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Endemic and Emerging Coronavirus Pulmonary Infections
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ABSTRACT
Coronaviruses are a well-known cause of upper and lower respiratory disease, and since 2002 have been a recognized source of potential pandemic spread. Over the past two decades, since the Severe Acute Respiratory Syndrome (SARS) outbreak, a large body of research has accumulated on the virology, clinical symptoms and signs, and experimental treatments of Coronaviruses. In 2020, a new form of Coronaviruses (SARS-CoV-2) emerged and spread rapidly throughout the globe. Given the wide-ranging clinical presentations of those infected with SARS-CoV-2, other viruses might be overlooked when evaluating at-risk patients. Furthermore, due to suboptimal testing capabilities, an early clinical diagnosis is not always possible. Here, we present a case of a patient with pneumonia thought to be caused by SARS-CoV-2 only to be found to have another Coronavirus. This emphasizes the need to be vigilant when evaluating patients with viral-like respiratory infections.

Key Indexing Terms: Virus; Lung; Chest imaging; Diagnosis and treatment. [Am J Med Sci 2020;360(6):728–732.]

INTRODUCTION
The most recent epidemic Coronavirus is the SARS-CoV-2 currently gripping the world, putting significant strain on healthcare systems, international economies, and locking down large portions of many nations. This novel coronavirus is believed to have originated as a virus of horseshoe bats in China, where other SARS-like viruses have been isolated.1 The nonspecific clinical presentation of the infection and the lack of adequate testing capabilities have hindered early diagnosis, which further contributed to the spread of the virus. Under such circumstances, it is not surprising that other pulmonary infections are overlooked, including Mycoplasma pneumonia and Influenza. Here, we present a case of a patient with acute progressive hypoxic respiratory failure caused by viral pneumonia in the context of underlying lung disease.

CASE PRESENTATION
In early February of 2020, a 72 year old female presented to a community hospital emergency department with a medical history significant for 25 pack-years of tobacco abuse and chronic obstructive pulmonary disease (COPD) that was described as mild (though spirometry values were unavailable). She had been discharged on room air from the same hospital two weeks earlier after being hospitalized for shortness of breath and sputum production. During that hospitalization, she was considered to have acute exacerbation of COPD and was treated accordingly, including a taper of corticosteroids that was still in progress when she returned to the emergency department.

The patient presented with rigors, cough, and worsening shortness of breath with associated hypoxemia. Her room-air hemoglobin oxygen saturation at presentation was found to be in the high 70s and she had tachycardia with a pulse of 110; other vital signs were within normal limits. Her hemoglobin oxygen saturation was corrected with the administration of 5 liters of oxygen supplementation delivered via a nasal cannula. Her physical examination showed an obese woman in no acute respiratory distress, though with coarse breath sounds bilaterally without crackles. She appeared to be euvolemic as she had no jugular venous distention, no peripheral edema, and her mucous membranes were moist. A chest x-ray showed mild bilateral pulmonary infiltrates (Figure 1), and initial lab work was significant for leukocytosis of 23.6.

She was started on bronchodilators and her corticosteroids were increased to 40 mg daily, and she was placed on empiric antibiotic therapy for hospital-acquired pneumonia. Within the first day of admission, a computed tomogram of the chest with pulmonary embolism protocol was performed, which was negative for thromboembolism, but demonstrated bilateral ground-glass opacities, predominantly in the periphery, at the bases, and posteriorly (Figure 1B). Samples for sputum culture and viral PCR testing were obtained. Over the next several days, her hypoxemia worsened, intermittently requiring high-flow nasal cannula and noninvasive positive pressure ventilation. Consistent with her deterioration, her chest radiograph also showed progression of disease (Figure 1C). The nasopharyngeal swab PCR viral test submitted from the emergency department returned positive for the NL63 Coronavirus.
Fourteen days after her initial presentation, her hypoxemia could not be reversed with high noninvasive supplementation settings, and the patient was intubated for acute respiratory distress syndrome. At the medical intensive care unit, she required repeated proning maneuvers, chemical paralysis, and inhaled prostanoids to maintain adequate oxygenation over the next six hospital days. The patient did not improve during that time, and the decision was made to move towards comfort directed care. The patient shortly thereafter expired.

DISCUSSION

Our patient was diagnosed with NL63 Coronavirus and not SARS-CoV-2 infection. Yet, similar to SARS-CoV-2 infection, her clinical course was characterized by respiratory symptoms, pneumonia, and, ultimately death from respiratory failure. New insights into the virology, diagnosis, and management of Coronaviruses, especially SARS-CoV-2, have emerged during the pandemic and are relevant to this case as discussed next.

Virology

Coronavirus is a well-known respiratory virus, responsible for endemic and epidemic disease of both humans and animals. First discovered in the 1960s, Human Coronaviruses were long believed to be primarily causes of mild upper respiratory illness, but they received new scrutiny once animal viruses were first noted to be able to pass to humans with the SARS epidemic of 2002. In the aftermath of that outbreak, research showed that the responsible coronavirus appeared to have emerged from a pathogen endemic in horseshoe bats (Rhinolopus sinicus), with likely transmission to civet cats (Paguma larvata) and racoon dogs (Nyctereutes procyonoides) before passing to humans. As the virus appeared to fade from human populations, research on the subject began to recede as well. The MERS outbreaks of 2012–2018 appeared to have originated in Egyptian tomb bats (Taphozous perforatus) and then amplified through dromedary camels (Camelus dromedarius) prior to infecting humans. MERS outbreaks, despite higher mortality, did not spark the same intensity of research interest possibly given the much smaller number of infected individuals. In 2020, a new form of Coronaviruses (SARS-CoV-2) emerged and rapidly expanded across the globe.

The Coronaviridae family includes alpha and beta coronaviruses, which infect mammals and birds, including bats and camels. Of these groups, two endemic species (229E and NL63) are Alphacoronaviruses. Beta-coronaviruses include the two endemic strains OC43 and HKU1, as well as the novel animal-originating epidemic viruses SARS-CoV and MERS-CoV. While official classification of the SARS-CoV-2 virus that causes the disease CoVID-19 is still pending, it shares the most genetic similarity among human pathogens with the SARS-CoV virus of 2002.

Similar to most viruses, Coronaviruses surface proteins are capable of binding with a protein on the host epithelial or endothelial cellular surface, and use that protein to gain entry to the cell. In the case of Coronavirus 229E, Aminopeptidase N is the cellular target, while strains OC43 and HKU1 both target sialic acid residues on the cellular surface. The other strains, both the endemic NL63, as well as SARS-CoV and SARS-CoV-2
target Angiotensin Converting Enzyme 2 (ACE-2) on cellular surfaces.\textsuperscript{8,9}

ACE-2 is a homolog of the more familiar ACE, but is instead involved in downregulating the Renin-Angiotensin System, leading to vasodilation and decreased blood pressure.\textsuperscript{10} More recent studies have demonstrated ACE-2 being present throughout the oropharynx and especially on the tongue, clarifying this enzyme’s role as an entry point for a respiratory pathogen.\textsuperscript{11}

Clinical syndrome and diagnosis

The clinical presentation of Coronavirus is one of the more variable presentations that have been described in the literature of viral pulmonary infections. Mild infection with endemic HCoVs is generally characterized by symptoms associated with “the common cold” such as nasal congestion and rhinorrhea, headache, cough, sore throat, and malaise.\textsuperscript{12} More severe infection is generally associated with pneumonia, and Coronavirus have been found to be one of the most common causes of lower respiratory infection.\textsuperscript{13} Additionally, nasal swab rtPCR tests have been found to be positive in up to 8\% of asymptomatic children, and this appears to be common among adults as well.\textsuperscript{14–16} Another cohort study found that Coronavirus testing is positive in about 8\% of acute exacerbations of COPD.\textsuperscript{17} Epidemic Coronavirus emerging from animals such as SARS and MERS have shown a more severe constellation of symptoms, including fever and dyspnea along with the symptoms seen with other Coronavirus.\textsuperscript{18,19}

The diagnosis of almost all respiratory viral illnesses is made with rtPCR technology in the modern era. The technology used in the patient presented here was the Biofire rtPCR film array system, which tests for 17 separate viruses and 4 bacteria, including the four endemic species of Coronavirus. No commercially available testing system includes rtPCR for SARS or MERS, however, testing platforms for SARS-CoV-2 are being deployed in the rising pandemic. Before the widespread advent of such PCR systems, viral illness was largely diagnosed by a mix of other technologies, including viral culture, enzyme immunoassays, fluorescent antibody staining, and trended viral-specific IgG serology. Each of these modalities present various drawbacks, and importantly, were largely ineffective at detecting Coronavirus.\textsuperscript{20}

Management

Currently, there are no therapies formally proven to be effective in the setting of any Coronavirus. However, in the wake of the current outbreak of SARS-CoV-2, much interest has been placed in earlier work on treatments trialed on the other epidemic Coronavirus. Prior to the 2002 SARS epidemic, there had been limited research into antiviral therapies for Coronavirus, and several trials exist from that era, as well as in the wake of MERS, which are now being revisited for SARS-CoV-2.\textsuperscript{21}

Ritonavir/Lopinavir were molecules designed to target HIV proteases that were later found to be effective at limiting SARS viral replication in a dose-dependent fashion in \textit{vivo} along with Ribavirin.\textsuperscript{21,22} This laboratory finding led to a prospective trial with matched historical controls at hospitals in Hong Kong, which showed statistically significant decline in 21-day mortality or development of SARS-related acute respiratory distress syndrome (ARDS).\textsuperscript{23} This trial also showed a drop in nasopharyngeal viral load among six of its intervention participants when compared with the historical control data.

There are now two published trials of this drug combination available for use in COVID-19. The first trial, performed in Singapore, was a case series of 18 patients of whom only 5 received Lopinavir/Ritonavir. Of these patients, three showed improvement, while two showed a decline in overall condition. This study was not seen to be conclusive as it dosed the medication at half of the manufacturer’s recommendations.\textsuperscript{24} The second trial, performed in China, randomized 200 patients to receive standard care or Ritonavir/Lopinavir. In this trial, the patients did receive the more standard dose consistent with the manufacturer recommendations, but no clinically significant difference was seen between the groups. Additionally, the endpoint seen in the original SARS trial (decreased viral load) was not observed in this trial.\textsuperscript{25} It is worth noting that neither of the studies performed on COVID-19 patients included the third drug used for SARS patients, Ribavirin.

Antimalarials have been showing promise as antiviral medications for decades, and were some of the many drugs studied in the wake of SARS. While no clinical trials were performed during that epidemic, \textit{in vitro} studies appeared to show an inhibiting effect on the glycosylation of the ACE-2 receptor used by the virus for cellular entry.\textsuperscript{26–28} Likely due to this inhibition of glycosylation, Chloroquine has shown \textit{in vitro} inhibitory effect against a range of enveloped viruses including HIV, SARS, and Zika,\textsuperscript{27–29} while increasing viral replication of Influenza or prolonging symptoms of Chikungunya.\textsuperscript{29,30} During the new pandemic SARS-CoV-2 species, antimalarials have been tried \textit{in vitro} with effect, as well as in a small open-label clinical trial recently published.\textsuperscript{31} While this trial met statistical significance, it followed endpoints such as viral clearance, which while utilized in other studies, have not been well validated for clinical outcomes.\textsuperscript{32} More recent concerns have been raised about the safety and efficacy of these drugs.

Remdesivir was developed later than the other drugs described here, and was originally designed to target another viral epidemic: Ebola and Marburg.\textsuperscript{33} Subsequent testing showed that the nucleotide analog was also effective at inhibiting replication of Coronavirus in animal models, including models of SARS.\textsuperscript{34,35} Compassionate use of the drug has been called for, and is being used in multiple countries after an \textit{in vitro} study showing similar inhibitory mechanisms against SARS-CoV-2.\textsuperscript{36}
Despite being used widely in patients afflicted with SARS, the use of corticosteroids remains controversial. Studies on both SARS and MERS patients have shown little or no clinical benefit, while also potentially prolonging viral shedding from these patients. Despite this, one retrospective cohort of severely ill COVID-19 patients with ARDS in Wuhan did show correlation with improved survival in patients receiving Methylprednisolone. There remains discussion whether or not to use stress dose steroids in Coronavirus patients with septic shock, given the results of these other studies. The impact of anti-IL-6 inhibitors, mTOR antagonists, convalescent plasma, and other interventions remain unclear as the results of clinical trials testing these interventions have not been published at the time of this writing.

In conclusion, Coronavirus are a well-known cause of upper and lower respiratory disease, and since 2002 have been a recognized source of potential epidemic disease. The recent SARS-CoV-2 pandemic has raised new interest in these viruses as they can cause respiratory disease ranging from a limited presentation to the development of progressive hypoxic respiratory failure sometimes culminating in death. Because of the overwhelming nature of the pandemic, other viruses and infectious agents might be overlooked when evaluating at-risk patients. Furthermore, due to suboptimal testing capabilities, an early clinical diagnosis is not always possible. Clinicians should be vigilant when evaluating patients with viral-like respiratory infections, but the scarcity of safe and effective therapies for the treatment of Coronavirus greatly limits the management of these patients.

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