

Successful Treatment of COVID-19 Pneumonia using Hydroxychloroquine, Azithromycin, and Tocilizumab

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Abstract

As of April 15, 2020 there were 1,914,916 confirmed cases of coronavirus disease 2019 (COVID-19) responsible for 123,010 deaths throughout the world. Facing mortality rates near 5%, the global medical community is racing to develop effective therapies against this viral pandemic. Current management of COVID-19 is largely supportive, with interventions directed at prevention and treatment of severe pulmonary complications including Acute Respiratory Distress Syndrome (ARDS), the leading cause of mortality in the disease. A small epidemiologic study of an early cohort of patients with laboratory-confirmed disease suggested a correlation between cytokine-driven inflammation and disease severity with progression to ARDS.³ Here we present the case of an acutely ill patient diagnosed with COVID-19 pneumonia who was successfully treated with a supportive care regimen which included tocilizumab.

Keywords: Disease • Covid-19 • Anti-phospholipid syndrome • Acute respiratory distress syndrome

Introduction

A 57-year-old male went on a trip to London, England from 3/5/20 through 3/14/20. He returned to the United States where he resumed normal activities. On 3/20/20 he presented to a local emergency department with symptoms of fever, chills, and generalized musculoskeletal pain. The patient's past medical history was significant for hypertension and hyperlipidemia. His outpatient medications included amlodipine 5 mg once daily and atorvastatin 40 mg once daily. Due to the patient's clinical presentation, recent international travel, and occupational risk as a physician, a nasopharyngeal sample was collected and sent to an outside laboratory for a Polymerase Chain Reaction (PCR) test to detect the presence of SARS-CoV-2, the virus that causes COVID-19. It was known at that time the results of the test would take several days to return. In the meantime, the patient was discharged from the emergency department with a diagnosis of febrile illness and instructions for self-care and quarantining [1,2].

Case Presentation

On 3/24/2020 the patient returned to the emergency department complaining of worsening headaches, fevers, chills, and nausea. Additionally, he reported a new onset non-productive cough accompanied by chest pain and dyspnea. Vital signs were significant only for a mildly elevated respiratory rate of 21 breaths/minute. Peripheral arterial oxygen saturation (SpO₂) was 96% on room air. On physical examination, lungs were clear to auscultation bilaterally. Pertinent laboratory findings included a leukocyte count of 3,400 cells/microliter with a normal differential distribution. Serum levels of C-reactive protein, ferritin, and lactate dehydrogenase were noted to be elevated (Table 1), while serum d-dimer and troponin levels were within normal limits. A baseline electrocardiogram was unremarkable. PCR testing for *Bordetella pertussis* and a panel of common viral respiratory pathogens were negative. Urinary

antigen testing for *Streptococcus pneumoniae* and *Legionella pneumophila* were negative. A blood culture was negative for growth and remained so after five days of incubation. A chest radiograph demonstrated a left lower infiltrate (Figure 1).

The patient was admitted on 3/24/20 for monitoring and treatment of community acquired pneumonia possibly due to COVID-19. On admission, orders were placed for: hydroxychloroquine 400 mg orally twice daily for 1 day followed by 200 mg twice daily for 4 days; azithromycin 500 mg intravenously every 24 hours; and ceftriaxone 1 g intravenously every 24 hours. The patient's home medications were also resumed on admission. Over the subsequent two days, the patient's clinical status remained unchanged. The patient was visibly short of breath, however SpO₂ remained >93% without supplemental oxygen. On 3/26/20 the hydroxychloroquine order was held due to intractable nausea. Serial chest radiographs demonstrated persistent patchy airspace opacities in the left lower lobe with progression to the right lower lobe (Figure 1). On 3/27/20 the results of SARS-CoV-2 PCR test returned as positive. Given the patient's stagnant clinical course and elevated inflammatory biomarkers (Table 1), the decision was made to administer tocilizumab 400 mg (4.7 mg/kg) intravenously. A second dose was administered 18 hours later. On 3/30/20 the patient was discharged home.

Discussion

At present, there are no medications with proven safety and efficacy for COVID-19. Therapeutic interventions aimed at the pandemic are currently limited and experimental in nature. Considering the etiology of COVID-19, medications with antiviral activity against SARS-CoV-2 are under investigation. Remdesivir, an adenosine analogue, has been shown to inhibit in-vitro replication of SARS-CoV-2; however, it is not widely available in the United States outside of clinical trials [3,4]. Hydroxychloroquine is an established antimalarial and antirheumatic drug that may interfere with SARS-CoV-2 entry into the host cell through alteration of endosomal pH and membrane receptors [5]. Hydroxychloroquine has been shown to inhibit SARS-CoV-2 replication in infected cell models [6]. We chose to use hydroxychloroquine in our patient's treatment regimen because of its potential to reduce viral replication and symptom duration. The macrolide antibiotic azithromycin has been used adjunctively with hydroxychloroquine for the treatment of COVID-19. Gautret et al. reported enhanced viral clearance in a small sample of COVID-19 patients following 6 days of hydroxychloroquine. It was observed that viral carriage was further reduced in a subset of patients who received azithromycin in additional

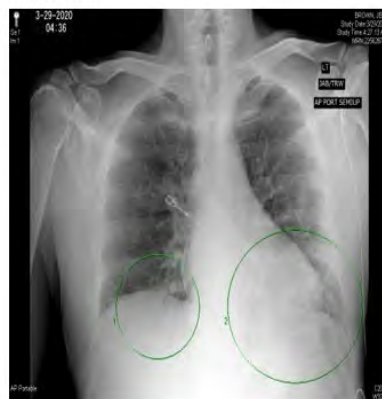
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3-24: Left lower lobe infiltrate



3-29: Left lower lobe infiltrate +RLL infiltrate.



3-30: Prior to Discharge- Appears clear



Figure 1. Chest radiographs.

Table 1. Inflammatory markers.

Parameter [Institutional reference range]	3/25/20	3/26/20	3/27/20	3/28/20	3/29/20	3/30/20
Ferritin (ng/ml) [26 to 388 ng/mL]	757	744	723	962	848	634
C-Reactive Protein (mg/L) [0 to 3 mg/L]	>9.5	>9.5	>9.5	>9.5	>9.5	>9.5
Lactate Dehydrogenase (U/L) [85 to 241 U/L]	253	232	310	-	302	317
Interleukin-6 (pg/ml) [0 to 15.5 pg/mL]	34.2	-	728.7	-	-	-

to hydroxychloroquine [7]. We chose to add azithromycin to our treatment regimen with hopes of synergizing hydroxychloroquine therapy.

The pathogenesis of COVID-19 may include a profound systemic inflammatory syndrome referred to as cytokine storm. Cytokine storm is characterized by multi-organ dysfunction and elevated serum levels of inflammatory markers, such as IL-6, ferritin, C-reactive protein, and lactate dehydrogenase. Tocilizumab is an IL-6 receptor antagonist indicated for rheumatologic conditions and reversal of cytokine storm caused by immunotherapies used to treat hematologic malignancies [8]. The use of tocilizumab for the treatment of patients with COVID-19 pneumonia with elevated serum IL-6 levels is supported by China's National Health Commission treatment guidelines [9]. A recently published case report described the clinical course of a patient with COVID-19 who was treated with tocilizumab and subsequently experienced favorable outcomes [10]. We chose to use an IL-6 receptor antagonist prior to the development of respiratory failure to prevent progression to ARDS.

Conclusion

This is one of the first cases where tocilizumab was used as an early intervention for COVID-19 pneumonia. Randomized controlled trials are needed to establish safety and efficacy of tocilizumab in the management of COVID-19.

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