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Disseminated histoplasmosis in an immunocompetent patient with COVID-19 pneumonia

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SUMMARY

Disseminated histoplasmosis is usually associated with immunosuppressive conditions like AIDS. People with respiratory distress syndrome secondary to SARS-CoV-2 pneumonia are vulnerable to bacterial infections. Additionally, coinfection with fungal pathogens should be considered as a differential diagnosis even in immunocompetent patients who remain on mechanical ventilation secondary to COVID-19. The case presents a 61-year-old immunocompetent man, admitted to the medical ward due to COVID-19 pneumonia. Despite appropriate therapy, the patient required transfer to the intensive care unit for invasive mechanical ventilation. He remained critically ill with worsening respiratory failure. Two weeks later, coinfection by disseminated histoplasmosis was detected. After immediate treatment with amphotericin B and itraconazole, the patient tolerated weaning from mechanical ventilation until extubation. Awareness of this possible fungal coinfection in immunocompetent patients is essential to reduce delays in diagnosis and treatment, and prevent severe illness and death.

BACKGROUND

At present, according to the Centers for Disease Control and Prevention, 770 461 people have died from COVID-19 in the USA.[1] This represents a public health challenge in the USA and worldwide. SARS-CoV-2 pneumonia combined with bacterial infections has been described in the literature.[2] On the other hand, cases of fungal coinfection in patients with COVID-19 pneumonia are uncommon.[3] COVID-19-associated fungal infections have been reported in several cases; nevertheless, these secondary fungal infections seldom involve *Histoplasma*.[4 5] Only a few cases have been reported worldwide in immunocompromised patients, and such presentation is unusual in immunocompetent patients.[6–10]

This case presents a 61-year-old immunocompetent man, affected by obesity, hypertension, hypothyroidism and type 2 diabetes mellitus, who was initially admitted to the medical floors on high-flow nasal cannula due to acute hypoxic respiratory failure secondary to COVID-19 pneumonia. Despite appropriate COVID-19-directed therapy with dexamethasone, baricitinib and empirical antibiotic coverage for bacterial coinfection, the patient remained critically ill and eventually required transfer to the intensive care unit (ICU) for intubation and mechanical ventilation. On hospital stay day 14, the patient tested positive for disseminated histoplasmosis and was subsequently treated with amphotericin B and itraconazole. Following this, the patient's oxygen requirements slowly trended downward, nonetheless, recovery was slow, likely limited by the underlying lung tissue damage from the initial COVID-19-induced cytokine storm.

CASE PRESENTATION

A 61-year-old man, born, raised and currently living in West Texas with a medical history significant for class I obesity with Body Mass Index (BMI) 34, benign essential hypertension, controlled type 2 diabetes mellitus (haemoglobin A1c 6.4%) and hypothyroidism who was not vaccinated for COVID-19, came into the hospital with cough and shortness of breath for 2 weeks. He had a dry cough and fever of 102° for 2 days, associated with decreased appetite, dysgeusia and anosmia. The patient denied any myalgias, nausea, vomiting, diarrhoea, recent travel or any sick contacts. He works as an accountant and admits not doing outdoor activities. At the emergency department, he was found to be saturating at 66% oxygen while breathing room air. He was initially placed on a non-rebreather mask but was still desaturating and subsequently placed on 60 L/min high-flow oxygen at 100% fractional inspired oxygen (FiO_2).

On physical examination, the patient was haemodynamically stable, afebrile, awake, alert, oriented and in acute distress due to difficulty breathing. Cardiothoracic examination revealed generalised coarse breath sounds bilaterally and S1/S2 heart sounds lacking murmur, gallop or rub. Furthermore, he was tachycardic but with regular rate and rhythm. His abdomen was soft, non-distended, non-tender to palpation, no guarding or rebound, with no organomegaly. Muscle strength was 5/5 on bilateral upper and lower extremities. Skin examination showed no cyanosis or mottling.

INVESTIGATIONS

On admission, the patient tested positive for SARS-CoV-2, laboratory results were significant for neutrophilic leucocytosis ($16.5\times10^3/\mu L$, neutrophils%: 92.3%). Ferritin, lactate dehydrogenase (1942 U/L), C reactive protein (22.1 mg/dL), erythrocyte sedimentation rate (32 mm/hour) and procalcitonin (0.30 ng/mL) were elevated. Arterial blood gas was notable only for hypoxia (O_2 partial pressure of 54 mm Hg or 7.19 kPa) on 60 L 100% FiO_2. Chest X-ray showed diffuse bilateral interstitial infiltrates (figure 1). The patient was admitted for acute hypoxemic respiratory failure secondary to SARS-CoV-2 pneumonia. His initial therapy included dexamethasone 6 mg daily, baricitinib

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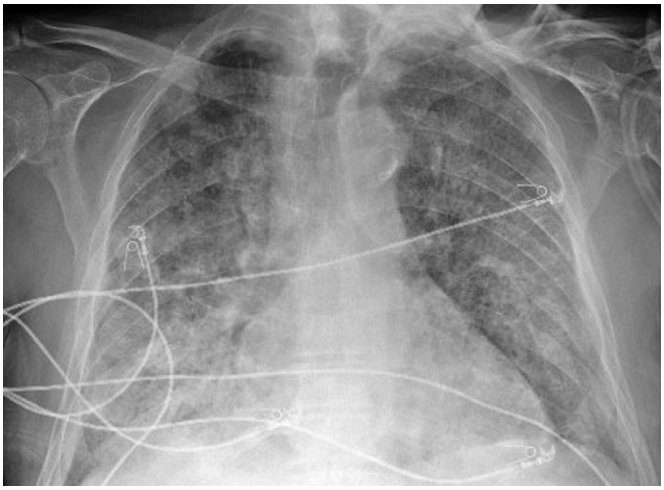

Figure 1 Chest X-ray shows diffuse bilateral infiltrates.

(Janus kinase inhibitor) 4 mg daily, ceftriaxone 2 g daily and doxycycline 100 mg two times per day.

During his hospital stay, the patient's medical condition slowly declined with worsening shortness of breath and deterioration of his mental status. CT of the thorax showed diffuse patchy and ground-glass opacities of the lungs, suspicious for multifocal pneumonia/COVID-19-related pneumonitis. He required transfer to the ICU for intubation and mechanical ventilation. In the ICU, the patient needed 100% FiO_2 and high positive end-expiratory pressure (PEEP) to maintain oxygen saturation above 90%. In addition to the medical management, prone position was used as an adjuvant therapy to enhance ventilation. The patient remained on high oxygen requirements for several days without an improvement, and blood test showed worsening of leucocytosis and inflammatory markers. Consequently, these findings prompt the investigation of possible secondary infection, and multiple studies were performed to rule out a differential diagnosis, including HIV, cytomegalovirus DNA, Epstein-Barr virus PCR, methicillin-resistant *Staphylococcus aureus* PCR, *Streptococcus pneumoniae* antigen, urine *Legionella* antigen, *Mycoplasma pneumoniae, Chlamydophlia pneumoniae, Coccidioides* antibodies, *Histoplasma* and *Aspergillus galactomannan* antigen, blood and respiratory cultures, along with other tests.

On hospital day 14, sputum culture was positive for *S. pneumoniae*, sensitive to levofloxacin. On the other hand, serum and urine *Histoplasma* antigen were positive, indicative of disseminated histoplasmosis. All other microbiological and serological tests were negative.

TREATMENT

After the patient tested positive for histoplasmosis, he received amphotericin B for 1 week and then was transitioned to itraconazole. Furthermore, he completed an antibiotic course for *S. pneumoniae*, dexamethasone and baricitinib for 14 days for COVID-19 pneumonia.

OUTCOME AND FOLLOW-UP

The patient remains hospitalised for over 1 month. Fortunately, the patient's oxygen requirements started to decrease, and his prognosis improved after appropriate treatment.

DISCUSSION

Histoplasmosis is a common pulmonary fungal infectious disease. Central and South America, Africa, Asia and Australia represent the main endemic areas worldwide.[11] Specifically, in the USA, histoplasmosis is mainly endemic to areas that surround the Mississippi and Ohio River valleys.[12 13] In fact, an estimated 60%–90% of people living in those areas have been exposed to the *Histoplasma capsulatum* at some point in their lives.[12 13]

Histoplasmosis infection occurs due to inhalation of spores coming from soil contaminated with bat and other bird droppings. Bat cave-related outbreaks in the USA have been reported primarily in Florida, Texas and Puerto Rico.[11]

Among the most common risk factors include prolonged exposure, immunosuppression, and age <2 years and >50 years old.[14] Specifically for people aged 65 years or older, the incidence of histoplasmosis in the USA is estimated to be 3.4 cases per 100.000 individuals.[15]

Presentation can vary from asymptomatic to severe multisystemic failure. Acute primary histoplasmosis can present with malaise, dry cough, myalgias and fever.[14 16] Chronic cavitary histoplasmosis receives its name due to the presence of upper pulmonary lesions similar to cavitary tuberculosis. This stage is also marked by worsening of cough and the presence of dyspnoea. Other symptoms such as weight loss, haemoptysis, night sweats and fever may be present.[16 17]

Progressive disseminated histoplasmosis is generally chronic. Although it occurs most commonly in immunosuppressed patients, it could also happen in immunocompetent patients. Symptoms at this stage are non-specific and similar to chronic cavitary histoplasmosis. The most important features are lymphadenopathy, hepatosplenomegaly and bone marrow involvement. Other manifestations could be oral ulcers, pneumonia, meningitis and adrenal gland involvement.[11 16–18]

Histoplasmosis can also coexist with other infectious diseases such as tuberculosis, pneumocystis pneumonia and cryptococcosis.[19 20] Coinfection is more frequently found in patients with HIV/AIDS or prolonged immunosuppressive therapy such as corticosteroids or tumour necrosis factor alpha inhibitors. In view of the COVID-19 pandemic, there are very few reports of coinfection with *H. capsulatum* and SARS-CoV-2. Furthermore, by the time this article was written, there were only two cases of histoplasmosis and COVID-19 in patients with HIV/AIDS[6 7] and four cases of coinfection in immunocompetent patients found.[8–10]

The two patients with HIV/AIDS diagnosed with histoplasmosis and COVID-19 presented to the emergency room with cough, dyspnoea with decreased oxygen saturation and fever. Common chest CT findings were mediastinal lymph node enlargement and pulmonary ground-glass opacities. SARS-CoV-2 was confirmed by PCR in both cases; while *H. capsulatum* was diagnosed in one patient by the presence of antigen in urine sample[6] and in the other patient by the presence of intracellular yeast in a skin lesion sample visualised by Giemsa stain.[7] Hospitalisation with supportive care plus antifungal therapy was recommended in both cases. Nevertheless, one patient declined hospitalisation and only agreed to receive oral itraconazole; follow-up was unsuccessful.[6] The other patient received intravenous amphotericin B deoxycholate for 14 days, then the antifungal therapy was switched to oral itraconazole. Discharge occurred after full recovery and reinstalment of antiretroviral therapy.[7]

The four reported cases of histoplasmosis and COVID-19 in immunocompetent patients had different presentations of symptoms. Three of these patients first presented respiratory symptoms of COVID-19, positive PCR confirmed the diagnosis. At that time, chest CT showed ground-glass opacities and the diagnosis of COVID-19-related pneumonia was made. They did not

require hospitalisation, and the management was social isolation and corticosteroids.[8 9] One of these patients also received a 5-day course of remdesivir at the time of the viral infection.[9] Later on, these three patients followed up with their providers due to persistent dry cough and fever. Repeated chest CT demonstrated reduction in ground-glass opacities and new nodular densities with mediastinal lymph node enlargement. Further history interrogation revealed risk factors for histoplasmosis including bat and dust exposure[8] and living in the Ohio River valley.[9] Sputum analysis, urine antigen and serology were used to diagnose histoplasmosis in two patients.[8] As for the third patient, fine-needle aspiration of the subcarinal node revealed budding yeast; finally, positive bronchoalveolar lavage, tissue biopsy and urine antigen confirmed the diagnosis.[9] Pancytopenia was present in one of the patients.[9] Outpatient management with oral itraconazole was the choice for two patients; they recovered successfully after 3 months of treatment.[8] The third patient was admitted with amphotericin B; discharge occurred after cessation of symptoms, and resolution of pancytopenia, and transition to fluconazole.[9]

In the presented case, the patient presented with typical symptoms of COVID-19 pneumonia, like cough, shortness of breath and fever. A positive PCR confirmed the diagnosis, as well as mild elevation of procalcitonin made bacterial infection at presentation less likely. In spite of receiving appropriate COVID-19-directed therapy with dexamethasone, baricitinib and empirical antibiotic coverage for bacterial coinfections, the patient's condition became worse, and he eventually required ICU transfer for intubation and mechanical ventilation. Due to the lack of improvement on broad-spectrum antibiotics that covered potential bacterial coinfections, the possibilities of less common microbial coinfections such as fungal coinfections were examined. In consideration of this, studies to rule out infections from *Aspergillus, Coccidioides* and *Histoplasma* were sent out, and on hospital day 14 the patient's urine test came back positive for the *Histoplasma* antigen, indicating a diagnosis of disseminated histoplasmosis. The patient was immediately started on amphotericin B and then transitioned to itraconazole. Following this, the patient's clinical condition gradually improved, and oxygen requirements gradually trended downward. Nonetheless, it is worth noting that recovery was slow and drawn out, likely from the underlying lung tissue injury sustained from the initial COVID-19-induced cytokine storm.

Also, it is noteworthy to mention that the possibilities of coinfections were only explored and sought after the initial 11-day hospital stay, when it was apparent that the patient was not improving and possibly in an immunosuppressed state due to baricitinib and dexamethasone therapy. The patient's test results returned positive for histoplasmosis on hospital stay day 14, and thus antifungal therapy was not initiated until 2 weeks after hospital presentation. This study did not reveal with certainty whether pulmonary histoplasmosis was present as a true coinfection on initial presentation or something that developed later as a super infection. If it was in fact a true coinfection, there is a possibility that diagnosing and treating it earlier may have prevented patient decline and need for an ICU transfer. Thus, study investigators advise clinicians to have a high index of suspicion for diagnosing co-occurring pulmonary infections when treating patients with SARS-CoV-2 pneumonia. Early identification and treatment of coinfections are associated with lower mortality and length of hospital stay.

Learning points

- The increasing prevalence of coinfections among patients with SARS-CoV-2 pneumonia who are critically ill and mechanically ventilated warrants a high index of suspicion to identify and treat these co-occurring respiratory pathogens.[21]
- The presence of coinfections in patients with SARS-CoV-2 pneumonia is associated with worse outcomes and increased mortality.[21]
- Co-occurring fungal infection is not only a problem limited to the immunosuppressed but is very well an emerging problem of immunocompetent patients with SARS-CoV-2 pneumonia.
- Correct identification and treatment of coinfections are paramount to the overall recovery of patients with COVID-19.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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