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Fulminant Superimposed Covid-19 Pneumonia on Coccidioidomycosis Disseminated Infection

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) is a novel virus with limited data regarding co-infection with fungal pathogens. A 35-year-old, immunocompetent, male with a past medical history of pulmonary coccidioides infection presented with worsening cough, shortness of breath and hemoptysis. Patient was found positive for COVID-19 via DNA PCR and Coccidioides reactivation via antibody testing. He had received treatment for Coccidioides infection previously, but it was unknown whether he finished it due to his lack of outpatient follow-up. Specifically for COVID-19, he was started on the standard 5-day course of Remdesivir, but he experienced rapid respiratory deterioration and ultimately died.

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Introduction

In December 2019, a cluster of severe pneumonia cases, now known to be caused by a novel strain (SARS-CoV-2) of the zoonotic beta-coronavirus family, was reported in Wuhan, China [1]. Having spread quickly internationally, by March 2020, the World Health Organization (WHO) declared it a global pandemic. Clinical features of this disease range from asymptomatic to fatal illness. The most common presentation requiring hospitalization is respiratory distress [1]. Co-infection with fungal pathogens appears to be uncommon with only seven other cases regarding coccidioides association appearing in the literature, but only this case reports rapid and fulminant decline [2-8].

Case Report

A 35-year-old Hispanic male presented after 2 weeks of experiencing progressive cough, shortness of breath and hemoptysis. He shared that the year prior he had been hospitalized and subsequently received outpatient treatment for an unspecified fungal pulmonary infection using Fluconazole, but he was unsure if medical treatment was complete because he had not attended follow-up appointments. His only persisting symptom was mild shortness of breath with activity.

On associated symptoms, the patient denied fevers, chills, headaches, conjunctival congestion, anosmia, ageusia, nausea, vomiting, or myalgias. On review of systems, he was positive for bilateral elbow and knee pain that had progressively worsened over the past year, but he attributed it to chronic overuse from physical labor.

He was unvaccinated for COVID-19. He had no recent travel history, pets, or sick contacts he could identify. He worked in landscaping where he had exposure to dust and dirt particles and frequent contact with customers, but he claimed he wore a mask regularly. He denied alcohol, tobacco or illicit drug use.

Vital signs were remarkable for a heart rate of 142 beats per minute, a respiratory rate of 38 breaths per minute and saturation of peripheral oxygen of 93%. His other vital signs were a temperature of 98 degrees Fahrenheit, systolic blood pressure of 120 mmHg, diastolic blood pressure of 78 mmHg, and a cuff mean arterial pressure of 89 mmHg.

Physical exam encompassing nine organ systems was remarkable for tachycardia, tachypnea and joint pain at the elbows and knees bilaterally but was otherwise normal including lungs clear to auscultation bilaterally.

Laboratory investigations on admission were significant for an arterial blood gas for pH 7.461 (reference range, 7.350 to 7.450) and an HCO3 Calculated Arterial of 26.5 (reference range, 18.0 to 26.0). Hematology complete blood count was significant for white blood cells 19.58 (reference range, 4.60 to 10.20), red blood cells (RBC) 4.142 (reference range, 4.70 to 6.10), Hemoglobin 13.5 (reference range, 14.10 to 18.40), hematocrit 40.9 (reference range, 43.5 to 53.7), mean platelet volume 11.25 (reference range, 7.4 to 10.4), red cell distribution width 15.2 (reference range, 11.6 to 14.8), Neutrophil percent Auto 85.1 (reference range, 37.0 to 80.0), lymphocytes percent 8.1 (reference range, 10.0 to 50.0). Coagulation revealed prothrombin time 16.5 (reference range, 9.8 to 14.6), international normalized ratio 1.44 (reference range, 0.67 to 1.40), and D Dimer quantitative 1,414 (reference range, 0 to 600). Chemistry complete metabolic panel revealed a sodium level of 130

(reference range, 136 to 144), potassium 3.4 (reference range, 3.6 to 5.1), chloride 100 (reference range, 101 to 111), carbon dioxide 21 (reference range, 22 to 32), blood urea nitrogen 5.4 (reference range, 8.0 to 26.00), glucose 178 (reference range, 79 to 110), calcium 8.2 (reference range, 8.9 to 10.3), albumin 2.89 (reference range, 3.50 to 4.80), alkaline Phosphatase 186 (reference range, 38 to 126), lactate dehydrogenase 244 (reference range, 98 to 192), protein total 11.2 (reference range, 6.1 to 7.9), globulin 8.3 (reference range, 1.5 to 4.3), ferritin 342 (reference range, 30.0 to 244.0) and c-reactive protein test 9.25 (reference range, 0.20 to 0.90). Other positive results included COVID19 SARS-CoV-2 PCR positive and Coccidioides antibody, complement fixation, with serum > = 1:4096. Sputum culture with gram stain panel positive 2+ Fungus two-days later. Otherwise, other lab values were unremarkable [Table 1].

Table 1: Summary of Negative Results

Respiratory Panel (PCR)	Other Tests
Influenza A	Complete Blood Count (CBC)*
Influenza B	Comprehensive Metabolic Panel (CMP)*
Legionella	Sputum Culture*
MRSA	Blood Culture x2
Mycobacterium tuberculosis	Urinalysis
Adenovirus	Urine Culture
Coronavirus 229E	Tuberculosis (TB) Culture
Coronavirus HKU1	Acid-Fast Bacilli (AFB) Smear
Coronavirus NL63	Hepatitis B core Antibody
Coronavirus OC43	Hepatitis Surface Antigen
Human Metapneumovirus	Hepatitis C Antibody
Human Rhinovirus/Enterovirus	Hepatitis-A Antibody IgM
Parainfluenza Virus 1, 2, 3 and 4	HIV 1 & 2 Antibody-Antigen 4th generation
Respiratory Syncytial Virus	
Bordetella Pertussis	
Mycoplasma Pneumoniae	
Strep A	
Clamydophilia pneumoniae	

*some abnormalities as stated in text

Table 2: Literature Review of Cases of Coccidioidomycosis and COVID-19 Co-infection

First Author	COVID Vaccinated	Clinical Summary	Therapy	Outcome
Passeri MF	No	35-year-old, immunocompetent, male with a past medical history of pulmonary coccidioides infection presented with worsening cough, shortness of breath and hemoptysis. Patient was found positive for COVID-19 via DNA PCR and Coccidioides reactivation via antibody testing. He had rapid respiratory deterioration since admission.	Received Fluconazole the year prior to admission. Received Remdesivir for COVID-19.	Death within 5 days from hospital admission.
Shah AS	No	48-year-old male with chronic pulmonary coccidioidomycosis presented with fever, cough, and body aches. Coccidioidal serology study and COVID-19 test were positive.	No specific treatment was given.	Patient did not require hospitalization and was discharged home.
Chang CC	No	48-year-old, immunocompetent, female presented with headache, shortness of breath, and cough. Initially diagnosed with COVID-19. Due to worsening symptoms coccidioidal serology was also performed which also returned positive.	Initially treated with ceftriaxone, azithromycin, Remdesivir, and dexamethasone. Fluconazole was started after testing positive for coccidioides.	Rapid resolution of symptoms occurred after initiation of fluconazole. Patient was discharged home with oral fluconazole and dexamethasone.
Nassif EF	No	67-year-old, immunocompetent, female, presented with shortness of breath, cough, and fatigue. COVID-19 PCR was positive. Initial serology for coccidioidal infection was indeterminate. Patient returned to hospital due to worsening symptoms, imaging revealed chest mass and pulmonary nodules. Repeat coccidioidal serology was positive for IgG and coccidioidomycosis complement fixation titer was 1:32.	Initially treated with supportive treatment for COVID-19 PNA. Once serology returned positive for coccidioides, the patient was started on oral fluconazole.	Patient continued to have asthenia and shortness of breath; however, the cough resolved. Imaging revealed a decrease in size of pulmonary nodules and chest wall mass.

Chen JC	Unknown	65-year-old, immunocompetent, male, presented with shortness of breath with a prior positive COVID-19 test. Discharged after a brief hospital stay with home oxygen. However, he returned with fever and worsening shortness of breath. Imaging revealed hilar and mediastinal lymphadenopathy, and diffuse, nodular, ground glass opacities in bilateral lungs. He was discharged again with home oxygen. Returned yet again with worsening symptoms and altered mental status. Eventually the patient was transitioned to comfort oriented goals by family. Posthumous punch biopsies from skin lesions isolated Coccidioides immitis and Candida albicans in tissue cultures. CSF Coccidioides complement fixation titers were 1:16 and serum Coccidioides antigen returned higher than the upper limit of detection.	Initially treated with oxygen supplementation. Broad spectrum antibiotics were administered during second hospitalization. During last admission, empiric iv liposomal amphotericin B was also administered.	Patient continued to progressively worsened and the family eventually decided on comfort prioritizing treatment goals.
Krauth DS	No	23-year-old, immunocompetent, male, tested positive with COVID-19 PCR during screening. He was asymptomatic and did not require any specific treatment. 30 days later the patient presented with 21 days of night sweats, unintentional weight loss, bony pain, and ulcerations on shoulder. Imaging showed ground glass opacities in the lung with hilar, axillary, mediastinal lymphadenopathy and lesions involving the axial and appendicular skeleton. Skin biopsies showed rare spherules with multinucleated giant cells and eosinophils consistent with Coccidioides. Serology for anti-Coccidioides was positive for IgM and IgG and complement fixation titer of 1:64 was detected.	Initially discharged with no specific treatment. When the patient returned, he was treated with iv liposomal amphotericin B with eventual transition to oral itraconazole.	The patient displayed continual clinical improvement once antifungal treatment was initiated.
Moradi N	Unknown	65 year old immunocompetent male, presented with shortness of breath, fever, cough, and diffuse chest discomfort. COVID-19 PCR tested positive. Imaging showed bilateral ground-glass opacities and left upper lobe cavitary lesion. Coccidioides antibody complement fixation was positive for IgG and IgM with titers of 1:256. Bronchiolar lavage cultures were positive for Coccidioides immitis and posadasii.	Treated with supplemental oxygen, antibiotic therapy, Remdesivir, and convalescent plasma transfusion.	Despite treatment, the patient unfortunately did not survive.
Ko J, Lee MM	Unknown	65 year old immunocompetent male presented with dyspnea and confusion. He was diagnosed and treated for COVID-19 PNA 3 months prior. Imaging revealed diffuse ground-glass opacities, consolidations, and innumerable small nodules in the lungs. Lumbar puncture and biopsy of skin lesions were performed. Posthumously results of serology, CSF analysis and skin biopsy revealed disseminated coccidioidomycosis.	Initially, COVID-19 was treated with steroids and supplemental home oxygen. When hospitalized after, he was intubated due to hypoxia. Empiric tuberculosis treatment was initiated.	Despite treatment, the patient did not improve. He developed multi organ failure and his family eventually decided on comfort prioritizing treatment.

Clinical pathology report was consistent with acute infection revealing marked neutrophilia with left shift, rare circulating blasts (1 to 2%) and toxic granulation. Macrocytic anemia with mild anisopoikilocytosis was observed, and platelets were within normal limits with occasional platelet clumps.

Records from previous admission one-year-ago revealed a right neck lymph node ultrasound-guided needle core biopsy with results showing *Coccidioides immitis* granulomatous inflammation.

Baseline EKG revealed sinus tachycardia without ST segment elevations or QT interval prolongation. Computed Tomography (CT) angiogram was obtained. For comparison, CT scan from previous admission one-year-ago was reviewed which revealed a large right upper lobe cavitary mass which appeared contiguous with an associated right hilar mass/lymph node concerning for cavitary infection [Figure 1]. There was also interlobular septal thickening within the adjacent right upper lobe with additional areas of multifocal tree-in-bud opacities [Figure 2]. CT angiogram on this admission revealed resolution of the cavitary infiltrate in the apical segment of the right upper lobe, but there were residual subpleural pulmonary air cysts [Figure 3]. There was a new cavitary consolidation in the apical posterior segment of the left upper lobe and the superior segment of the lingula with additional peripheral cavitary nodules in both lungs [Figure 4]. Additionally, there was a diffuse miliary micronodular pattern and dependent consolidations consistent with ARDS [Figure 5]. The initial report from radiology indicated suspicion of miliary tuberculosis.

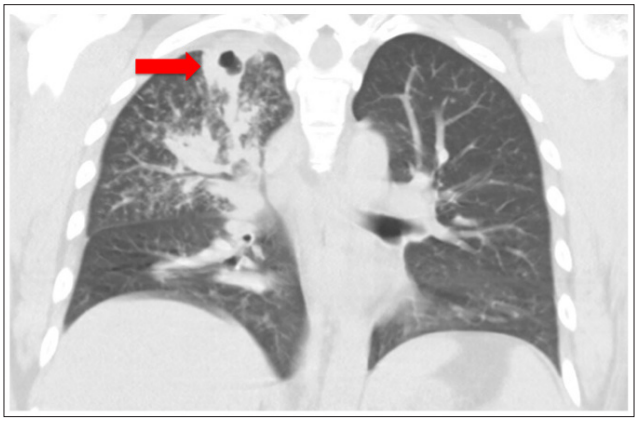

Figure 1: CT Chest with/without contrast – Coronal Section

Large right upper lobe cavitary mass contiguous with an associated right hilar mass/lymph node concerning for cavitary infection consistent with Coccidioides

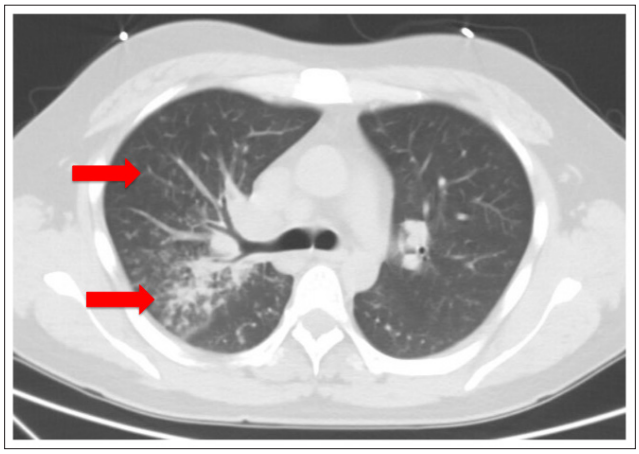

Figure 2: CT Chest with/without contrast – Transverse section

Interlobular septal thickening of right lobe with additional areas of multifocal tree-in-bud opacities

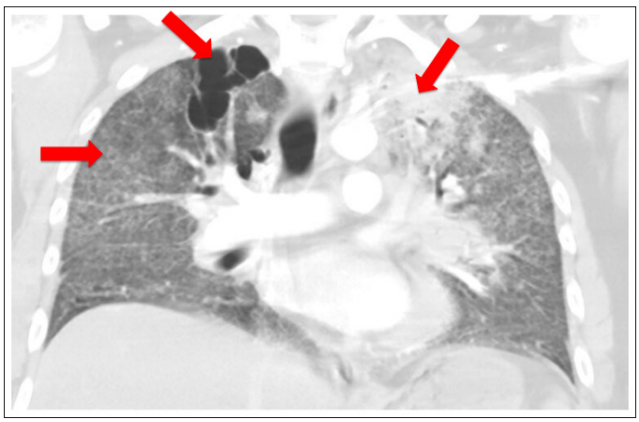

Figure 3: CT Chest Angiogram with Pulmonary Embolism protocol – coronal section

Resolution of prior cavitary infiltrate in the apical segment of the right upper lobe, development of subpleural pulmonary air cysts , bilateral lungs show diffuse disseminated Coccidioides and SARS-CoV-2 infection

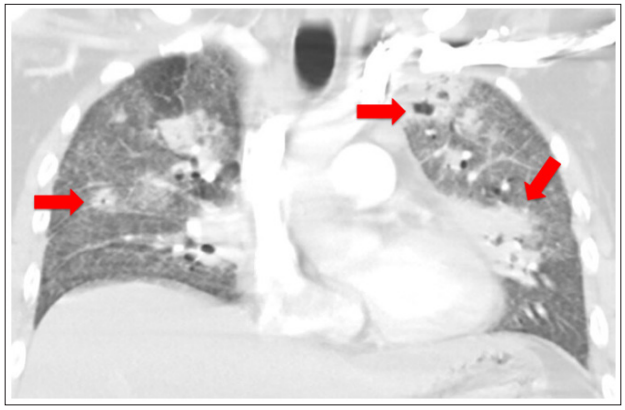

Figure 4: CT Chest Angiogram with Pulmonary Embolism protocol – coronal section

New cavitary consolidation in the apical posterior segment of the left upper lobe and the superior segment of the lingula with additional peripheral cavitary nodules in both lungs

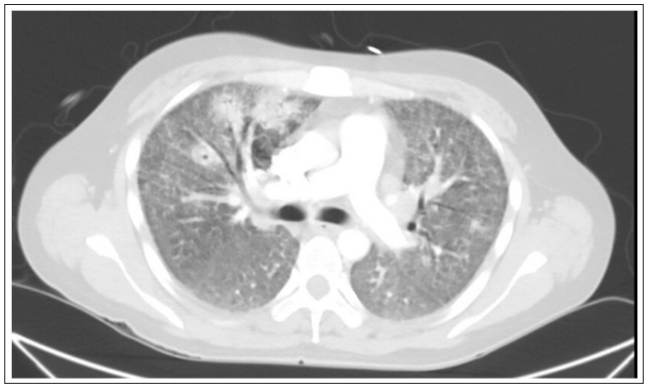

Figure 5: CT Chest Angiogram with Pulmonary Embolism protocol – transverse section

Bilateral diffuse disseminated Coccidioides and SARS-CoV-2 infection evidenced by diffuse miliary micronodules consistent with a miliary pattern and dependent consolidation consistent with ARDS

Because at the time not all laboratory results were available, empiric broad-spectrum antimicrobial treatment for pulmonary infections was started using vancomycin, azithromycin, and piperacillin-tazobactam. Antifungals were not given as tuberculosis was suspected. COVID-19 specific treatment provided was Remdesivir.

Overnight, the patient experienced oxygen desaturation and was placed on bilevel positive airway pressure with settings titrated throughout the next day as his oxygen demand escalated. On day three, respiratory status declined precipitously and was intubated. Vasopressor support was initiated using phenylephrine due to persistent tachycardia, while sedation was performed using propofol and hydromorphone. Unfortunately his respiratory status continued to worsen on day four and he went into cardiopulmonary arrest. Resuscitation efforts were unsuccessful in achieving return of spontaneous circulation.

Discussion

Coccidioides immitis is a dimorphic fungus that causes coccidioidomycosis. It typically presents asymptomatically or as a respiratory infection after inhalation of its spores. The fungus is known to live in the soil in the southwestern United States

and parts of Mexico [9]. Our patient originates from central Mexico and worked in an area endemic to coccidioidomycosis in the United States, which also suffered from high infectivity of COVID-19 at the time of co-infection [10]. Of the seven known cases of COVID-19 associated with Coccidioides immitis, our case was unique in that rapid and fulminant decline happened within days of co-infection [2-8]. This is important because early detection may be crucial to survival.

Disseminated infection is a rare occurrence in immunocompetent individuals [11]. Post-mortem review of records, including outpatient and inpatient, revealed no immunocompromising pathologies nor recent history of immunosuppressive therapies that would place him at major risk for disseminated coccidioidomycosis. However, incomplete treatment is a known risk factor [12, 13]. Although treatment is typically for a length of 3-to-6 months, our patient did not attend follow-up appointments that would affirm therapy was complete [13]. Also, though resolved during last hospitalization, the previous presence of extrapulmonary disease, in the form of cervical lymphadenopathy, means he already once experienced disseminated disease and recurrence would be unsurprising.

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It is unknown if Coccidioides infection re-emerged in the interim by itself or happened as a result of COVID-19 association, but given his persistent shortness of breath with activity and unspecified progresive bilateral elbow and knee pain, it is likely to have occurred prior. Bone or joint involvement is common when coccidioidomycosis becomes disseminated [13].

COVID-19 infection has been linked to immune dysregulation and may present with lymphopenia and significant thrombocytopenia, as seen in our patient. Immune dysregulation is suggestive of a lower ability to regulate coccidioidomycosis where COVID-19 may have reactivated *Coccidioides immitis* leading to rapid death [14-16].

SARS-CoV-2 is known for creatiating CD8+ T-cell senescence that contributes to diminished cell-mediated signaling as a result of functional depletion [17]. Coccidioides infection initiates prolonged Th1 and cytotoxic T-cell response leading to impaired cytokine signaling from CD4+ Th1 and cytotoxic CD8+ T-cells, but these same CD8+ T-cells are essential for clearance and recovery in immune host defense in SARS-CoV-2 infection [16].

Host immune response to Coccidioides requires both innate and adaptive immunity, whereby tumor necrosis factor-alpha signaling regulates adaptive immunity [17]. Both CD4+ T-helper 1 and cytotoxic CD8+ T-cells coordinate humoral responses to Coccidioides. During SARS-CoV-2 infection, there is a large variation of host responses given that there is both immunologic impairment and hyperactivation of the immune system. SARS-CoV-2, uses its spike-S protein to bind to the host respiratory tract via human angiotensin-converting enzyme receptor 2. Cell mediated response is initiated following endocytosis creating an inflammatory NF-kappa B cascade, stimulating macrophages to activate Th1 and cytotoxic T-cells. This may correlate to the degree of SARS-CoV-2 infection severity. Along with immune modulation, it has been observed there is increased expression of CD57, a marker of cellular senescence, as well as decreased potential of cell mediated proliferation [16]. Together, this interplay of immune cells contributes to rapid progression of disease which may lead to death.

Underlying respiratory illness is a major risk factor for severe COVID-19 disease [14]. Considering the overlap of risk factors for severe disease from both coccidioidomycosis and COVID19, future studies are needed to evaluate whether elevated death rates in severe disease associated with either are a result of co-infections or serial infections.

In sum, this case report presents a rare occurrence of disseminated coccidioidomycosis with fulminant superimposed COVID-19 pneumonia in a young, relatively healthy male. This case highlights the importance of early detection and treatment of respiratory co-infections to prevent further dissemination and reduce the risk of morbidity and mortality.

Data Availability
Upon request to the corresponding author.

Patient Consent
Consent was obtained to use patient's case for academic purposes such as this case report

Conflicts of Interest
The authors do not have any conflicts of interest.

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