Case Report

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What are we missing? Three cases of severe COVID-19 pneumonia with negative testing

Aisha Siddiqui[1], Sukhdev Singh[1], Zohaib Khan[1], Allison Foster[1], Muhammed Atere[2] and Jay M Nfonoyim[3]

Abstract

The COVID-19 pandemic has drastically affected health care systems globally. Reverse transcriptase-polymerase chain reaction is currently the preferred method of detecting COVID-19; however, sensitivity of this test remains questionable. Incidental transmission and potential harm to infected individuals are some consequences of the failure to identify high-risk patients. We report three cases of symptomatic patients that required intensive care management with labs and imaging consistent with COVID-19 with initial false-negative reverse transcriptase-polymerase chain reaction testing. Improper sampling, viral load, and manufacturer variances of tests all contribute to reduced sensitivity. A clinical diagnosis should supplant such cases.

Keywords

Infectious diseases, critical care/emergency medicine, epidemiology/public health

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Introduction

Coronavirus strain SARS-CoV-2, the viral pathogen responsible for COVID-19, was first identified in Wuhan, China and rapidly ignited a pandemic in early 2020.[1] Both severity and clinical presentation are variable, involving the pulmonary, gastrointestinal (GI), hematological, and even neurological systems.[1] With increasing incidence, it is apparent that some patients present with various clinical and radiographic features of COVID-19 despite negative test results for SARS-CoV-2. Invasive procedures are often required to provide respiratory support; therefore, recognition of the initial false-negative rate of reverse transcriptase-polymerase chain reaction (RT-PCR) is crucial to protect healthcare workers as well as containing the spread of the virus. In this report, we discuss three cases that presented with a clinical picture consistent with COVID-19 despite initially testing negative for SARS-CoV-2. It is important to recognize patients with negative results due to the potential of worsening spread if appropriate precautions are not implemented.

Case report

Case 1

A 19-year-old morbidly obese female presented to the Emergency Department (ED) with subjective fever, headache, nausea, vomiting, chills, productive cough, and diarrhea for 7 days. She developed worsening dyspnea and chest pain prompting her to come into the ED. She endorsed a positive COVID-19 case in her school but denied direct contact. Initial vitals showed a temperature of 37.9 C, the pulse rate of 143 beats/min, respiratory rate of 24 breaths/min,

[1]College of Medicine, American University of Antigua, New York, NY, USA
[2]Department of Internal Medicine, Richmond University Medical Center, Staten Island, NY, USA
[3]Richmond University Medical Center, Staten Island, NY, USA

Corresponding Author:
Aisha Siddiqui, College of Medicine, American University of Antigua, One Battery Park Plaza, New York, NY 10004, USA.
Email: AishaS@auamed.net

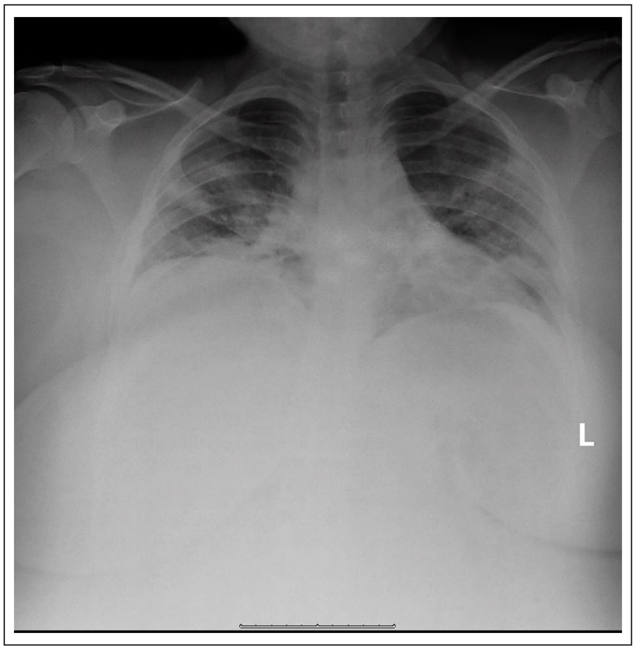

Figure 1. AP chest X-ray, 19-year-old female, bilateral patchy infiltrates.

blood pressure of 126/84 mmHg, and oxygen saturation 88% on ambient air. Auscultation of the chest revealed bilateral rales at the lung bases and initial chest X-ray (Figure 1) revealed bilateral patchy infiltrates. She was admitted to the pediatric floor for further management. On hospital day 2, she was transferred to the pediatric intensive care unit (PICU) due to increased oxygen demand and was placed on bimanual positive airway pressure (BPAP). In the intervening days, multiple nasopharyngeal swabs were collected for SARS-CoV-2 testing; however, all returned negative. After 5 days of non-invasive positive pressure ventilation (NIPPV), her respiratory status further deteriorated and on PICU day 7 she was sedated, intubated, and mechanically ventilated. An endotracheal sputum sample tested positive for COVID-19. Her condition worsened with development of severe acute respiratory distress syndrome (ARDS). After a prolonged course of mechanical ventilation, she was extubated following a spontaneous breathing trial on PICU day 20. At the time of writing, PICU day 27, she remains under close observation.

Case 2

A 47-year-old obese male with hypertension presented to the ED with a 1-week history of anorexia, fatigue, malaise, and diarrhea. On presentation, the temperature was 39.1 C, the pulse 117 beats/min, the respiratory rate 18 breaths/min, the blood pressure 120/82 mmHg, and oxygen saturation of 87% on non-rebreather mask on 15-L high flow oxygen with FiO_2 100%. Auscultation of the chest revealed bilaterally decreased sounds at the lung bases. Chest X-ray

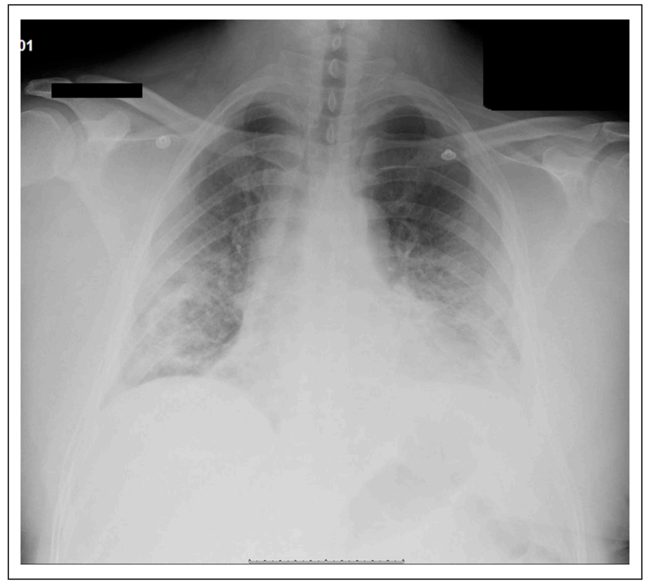

Figure 2. AP chest X-ray, 47-year-old male, diffuse bilateral multi-lobar opacities.

(Figure 2) showed diffuse bilateral multi-lobar opacities suspicious for COVID-19 pneumonia. SARS-CoV-2 real-time RT-PCR testing for nasopharyngeal swab returned negative. Regardless, he was placed in isolation with contact and droplet precautions and was managed empirically with azithromycin and ceftriaxone. Over the next few days, his condition worsened, requiring continuous positive airway pressure (CPAP) due to progressive respiratory decline. Prone positioning for lung volume recruitment showed no improvement. On day 7, he was started on Tocilizumab and steroids due to increased inflammatory response and concerning X-ray findings of ARDS. Despite NIPPV, on hospital day 8, his oxygen saturation fell to the 40% range, and arterial blood gas (ABG) showed acute respiratory acidosis with a widened A-a gradient, prompting intubation for acute hypoxic respiratory failure and transfer to the intensive care unit (ICU). On day 9, his second swab, done endotracheally for SARS-CoV-2 RT-PCR, returned positive.

Case 3

A 56-year-old male presented to the ED with fever, hypotension, and altered mental status. His nursing home stated he was unusually drowsy with episodes of oxygen desaturation down to 60% with shallow breathing and unresponsiveness. His medical history was significant for hypertension, congestive heart failure, and schizoaffective disorder. On presentation, the temperature was 37.8 C, the blood pressure 67/42 mmHg, the pulse 76 beats/min, the respiratory rate 20 breaths/min, and oxygen saturation 60% on ambient air. He was unresponsive to painful stimulation. Labs were notable for thrombocytopenia (77k/µL), absolute lymphopenia (0.49k/µL), blood urea nitrogen of 53 mg/dL, and creatine

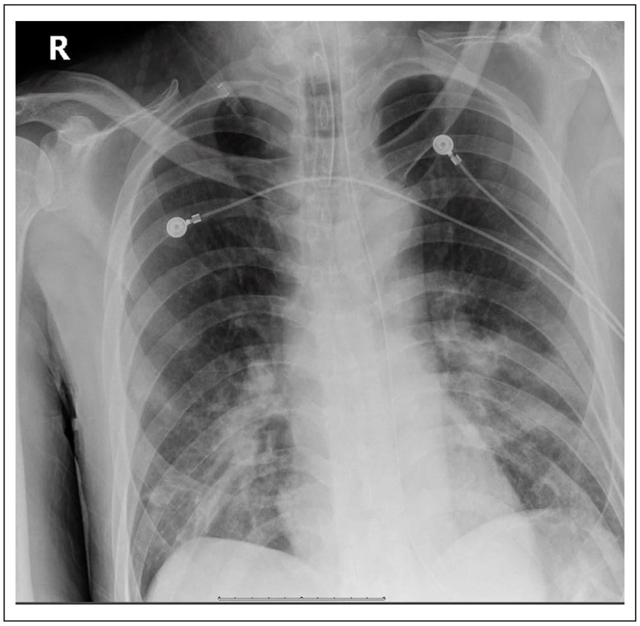

Figure 3. AP chest X-ray, 56-year-old male, diffuse bilateral multi-lobar opacities.

of 1.9 mg/dL. Initial chest X-ray (Figure 3) revealed bilateral patchy infiltrates in middle and lower lung fields consistent with pneumonia. Norepinephrine drip and fluids were given for management of hypotension. Given his low oxygen saturation, he was intubated for mechanical ventilation and admitted to the critical care floor. Nasopharyngeal swab for SARS-CoV-2 RT-PCR was negative. On hospital day 3 of admission, another nasopharyngeal swab was sent and returned positive for SARS-CoV-2. On day 7, he was extubated following a spontaneous breathing trial with oxygen saturation 99% on 4 L of nasal cannula. At the time of writing, during day 8, he had symptomatic improvement while saturating at 96% oxygen on ambient air.

Discussion

SARS-CoV-2 was declared a global health emergency by the World Health Organization (WHO) on 30 January, 2020. Fever, cough, sore throat, congestion, myalgias, and headache are the most common symptoms.[1] Supportive measures are the mainstay of treatment of COVID-19. No definitive treatments have been identified and thus preventive measures are currently the best strategies to limit the spread.[1] Interestingly, although our patients presented with symptoms and imaging consistent with COVID-19 pneumonia, their RT-PCR serologies were all initially negative. We discuss further the importance of maintaining a high index of suspicion of COVID-19 even if serology remains negative.

Serology testing

Nucleic acid amplification testing using real-time RT-PCR has been the standard diagnostic testing for COVID-19. However, the false-negative rate has been reported to be as high as 20%.[2] Potential reasons include faulty lab techniques, specimens with inadequate viral load, and issues relating to transport of samples and improper sampling techniques.[3,4] The importance is to recognize the harm of falsely ruling out COVID-19 as it may potentiate the spread of the virus. Furthermore, studies from Wuhan indicated that viral load was highest during the first week of symptom onset and declined with time, contrary to popular belief that there was a lower viral load in early infection. Endotracheal aspirate viral load was generally available 8 days after symptom onset and showed a non-significant decline, but the upper respiratory tract (i.e. nasopharyngeal swabs) had the highest viral load near presentation.[5]

Follow up and correlation of negative RT-PCR results with imaging and clinical presentation are crucial. In highly suspicious cases, a clinical diagnosis should be made based on features including fever with or without respiratory symptoms, early onset of decreased lymphocyte counts, and signs of pneumonia on radiographic imaging.[4] A supporting study from Wuhan has suggested that a clinical diagnosis should be the basis for placing patients in isolation as opposed to the results of PCR-SARS-CoV-2 testing due to an elevated rate of initial false-negative results.[3]

Imaging studies

All three of our cases had baseline chest X-rays consistent with COVID-19 pneumonia. As the pandemic continues to peak in various locations, it is imperative for physicians to recognize features of COVID-19 pneumonia on chest imaging; RT-PCR results can take up to 24 hours in some locations, and relying on computed tomography (CT) images places an undue burden on radiology teams. As the pandemic spreads to smaller cities in the United States, it is also likely that CT imaging may not be available in all cases. As such, chest radiographs should play a role in triage and presumptive diagnosis of COVID-19 pneumonia. Patients most often had consolidation on baseline chest radiography with bilateral peripheral and lower zone involvement. Ground-glass opacities were also seen. Furthermore, chest X-ray findings consistent with COVID-19 pneumonia were seen in some individuals with mild or no symptoms of respiratory illness and clinically presented as walking pneumonia. A cohort from Hong Kong revealed 9% of COVID-19 patients had negative results for SARS-CoV-2 RT-PCR with abnormalities on baseline chest X-ray; they did eventually test positive for SARS-CoV-2 with RT-PCR. Baseline with follow-up chest X-ray had a sensitivity of 69% compared with 91% for initial RT-PCR testing.[6]

The high sensitivity of chest CT in symptomatic COVID-19 patients has been widely reported, making it a useful surrogate supporting the diagnosis when RT-PCR is negative. In one study, the sensitivity of CT was reported to be greater than that of RT-PCR (98% vs 71%).[7] Similarly, findings from Rome, Italy, showed a sensitivity of 97% and a specificity of 72% of chest CT.[8]

In a prospective series of 41 patients with COVID-19, CT findings consistent with pneumonia were present in 100% of COVID-19 cases.[9] The most common pattern seen on imaging include bilateral ground-glass opacities and consolidation.[2,8] Peripheral location and bilateral lung involvement with predominance in the lower lungs in a multi-focal arrangement is most common distribution pattern.[10] The ground-glass opacities are most commonly round, crazy paving, or predominantly linear.[10] Involvement of all five lobes of the lung was seen in the majority of cases with the right middle lobe as the most consistently affected site. Multi-lobar and sub-segmental consolidations have been reported as the most common chest CT findings of COVID-19-confirmed patients admitted to the ICU.[9]

Clinical implications

The variability in testing methods directly affect healthcare delivery during a pandemic. Symptomatic, hospitalized patients with negative RT-PCR tests should not be taken at face value. If the entire clinical picture is not considered, healthcare workers and other patients are at an increased risk of contracting COVID-19.

It is also important to note that COVID-19 patients oftentimes present with a puzzling clinical scenario of pronounced hypoxemia with relatively few symptoms. They have been termed "happy hypoxemics" because their PaO_2, normal range of 75–100 mmHg, is dangerously low, ranging between 36 and 45 mmHg with little to no indication of distress.[11] Silent, or happy, hypoxemia is not exclusive to COVID-19 and is sometimes seen in patients with atelectasis, intrapulmonary shunts like arteriovenous malformations, or right-to-left intracardiac shunt. Arterial hypoxemia in COVID-19 pneumonia is primarily caused by perfusion and ventilation mismatch and persistence of pulmonary arterial blood flow to non-ventilated alveoli.[12] Ground-glass opacities and consolidation on chest imaging can be seen due to increased lung edema, surfactant loss, and alveolar collapse.[13] Of note, the severity of hypoxemia in patients with COVID-19 is an independent predictor of in-hospital mortality and can be a predictor of ICU admission.[14]

Although the numbers are changing, current information indicates that approximately 5% of patients who test positive for COVID-19 pneumonia develop a severe form that ultimately requires ICU admission, and two-thirds of those patients develop ARDS. The survival rate for these patients is about 25%.[15] ARDS is identified by refractory hypoxemic respiratory failure with bilateral lung infiltrates caused by pulmonary edema leading to decreased lung compliance; this can occur from direct damage to alveolar epithelium, as in the case with pneumonia, or indirectly through damage to the vascular endothelium, more commonly seen in sepsis patients. After the lung injury, an extensive release of cytokines causes widespread inflammation and generally requires tracheal intubation, mechanical ventilation, and intensive care.[16]

Studies have been focused on the etiology and treatment of COVID-19, but relatively little is known about the recovery and consequences of infection. As new information emerges, it is important to keep in mind that the aftermath of COVID-19 ARDS could be catastrophic. Patients who develop ARDS can develop a disorder characterized by persistent fatigue, weakness, limited exercise tolerance, and chronic pain, partially attributed to the use of corticosteroid in the intensive care.[17] Physicians should also consider the effects of ICU admission and survival on patients' mental health; there should be an expected rise in mental health issues in this population. The rise can be attributed to separation from support networks, prolonged sedation, and concern over their own mortality, health conditions, and survival. It should be noted that these patients are also at an increased risk for developing post-traumatic stress disorder (PTSD).[17] As such, when discharging patients after COVID-19 recovery, physicians in charge of their care should advise patients to seek counseling or make an appointment with a mental health specialist.

As discussed above, an early negative result for SARS-CoV-2 RT via PCR does not rule out infection, nor does it rule out the risk of ARDS as the disease progresses. All three of our patients had suspicious imaging with no detection of SARS-CoV-2 on RT-PCR, and all three patients required intubation and mechanical ventilation despite the intial negative RT-PCR result. When re-tested, multiple times in some cases, all three tested positive. Intubation is a high-risk procedure with a greater risk of generating aerosolized particles of SARS-CoV-2. Other aerodigestive procedures including bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, prone positioning for lung recruitment, disconnecting the patient from the ventilator, NIPPV, tracheostomy, endoscopy, and cardiopulmonary resuscitation also carry great risk of generating airborne particles that may remain for three or more hours post-procedure.[18]

Conclusion

Due to the high risk of contracting and transmitting COVID-19 during aerosolizing procedures, healthcare workers must be mindful that a negative RT-PCR does not necessarily exclude a COVID-19 infection and should not be used as the only criterion for treatment or patient management decisions. It seems that the combination of real-time RT-PCR and clinical features facilitates the management of the SARS-CoV-2 outbreak. Patients with suggestive clinical and laboratory findings should be managed with high suspicion. Lack of protective precautions in such patients may result in widespread dissemination of the disease infecting more patients as well as compromising health care work force. Furthermore, with the advent of rapid testing and more available testing for the community at large, caution should be exercised. Social distancing and enforced wearing of masks despite negative test results should curb the spread of disease as negative test results are often inaccurate. Clinicians should be aware that patients with hypoxemia and relatively little respiratory distress should be hospitalized and monitored for rapid deterioration, regardless of confirmation of SARS-Cov-2 via RT-PCR results. Finally, patients who do recover from COVID-19-related ARDS are at increased risk for post-ARDS with physical and emotional manifestations and as such should be monitored closely after discharge.

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Ethical approval

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Informed consent

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ORCID iDs

Aisha Siddiqui https://orcid.org/0000-0002-9566-2618
Sukhdev Singh https://orcid.org/0000-0002-7922-9590
Zohaib Khan https://orcid.org/0000-0002-1702-0388
Allison Foster https://orcid.org/0000-0001-5900-7969

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