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Case report

False negative SARS-CoV-2 PCR - A case report and literature review

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A B S T R A C T

The first case of the novel Coronavirus Diseases (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was detected in Wuhan, China in December 2019. On January 30, 2020, the World Health Organization declared a global health emergency. Countries around the world advised social distancing, businesses and schools closed, while health care workers faced a viral war. With the declaration of a global emergency, a test to rapidly detect the SARS-CoV-2 was developed to ensure swift isolation of infected persons to prevent spread of disease. Currently, the gold standard for test is Reverse Transcriptase Polymerase Chain Reaction (RT-PCR); however, patients with a high clinical suspicion for COVID-19 can sometimes have multiple negative tests. We discuss a patient under investigation (PUI) who had classic findings of COVID-19 but repeatedly tested negative from nasopharyngeal swabs until a fifth sample obtained from a deep suctioning was tested.

1. Case description

This is a 52-year-old male with a past medical history of alcohol use disorder and a recent admission for chest wall abscess who presents with a dry cough and shortness of breath that began approximately 24 hours prior to admission (Fig. 1).

On arrival to the emergency department, he was afebrile, hemodynamically stable, with SpO2 95% on room air. Significant labs include lymphopenia of 0.8 Thou/uL without leukocytosis, ESR of 25 MM/HR, ferritin of 1137 μg/L (see Tables 1 and 2). CT chest showed hazy interspersed peripheral groundglass opacifications (See Fig. 2). A nasopharyngeal SARS-CoV-2 PCR was obtained on day 1 of his admission and was negative. He was started on IV ceftriaxone and oral doxycycline for a presumed bacterial respiratory infection.

In spite of his negative PCR, the suspicion for SARS-CoV-2 remained elevated due to persistent shortness of breath, worsening lymphopenia, thrombocytopenia and increasing inflammatory markers (see Tables 1 and 2). A second nasopharyngeal PCR was negative on day 2 of admission. Over the next few days, the patient began to have increasing oxygen requirements. A repeat chest x-ray showed bilateral interstitial opacifications. A third nasopharyngeal PCR was sent on day 4 of admission which was negative.

On day 6 of admission he developed fevers (T-max of 102.7 °F) and increasing oxygen requirements. His PaO2 on nasal cannula at 4 L was noted to be 47. Chest X-Ray demonstrated worsened diffuse interstitial opacifications in the bilateral lung fields (See Fig. 3). He was transferred to the ICU. A fourth nasopharyngeal PCR was again negative for SARS-CoV-2. On day 7, CXR showed continued worsening of the interstital opasifications (see Fig. 4)

On day 8 of admission, he was intubated for hypoxemic respiratory failure and severe acute respiratory distress syndrome. On day 9 of admission, a repeat CT was obtained which showed marked orsening of the diffuse groundglass opacifications noted on day 1 (see Figs 2 and 5). A 5th PCR for SARS-CoV-2 was sent from sputum via deep suctioning of the airways through the endotracheal tube. This sample came back positive for SARS-CoV-2 on day 10. He received Tocilizumab the same day. Unfortunately, the patient had already developed septic shock with significant multiorgan failure as well as Candida albicans fungemia. He passed away the following day.

2. Discussion

This case highlights multiple negative nasopharyngeal SARS-CoV-2 PCR swabs in a patient with high clinical suspicion for SARS-CoV-2, who ultimately tested positive when deep sputum was sent for PCR nine days into his admission (10 days after respiratory symptoms

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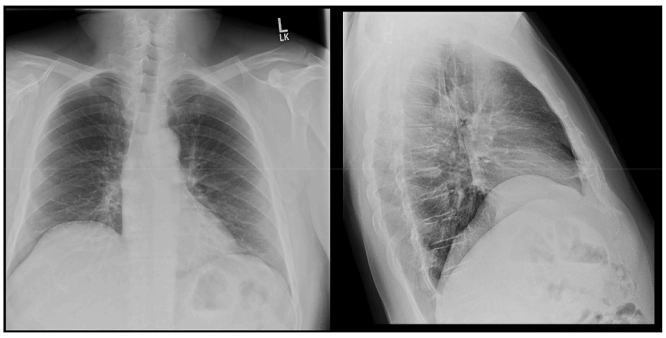

Fig. 1. AP and lateral chest x-ray from previous hospitalization (5 days prior to admission) for a right chest wall abscess.

Table 1
Inflammatory markers.

	Day 1	Day 7	Day 11
LDH (U/L)	221	583	1799
Ferritin (ug/L)	1173	3250	14630
CRP (mg/L)	>10	>10	>10
D-Dimer (ng/mL)	<150	402	6444

Table 2
Notable labs.

	Day 1	Day 7	Day 11
WBC (thou/uL)	4.6	6.8	20.4
Abs lymphocyte count (thou/uL)	1.2	0.80	1.2
Abs Neutrophil count (thou/uL)	65.6	5.65	18
BUN (mg/dL)	13	11	62
Cr (mg/dL)	1.2	1.0	6.6
AST (U/L)	24	60	642
ALT (U/L)	10	18	203
ALK PHOS (U/L)	64	37	144

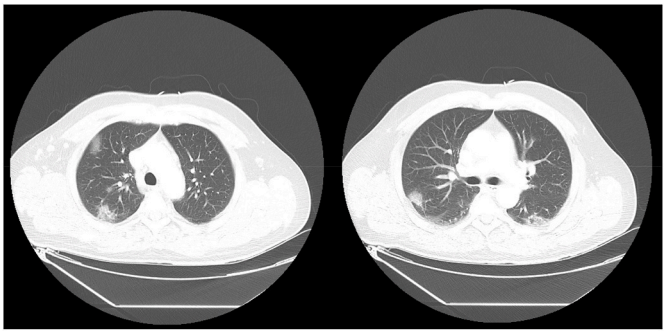

Fig. 2. CT chest on Day 1 of admission, demonstrating focal peripheral ground glass opacifications.

started). All samples were run using the Abbott RealTi*m*e SARS-CoV-2 assay at our in-house lab. This assay is reported to have a 100% sensitivity in samples with as low as 200 viral copies per mL and a 95.2% sensitivity at 100 viral copies per mL [14]. However, the sensitivity of the assay is dependent on viral load with peak levels occurring on day 4 based on virological studies [1]. All the nasopharyngeal swabs were obtained by trained internal medicine attendings who reported following the proper procedure for obtaining a nasopharyngeal swab [2,14]. Based on the time of his symptom onset, he was far enough into the course of the illness to test positive [3,4]. The possibility of this being a false negative result because of clinician sampling error is low in this setting.

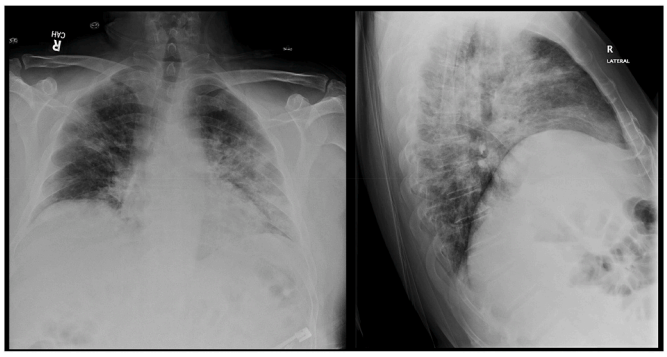

Fig. 3. Follow-up chest x-ray on day 6 of admission, which demonstrates diffuse interstitial opacifications in the bilateral lung fields.

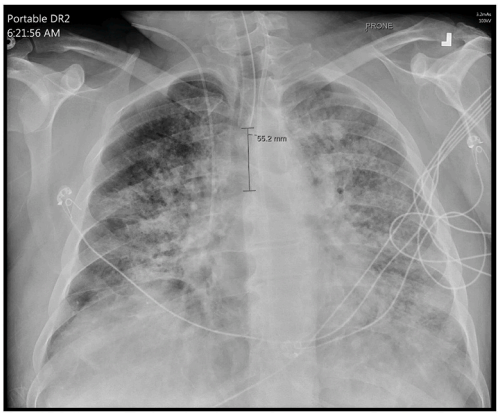

Fig. 4. Portable chest x-ray on day 7, which demonstrates worsening diffuse interstitial opacifications.

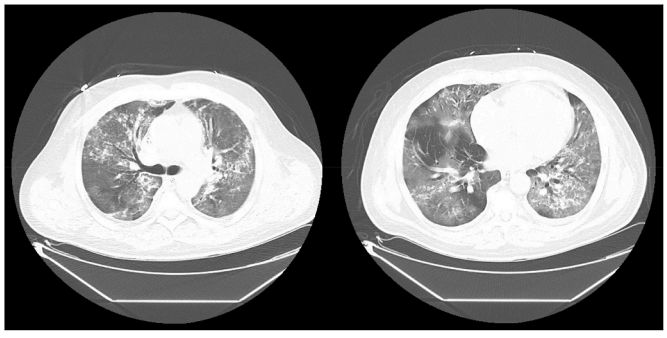

Fig. 5. CT thorax, on day 9 of admission, demonstrating diffuse groundglass opacifications.

SARS-COV-2 binds to ACE2 receptors in the endothelial cells of the nasopharynx where it begins the process of replicating, propagating down the respiratory tract and eventually gaining access to the rest of the body via the circulatory system [5,6]. As this infection progresses it induces excessive cytokine release from peripheral blood mononuclear cells, resulting in the feared acute respiratory distress syndrome (ARDS) [4]. The pandemic surrounding the novel COVID-19 virus has impacted the global community at an unprecedented level with no predilection for ethnicity, young or old, healthy or chronically ill. Viral nucleic acid detection by reverse transcriptase PCR (RT-PCR) is considered the gold standard for diagnosis of the novel COVID-19 [7], which relies on sufficient viral levels for gene amplification [8]. Furthermore, the reliability of the test is limited by the timing of sample collection with regards to symptom onset and user technique with nasopharyngeal

swabs. False negatives can have grave consequences in terms of preventing spread of disease, providing adequate care to highly suspicious patients and protection for healthcare workers. Therefore, to improve the odds of making a definitive diagnosis, additional testing methods such as sputum for PCR and serology testing should be considered in patients with a high clinical suspicion of COVID-19 who have a negative nasopharyngeal PCR.

Numerous publications have questioned the sensitivity and reliability of the RT-PCR test given negative results in patients highly suspicious of having the virus, yet tested negative [7,9,10]. Subsequently [7], conducted a study on 127 patients in Beijing Ditan Hospital comparing RT-PCR versus droplet digital PCR (ddPCR) testing, which is reported as being more sensitive in virus detection, in addition to assessing viral load with disease progression. The study concluded that ddPCR was better at detecting samples with low viral load, with a greater number of positive samples collected from sputum (66.4%) in comparison to throat (37.3%) or nasal swabs (16.4%) [7]. Furthermore, the viral load was found to be significantly higher in the early and progressive stages of the disease [7], which also corroborates with a virological analysis conducted by Wölfel et al. showing that nine proven COVID-19 cases had highest pharyngeal shedding during the first week of illness with peak viral load on day 4. In our patient, four nasopharyngeal samples were tested before we decided to test a deep-suction sputum sample collected on day 9 of admission following intubation. This sample was positive for SARS-CoV-2.

Bronchial alveolar lavage has also been preferable due to the fact that the viral load in these samples is much higher than samples obtained from throat swabs [8,11,12].

[8] studied the timing of humoral response against COVID-19 to aid diagnosis. The study showed that 85.4% of samples collected detected IgM within 7 days of symptom onset [8]. showed that PCR was 90% accurate on days 1–3 of symptom onset; however, decreased to 80% by day 6. In fact, IgM was more effective in patients presenting 5 days after symptom onset with a 98.6% positive detection rate in patients who are PCR negative [8]. Additionally, the efficacy of antibody testing was shown by the fact that 6 of the 7 patients who were PCR negative for the second swab, were IgM positive. The authors suggested that antibody response can provide better sensitivity than PCR testing alone [8]. Given the numerous negative nasopharyngeal swabs with RT-PCR in our patient, perhaps testing for IgM in conjunction with sputum PCR would have also aided in earlier detection and intervention.

The repercussions of false negatives are evident in this case. The fact that this patient was taken off of precautions and remained off precautions for a couple of days placed our staff at risk for exposure to the virus. Although the suspicion for COVID-19 was high, he did not receive optimal therapy early because investigational therapies like remdesivir, tocilizumab and convalescent plasma are guarded by stringent guidelines, which necessitates a positive SARS-COV-2 PCR. Furthermore, he received pulse dose steroids as alternative diagnoses were considered. The use of steroids in COVID-19 infection is controversial, and there is some concern that it will prolong viral shedding [13].

3. Conclusion

Although nasopharyngeal RT-PCR remains the gold standard for diagnosing COVID-19, false negatives abound. When clinical suspicion for COVID-19 is high, clinicians should maintain appropriate precautions and consider alternative testing methods such as serology testing in combination with deep-suctioned sputum or Brocho-alveolar lavage for SARS-COV-2 RT-PCR.

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Declaration of competing interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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