequencing with 100% (607/607 nucleotides) identity to *C. posadasii* CBS 113847.

Retrospectively, serologic tests confirmed both SARS-CoV-2 and *Coccidioides* infections. As summarized in Table 1, both SARS-CoV-2 IgM and IgG were positive from serum collected on HD 17. *Coccidioides* IgM was not detected by enzyme-linked immunosorbent assay (ELISA) on the initial (HD 1) sample but was positive on the convalescent-phase serum collected on HD 17. *Coccidioides* IgG was found to be equivocal (titer, <1:2) on the initial blood sample and converted to positive (titer, 1:256) on the convalescent-phase serum.

Data availability. The nucleotide sequence of the *C. posadasii* isolate recovered from the patient was deposited in GenBank under accession number MW406989.

**DISCUSSION**

The genus *Coccidioides* contains two highly pathogenic species: *C. immitis* and *C. posadasii*, both of which cause coccidioidomycosis (1). *Coccidioides* is endemic in several parts of the United States from Central and Southern California to desert regions of Nevada, Arizona, New Mexico, and West Texas. The biggest difference between the two species of *Coccidioides* is their geographic distribution; otherwise, they are morphologically and phenotypically identical but can be distinguished by sequencing (1).
It is estimated that about 50% of all people living in regions of high endemicity, like Southern Arizona, have been exposed. Of those, 60% may develop an asymptomatic infection or a mild respiratory illness, and the rest will develop the disease in a variable manner (1, 2). Individuals with HIV/AIDS and recipients of immune-modulating drugs, immunosuppressive drugs, or high-dose corticosteroids are at high risk for dissemination and chronic infection. Diabetes mellitus, chronic structural lung disease, and cardiopulmonary disease are also significant predisposing risk factors for severe pulmonary infection (3). Since December 2019, when the SARS-CoV-2 virus first emerged in the human population, treatment recommendations have constantly adjusted to new information discovered about the virus and COVID-19 disease course. One of the current recommendations is treatment with dexamethasone (6 mg/day; administered

**FIG 2** Macroscopic and microscopic images of the *Coccidioides* culture. (A) Fluffy, white fungal growth on inhibitory mold agar. (B) Lactophenol cotton blue tape mount of the organism shows characteristic darkly stained barrel-shaped arthroconidia alternating with lighter segments.
orally or intravenously for 10 days), and it has been shown to significantly reduce mortality and shorten hospitalization course (4, 5).

Dexamethasone is a powerful glucocorticoid with known immunosuppressive effects, specifically on cellular immunity (6). Balow et al. have demonstrated that glucocorticoids could reduce the number of mononuclear leukocytes and deplete circulating T lymphocytes by 40% and 50%, respectively, after administration of glucocorticoids, and these effects persisted for 24 h (7). However, not all glucocorticoids have equal anti-inflammatory effects: dexamethasone has been shown to cause more severe defects in lymphocyte-mediated cytotoxicity than hydrocortisone and prednisone in humans (8). It also had more potent activity against some proinflammatory cytokines, like interleukin-6, in humans (8), which is why it has been recommended in the treatment of COVID-19 patients at risk for developing ARDS. However, therapy with corticosteroids has been observed to facilitate reactivation and dissemination of latent underlying infectious diseases, including invasive fungal infections such as coccidioidomycosis (4). In addition, glucocorticoids have been shown to enhance the growth rate of fungi independent of host immunosuppression, indicating that additional mechanisms may also be responsible for the increased risk of invasive fungal infections (9). Several studies have demonstrated that patients receiving glucocorticoid treatments have developed primary or reactivated invasive infections with the following fungi: *Aspergillus*, *Cryptococcus*, *Histoplasma*, *Fusarium*, zygomycetes, and *Coccidioides* (10–15).

Our patient was a long-term resident of West Texas with poorly controlled diabetes who was hospitalized with severe COVID-19 and did not improve despite standard COVID-19 therapies and empirical antimicrobials. In retrospect, his worsening clinical status may be attributed to a very recent acute *Coccidioides* infection or a reactivated latent infection based on his serology. The *Coccidioides posadasii* isolated from the BAL of this patient is consistent with the location of the patient’s residence and the geographic distribution of this species, and the progressing dense pulmonary infiltrates, fever, and respiratory failure are consistent with the clinical manifestations of coccidioidomycosis. Nevertheless, the patient had been airlifted approximately 600 miles away from his home for medical care, and after intubation was unable to provide pertinent aspects of his history, including employment, geography, or travel history. Moreover, his family was unavailable due to restrictions on COVID-19 visitation. As such, recognition of coccidioidomycosis was made posthumously, evoking a heightened index of suspicion in the future and guiding away from anchoring bias. Therefore, the importance of obtaining thorough social histories from patients or family members cannot be overstated.

Texas is one of the overlapping areas in the United States with endemic histoplasmosis (East Texas) and coccidioidomycosis (West Texas). While there are significant differences between the clinical syndromes resulting from infection with these endemic fungi, it can sometimes be beneficial to pair laboratory tests for suspected histoplasmosis with tests for coccidioidomycosis or vice versa. Clinically, the

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**TABLE 1 Serology tests completed retrospectively using serum samples collected on HD 1 and HD 17**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Serum collection day (HD)</th>
<th>Method(s) (performance laboratory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2 IgM</td>
<td>Positive</td>
<td>17</td>
<td>The Access SARS-CoV-2 IgM by UniCel DxI 600 system, Beckman Coulter, Chaska, MN (UTMB)*</td>
</tr>
<tr>
<td>SARS-CoV-2 IgG</td>
<td>Positive</td>
<td>17</td>
<td>Anti-SARS-CoV-2 IgG testing by Vitros, Ortho-Clinical Diagnostics, Rochester, NY, USA; SARS-CoV-2 IgG assay by Architect, Abbott, Abbott Park, IL (UTMB)</td>
</tr>
<tr>
<td><em>Coccidioides</em> IgM</td>
<td>Negative</td>
<td>1</td>
<td>ELISA with confirmation by immunodiffusion tube precipitin and complement fixation tests (ARUP Laboratories, Salt Lake City, UT)</td>
</tr>
<tr>
<td><em>Coccidioides</em> IgG</td>
<td>Equivocal; titer, &lt; 1:2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><em>Coccidioides</em> IgM</td>
<td>Positive</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td><em>Coccidioides</em> IgG</td>
<td>Positive; titer, 1:256</td>
<td>17</td>
<td></td>
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*UTMB, University of Texas Medical Branch.*
treatment is very likely to be similar, and the pairing of tests is likely to reduce delays in diagnosis and assist in cases where pertinent medical history is unavailable to help discern the diagnosis on clinical grounds. Nonetheless, the pairing of tests should be done judiciously for select cases, as it can lead to unnecessary testing and added costs.

Likewise, this case demonstrates that it is paramount to seek alternative diagnoses. While it may be challenging for clinicians to determine appropriate treatment when the clinical course of COVID-19 is at baseline unpredictable, worsening respiratory failure in patients receiving standard of care management can be suggestive of coinfection or superinfection. Indeed, we have found other clinically significant coinfections superimposed on COVID-19 cases, including cytomegalovirus (CMV) pneumonitis in a solid-organ transplant patient and reactivated pulmonary tuberculosis. More important than unexpected coinfections, however, is the recognition that patients with COVID-19 can and do frequently have superimposed pulmonary edema, nosocomial pneumonias, bacteremias, and thrombotic events complicating their clinical courses, often facilitated by corticosteroid-induced hyperglycemia. As such, relying on COVID-19 as a sole explanation for all medical problems can be risky.

In summary, this case report highlights the importance of maintaining a high index of clinical suspicion for alternative diagnoses in patients with severe COVID-19 in particular and in patients with unrelenting respiratory failure in general. Similarly, this case underscores the value of obtaining a thorough social history from patients, including their geographical residence and travel history. Lastly, it demonstrates the need to consider latent fungal infection before treatment with high-potency glucocorticoids.

**SELF-ASSESSMENT QUESTIONS**

1. Where is *Coccidioides* endemic in the United States?
   - a. Northeast
   - b. Southeast
   - c. Southwest
   - d. Northwest

2. How does prolonged glucocorticoid treatment increase host susceptibility to fungal infection?
   - a. Glucocorticoids suppress the host’s cellular immunity
   - b. Glucocorticoids suppress the host’s humoral immunity
   - c. Glucocorticoids are used as an energy source by many fungi
   - d. Glucocorticoids cause an increase in host respiration rate

3. Which laboratory tests should be ordered if physicians suspect latent or past *Coccidioides* infection?
   - a. Respiratory culture
   - b. *Coccidioides* serology tests
   - c. *Coccidioides* PCR on sputum
   - d. Fungal blood cultures

**REFERENCES**


