CLINICAL PRACTICE
Clinical Vignettes

Acute Hypoxemic Respiratory Failure with High Clinical Suspicion of COVID-19 Despite Negative PCR: a Case for Empiric Corticosteroids and Role of Serum Antibody in Diagnosis

Vannesa Cederstrom, MD[1], Heidi Erickson, MD[2,3], and James Leatherman, MD[2,3]

[1]Internal Medicine, Department of Medicine, Hennepin County Medical Center, Minneapolis, MN, USA; [2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Hennepin County Medical Center, Minneapolis, MN, USA; [3]University of Minnesota, Minneapolis, MN, USA

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CASE

HN cis a 39-year-old healthy male who worked as an essential worker in a healthcare setting. He first presented to clinic in November 2020 with 3 days of fatigue, myalgias, and chills after a high-risk encounter with a confirmed COVID-19-positive person. Nasopharyngeal samples for COVID-19 and influenza by PCR were collected and both were negative. Eight days after symptom onset, he returned to clinic with additional symptoms of dry cough and diarrhea. Again, his COVID-19 and influenza PCRs were negative. Ten days after symptom onset, the patient was admitted from clinic, at which time his exam was notable for decreased breath sounds at the bases and he had hypoxemia requiring 2 LPM of supplemental oxygen. A chest x-ray showed bilateral patchy infiltrates (Fig. 1). On admission, he had additional symptoms of shortness of breath, sore throat, nausea, and headache. Initial work-up was highly suggestive of COVID-19 pneumonia, with elevated inflammatory markers (D-dimer 317 ng/ml, ferritin 3,562 ng/ml, CRP > 300 mg/l), a white blood cell count of 8.1 k/cmm with normal differential, and a CT pulmonary angiogram that showed bilateral extensive patchy ground glass opacities without pulmonary emboli (Fig. 1). Because of high clinical suspicion of COVID-19, he was given a dose of dexamethasone, but the COVID-19 nasopharyngeal PCR collected in the emergency department was again negative. Pulmonology and infectious disease were consulted. Due to three negative COVID-19 PCRs, a work-up for alternative diagnoses was pursued, with the differential diagnosis including atypical bacterial pneumonia, viral pneumonia, eosinophilic pneumonia, heart failure, acute interstitial pneumonitis, and cryptogenic organizing pneumonia. While awaiting these results, the patient was started on azithromycin and ceftriaxone, but no further corticosteroids were given. Over the next 3 days of hospitalization, his shortness of breath and dry cough worsened. Fourteen days after symptom onset, his oxygen requirement increased from 2 to 5 LPM and a repeat chest x-ray showed worsening bilateral opacities. Thus far, the patient's work-up was notable for a normal transthoracic echocardiogram, low procalcitonin, negative HIV, negative legionella PCR, negative respiratory viral panel, and a third negative influenza PCR. Due to lack of a diagnosis and worsening respiratory status, he underwent bronchoscopy with bronchoalveolar lavage (BAL) 15 days after symptom onset. On the day of bronchoscopy, his serum COVID-19 antibody that had been collected the previous day was reported to be positive. Although we were unable to be certain as to the chronicity of his infection, the positive serum antibody was believed to support a presumptive diagnosis of severe COVID-19 pneumonia and he was treated with corticosteroids. Cultures and stains of the BAL were negative for bacteria, fungi, mycobacteria, and pneumocystis. However, a PCR for SARS-COV-2 on the BAL came back positive, confirming a diagnosis of COVID-19 pneumonia. Corticosteroids were continued as dexamethasone 6 mg/day for 10 days and he was also given remdesivir. Over the next few days, he rapidly improved and was discharged home on hospital day 11, 21 days after symptom onset.

Notably, within 3 months of this patient's admission, we cared for 4 additional patients who had a similar presentation of acute hypoxemic respiratory failure due to severe COVID-19 pneumonia with a negative PCR and positive serum antibody at the time of hospitalization. The clinical and laboratory features of these 5 patients are summarized in Table 1, and radiographic features depicted in Figure 1.

DISCUSSION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first was recognized in late 2019. Since then, hospitals have been overwhelmed with patients admitted with severe COVID-19 pneumonia, defined by the need for supplemental oxygen. A variety of medications have been used to treat severe COVID-19, but the results for the most part

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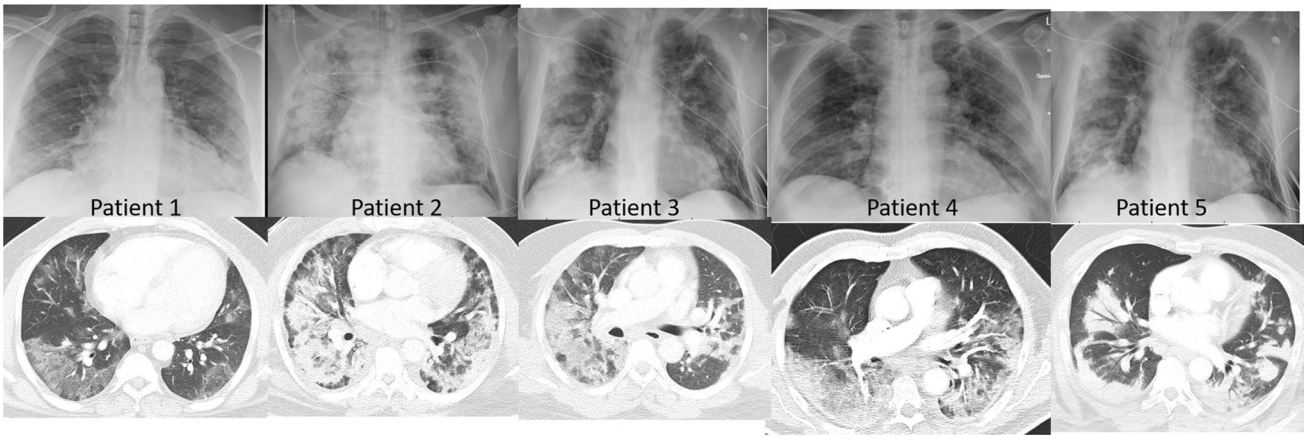
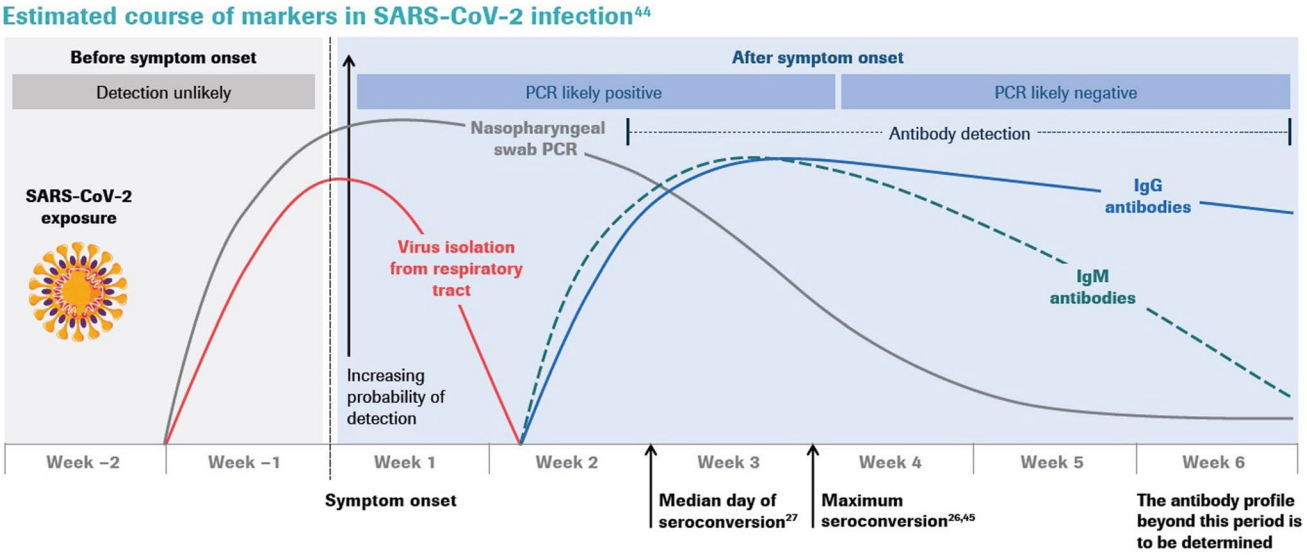


Figure 1 Chest x-rays and CT scans of patients showing bilateral infiltrates.

Table 1 Clinical and Laboratory Features of the 5 Patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/sex	39/male	52/male	47/male	71/male	56/male
Ethnicity	Iraqi	Hispanic	Somali	Hispanic	Caucasian
Underlying health conditions	None	None	DM Type 2	DM type 2 Hypertension	DM type 2 Schizophrenia
Symptoms	Myalgias Fatigue Fever Dry cough Diarrhea Sore throat Nausea Headache	Dry cough Loss of taste/smell Dyspnea	Myalgias Fatigue Fever Dry cough Dyspnea Loss of taste/smell	Fatigue Myalgias Fever Headache Dry cough Loss of taste/smell	Fever Dyspnea
Known exposure	Yes	Yes	No	No	No
Labs D-dimer < 229 ng/mL Ferritin 30–400 ng/mL CRP < = 5.00 mg/L Procalcitonin < 0.50 ng/mL	D-dimer 317 Ferritin 3,562 CRP > 300 Procalcitonin 0.24	D-dimer 6,445 Ferritin 406 CRP 220 Procalcitonin 0.60	D-dimer 330 Ferritin 820 CRP 143 Procalcitonin 0.11	D-dimer 360 Ferritin 624 CRP 13 Procalcitonin 0.7	D-dimer - Ferritin - CRP - Procalcitonin 0.62
COVID PCR	-, -, -, +*	-	-,-,-	-,-	-,-,-,-
COVID Antibody	+	+	+	+	+
# days from encounter to steroids	11 days	0 days	5 days	9 days	19 days
Hospital course	Maximum respiratory support: 5 L Alternative diagnosis found: no Outcome: Discharged to home on room air	Maximum respiratory support: mechanical ventilation Alternative diagnosis found: no Outcome: Extubated on HD#7. Discharged to home on room air	Maximum respiratory support: 10 L Alternative diagnosis found: no Outcome: discharged home on room air	Maximum respiratory support: High-flow Nasal Cannula Alternative diagnosis found: no Outcome: discharged to home on room air with steroid taper	Maximum respiratory support: mechanical ventilation Alternative diagnosis found: no Outcome: anoxic encephalopathy after out-of-hospital cardiac arrest resulting from severe hypoxemia; died on day 7 after palliative extubation

*Positive PCR obtained from bronchoalveolar lavage



"Estimated course of markers in SARS-CoV-2 infection." Adapted from "Elecsys® Anti-SARS-CoV-2," Roche. June 2, 2021, from https://diagnostics.roche.com/us/en/products/params/elecsys-anti-sars-cov-2.html.

Figure 2 Time course of PCR and antibody positivity in Covid-19.

have proved disappointing, with two exceptions being corticosteroids and remdesivir. The RECOVERY trial found that dexamethasone reduced 28-day mortality in COVID-19 patients who required supplemental oxygen, with the impact being greatest in those who required mechanical ventilation.[1] Subsequent meta-analyses of additional observational studies and randomized controlled trials have confirmed the beneficial effect of corticosteroids on short-term mortality in severe and critical COVID-19 pneumonia.[2,3] Besides reducing the risk of death, corticosteroids also reduced the likelihood of progression to overt respiratory failure and need for mechanical ventilation in non-intubated patients with severe COVID-19.[1,2] Current Infectious Diseases Society of America (IDSA) guidelines make a strong recommendation for early use of corticosteroids for all hospitalized patients with a confirmed diagnosis of severe COVID-19 pneumonia and delays in instituting corticosteroids may increase the risk of progression to respiratory failure.[4].

COVID-19 is initially suspected on the basis of a typical clinical presentation and radiographic findings. The gold standard for diagnosis of COVID-19 diagnosis is a positive nucleic acid amplification test (NAAT) for SARS-CoV-2 by RT-PCR.[5] When a diagnosis of COVID-19 is established by a positive nasopharyngeal or oral RT-PCR, initiation of corticosteroids for patients who require supplemental oxygen is currently accepted as the standard of care.[1–3] In patients with a clinical presentation consistent with COVID-19, but who have repeatedly negative COVID-19 PCRs, the approach to treatment remains less clear. The IDSA suggests using IgG antibody to provide evidence of COVID-19 infection in symptomatic patients with a high clinical suspicion and repeatedly negative NAAT testing; however, this is a weak recommendation with low certainty of evidence and does not comment on empiric treatment with corticosteroids.[6] It has been well-documented that the sensitivity of a PCR can be as high as 90% during the first 5 days of symptom onset, contingent upon adequacy of specimen collection.[7] The sensitivity thereafter decreases as humoral response to the infection increases. Ultimately, the PCR sensitivity decreases to approximately 70–71% from days 9 to 11.[7] In contrast, serum antibody sensitivity is initially low early in the disease but will typically appear in serum 7–10 days after the onset of infection, with a sensitivity of > 80% after day 12 and 100% by day 21. [7] This progressive change is depicted in Figure 2.

Our cases demonstrate that a positive serum antibody may be a complimentary aid in diagnosis of COVID-19 in the unvaccinated patient.[7–9] This is especially relevant when patients present relatively late in the course of their illness, since they may have a detectable antibody at a time when risk of a false negative PCR is increased due to reduced viral load in the upper airway. A negative PCR often leads to a search for an alternative cause of hypoxemia with radiographic infiltrates such as pulmonary edema, pneumonia caused by bacteria, viruses, or pathogenic fungi or one of the non-infectious causes of acute lung injury such as cryptogenic organizing pneumonia. Investigations may include respiratory cultures, viral respiratory panels, and sometimes bronchoscopy with bronchoalveolar lavage, as occurred with our patient. While awaiting results of microbiologic studies, corticosteroids are often withheld. As a result, patients with a negative PCR whose pneumonia is in fact due to COVID-19 may not receive the single treatment that most

significantly reduces their risk of death or progression to need for mechanical ventilation.

Given the importance of corticosteroids for severe COVID-19, we believe that clinicians should consider initiating therapy when the clinical and radiologic presentation strongly suggests COVID-19, even in the absence of a positive PCR. Early empiric corticosteroids may lessen the risk of progression, reduce the need for mechanical ventilation, and unequivocally lower the mortality in severe COVID-19.[1–3,10] The risks of corticosteroids are well-known. With the exception of glucose intolerance, however, most of these occur with prolonged use and there is minimal evidence that short-term use increases risk of nosocomial bacterial or fungal infections.[11] One meta-analysis of randomized trials of corticosteroids for patients with severe and critical COVID-19 found that adverse events occurred more often in those given placebo than in those who received corticosteroids.[3] Our case, in addition to the 4 additional cases encountered within a short time frame, demonstrates the potential utility of a positive COVID-19 antibody in the unvaccinated patient to support initiation of steroids when the PCR is negative.

In summary, patients who fit the clinical diagnosis of severe COVID-19 pneumonia but have a negative PCR should be considered for treatment with empiric corticosteroids in the absence of a clear alternative diagnosis or contraindication, to avoid undue delays in treatment. Although this does not negate the need to continue further work-up, we believe that it may provide benefit in patients who ultimately are found to have presumed COVID-19 pneumonia. In such cases, serum antibody to COVID-19 may be positive when symptoms have been present for more than 7–10 days and may have diagnostic value.

Author Contribution Each of the authors participated in preparation of the manuscript.

Declarations

Conflict of Interest The authors declare that they do not have a conflict of interest.

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