Title: Pneumatocele Induced Pneumothorax in a patient with Post-COVID-19 Pneumonitis. A Case Report

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Authors Contribution Statement:

Contributor Role	Role Definition	1	2
Conceptualization	Ideas; formulation or evolution of overarching research goals and aims.	X	X
Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse.	X	-
Formal Analysis	Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data.	-	-
Funding Acquisition	Acquisition of the financial support for the project leading to this publication.	-	-
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection.	X	X
Methodology	Development or design of methodology; creation of models	-	-
Project Administration	Management and coordination responsibility for the research activity planning and execution.	X	-
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools.	X	X
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components.	-	-
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.	X	-
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs.	X	-

Visualization	Preparation, creation and/or presentation of the published work, specifically visualization/data presentation.	X	X
Writing – Original Draft Preparation	Creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation).	X	-
Writing – Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages.	-	X

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Highlights:

- COVID-19 recovery complications are not emphasized in literature as much as pathophysiology, clinical treatment, and epidemiology.
- As the pandemic is taking its course, many patients are recovering from COVID-19 but may be at risk for complications.
- To ensure pneumatoceles are diagnosed and tracked in anticipation of spontaneous pneumothorax, we recommend that patients post COVID-19 pneumonitis are assessed radiographically before hospital discharge and within 2 weeks after discharge. This will lead to early detection of pneumatoceles and will provide an insight into a subgroup of COVID-19 patients that may be at risk for multiple pathological pulmonary events after COVID-19 hospitalization. This will aid physicians in being cognizant regarding this subgroup of patients who will benefit from a more stringent monitoring.
- Larger studies are warranted to distinguish between Long COVID/Long haul COVID/Post-acute sequelae SARS-CoV-2 (PASC) and Post-COVID-19 pneumonitis as well as the complications related to both these conditions.

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Discussion Points:

1. Pneumothoraces complicating COVID-19 pneumonia.
2. What causes pneumothorax in COVID-19 pneumonia patients?
3. Pneumatoceles complicating COVID-19 pneumonia.
4. Are pneumatoceles common in COVID-19 patients?
5. Are pneumothoraces common in patients, post COVID-19 hospitalization?
6. Long COVID/Long-haul COVID/PASC

ABSTRACT

Background: The COVID-19 pandemic has been challenging medical professionals and facilities for over a year now. Much of the literature describes pathologic lung changes and complications associated with SARS-CoV-2, with pneumothorax and pneumatoceles not being uncommon.

The Case: We describe a case involving a patient that presented to the emergency department with a pneumothorax. Three weeks prior, the patient was hospitalized for 10 days in acute respiratory distress secondary to COVID-19 pneumonitis, which did not require ventilator support. Follow up imaging revealed a 7 cm (AP) x 4.6 cm (transverse) x 2.5 (cc) cm pneumatocele.

Conclusion: We speculate that antecedent rupture of an unrecognized pneumatocele likely caused lung collapse leading to the patient's pneumothorax. This review delves into the etiology of both pneumothoraces and pneumatoceles along with their relation to COVID-19 pneumonia.

Keywords: COVID-19, Pneumatocele, Pneumothorax, Tension Pneumothorax, SARS-CoV-2;

INTRODUCTION

This article describes the clinical course of a patient that presented to an emergency department with a spontaneous pneumothorax post COVID-19 pneumonia, with a pneumatocele discovered via radiography. While pneumatoceles are more common within the post-pneumonia, pediatric population (1), a retrospective study has shown pneumatocele development as a missed diagnosis in up to 37% of their 78 patients with the coronavirus disease (2). Other studies show varying numbers with pneumatocele development seen in 10% of 81 symptomatic patients in the study by Shi et al. (3) and in 5.3% of 57 COVID-19 positive patients in the study Qi et al. (4). Radiologic studies use terms such as 'cystic air spaces' (2), 'cystic changes' (3), and 'emphysema' (4) which are synonymous with pneumatocele. Pneumatoceles, in relation to COVID-19, are highly variable in size; some categorized as 'giant bullae' (5) and typically present in multiples rather than a singular lesion (6).

A predictable complication of pneumatoceles is pneumothorax (1,5). A few case studies report pneumothoraxes as a rare complication of COVID-19 (7,8). Risk factors for pneumothorax include young age, chest trauma (1), individuals with imaging demonstrating fibrotic lung changes (9), individuals with a more severe clinical course, prolonged pneumonitis duration, and higher neutrophil counts (10). In our experience with COVID-19 management, pneumothorax is more common in mechanically ventilated patients, which is as high as 13% in one study (11), likely due to barotrauma. However, patients are presenting with pneumothoraces well before ventilatory support is provided.

THE CASE

A 28-year-old African American male presented to an emergency department reporting chest and back pressure/pain along with shortness of breath. Three weeks prior, this patient presented to the same ED in respiratory distress secondary to PCR confirmed COVID-19 pneumonitis. He was hospitalized for 10 days, receiving oxygen, remdesivir, dexamethasone, tocilizumab, and enoxaparin therapy. The patient did not require mechanical ventilation during the prior hospitalization. During the current presentation to the ED for respiratory distress he was saturating to 82% on room air, which improved to 92% on 4 liters per minute of nasal cannula oxygen. Chest radiographs showed a large right pneumothorax with subsequent mediastinal shift to the left (Figure 1). A pigtail catheter was inserted at the 2nd intercostal space along the midclavicular line.

After two days, the catheter accidentally dislodged from the patient's pleural space and serial CXRs were performed to determine whether the pneumothorax had resolved. Although the patient was clinically asymptomatic, the radiographs showed worsening of the pneumothorax; therefore, a pigtail catheter was reinserted at the 4th intercostal space along the mid axillary line. The CXR on day 4 also showed formation of a round lesion with central air-fluid levels that was speculated to be a pneumatocele (Figure 2). On subsequent imaging, the pneumothorax appears to have improved, although not completely resolved (Figure 3). The lesion was monitored by a local pulmonologist and treated daily with fluticasone inhaled therapy, until resolution 7 weeks later.

DISCUSSION

Textbook pneumothorax patients often have a history of a connective tissue disorder, such as Marfan syndrome or Ehlers-Danlos syndrome, have a characteristic marfanoid habitus, COPD, smoking, or pregnancy (12). Our patient denied a recent history of trauma, denied a history of smoking, and had a body mass index of 35.9 kg/m^2. This patient does not fit into the standard demographic of patients at an increased risk of pneumothorax and there are still uncertainties regarding COVID-19 related lung changes and complications. This led us into hypothesizing that pneumatoceles may well be a potential mechanism behind this pneumothorax.

The percentage of COVID-19 cases that are complicated by pneumatocele development, has yet to be determined. Pneumatoceles typically appear 5-6 days after the infectious process secondary to SARS-CoV-2 (13). However, spontaneous pneumothorax is a known, rare complication of COVID-19 and can occur in the absence of mechanical ventilation (14), with studies showing that pneumothorax occurs within a window of 14-37 days after hospitalization (7). Pneumothorax is also not a common sequel to pneumatoceles as the majority of pneumatoceles resolve spontaneously within a few weeks to a year, without intervention (1). In this case, while no pneumatocele was identified before or at presentation, antecedent rupture of an unacknowledged pneumatocele could have led to the pneumothorax. The single pneumatocele lesion likely formed due to parenchymal inflammation secondary to ARDS, which is not uncommon (15). There have not been any studies that deduce a specific mechanism for COVID-19 infection itself eliciting pneumatocele formation, without pneumonitis underplay.

Pneumothoraces are rarely fatal however they have recurrence rate of up to 32% within 12 months, according to one meta-analysis (16). This patient's pneumothorax pathology could have occurred either through pneumatocele rupture, which has been reported in other case studies (8), or due to COVID-19 induced pulmonary parenchymal injury and necrosis with development of air leaks into the pleural cavity. While the former has not been thoroughly studied due to the relative novelty of COVID-19, the latter was noted previously during the SARS outbreak (16,17). If pulmonary necrosis led to pneumothorax, then the pneumatocele seen in this patient was likely an incidental finding.

As per the World Health Organization (WHO) most COVID-19 patients experience a mild to moderate clinical course, with 10-15% of patients progressing to a severe clinical presentation and 5% progressing to critical illness. In general, recovery can take anywhere from 2-6 weeks, depending on the severity of the case. Unfortunately, some patients experience symptoms for weeks to months, regardless of disease severity (18). These patients were colloquially deemed 'long COVID' or 'COVID-long haulers', which later became 'post-acute sequelae of SARS-CoV-2 (PASC). Studies suggest that roughly ⅓ of those infected with SARS-CoV-2, whether asymptomatic during infection or not, may develop PASC (19,20). According to a study, conducted by Lambert et. al, of the 5,875 COVID-19 survivors surveyed 5,163 reported

symptoms persisting longer than 21 days (21). The most common symptom reported was fatigue (79.0%) and the other symptoms reported were headache/migraines (55.3%), shortness of breath (55.3%), difficulty concentrating (53.6%), cough (49.0%), changed sense of taste (44.9%), diarrhea (43.9%), muscle/body aches (43.5%), and heart palpitations (39.5%) (21). Another study surveying 3,762 respondents from 56 countries reported the most frequent symptoms being fatigue (77.7%) post-exertional malaise (72.2%), and cognitive dysfunction (55.4%) (22). Risk factors for PASC include hypertension, obesity, prior mental health conditions (21), and female gender (two times increased risk as compared to males) (23). While COVID-19 is at the forefront of research, a clear distinction must be made between individuals suffering from PASC and Post-COVID-19 pneumonitis, as well as their respective complications. Larger retrospective cohort studies and case reports, pertaining to both PASC and Post-COVID-19 pneumonitis are warranted.

Conclusion

Cystic lesions, pneumatoceles, and subsequently pneumothoraces are likely to result from prolonged COVID-19 pneumonitis causing air leaks. This is similar to the clinical course which was observed in patients with SARS, caused by a virus within the same *Coronaviridae* family, during the 2003 outbreak. To ensure pneumatoceles are diagnosed and tracked in anticipation of spontaneous pneumothorax, we recommend that patients post COVID-19 pneumonitis, especially those given ventilator support, are assessed radiographically before hospital discharge and within 2 weeks after discharge. This will lead to early detection of pneumatoceles and will provide an insight into a subgroup of COVID-19 patients that may be at risk for multiple pathological pulmonary events after COVID-19 hospitalization. This will aid physicians in being cognizant regarding this subgroup of patients who will benefit from more stringent monitoring. Furthermore, larger studies are warranted to distinguish between Long COVID/Long haul COVID/Post-acute sequelae SARS-CoV-2 (PASC) and Post-COVID-19 pneumonitis as well as the complications related to both these conditions.

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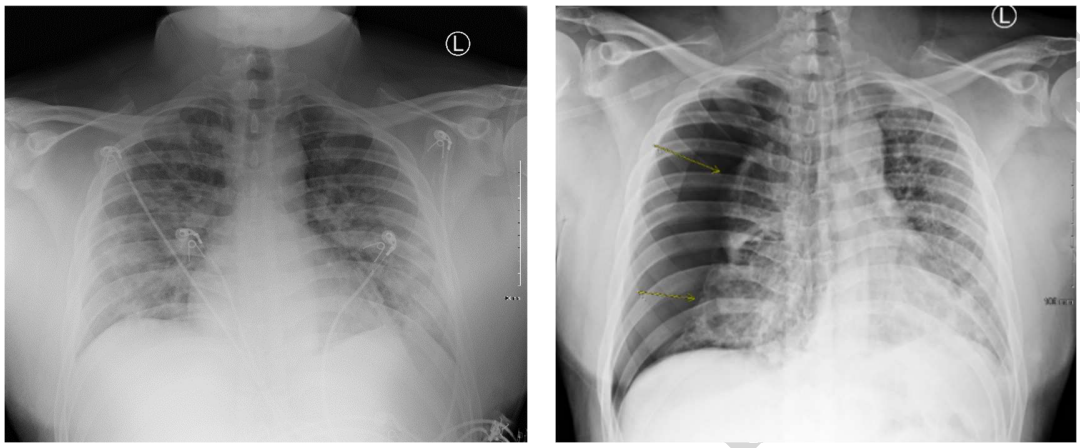
FIGURES AND TABLES.

Figure 1: Patient's chest x-ray taken during the previous hospitalization, showing extensive bilateral interstitial airspace opacities throughout the right and left lungs (left). Patient's chest x-ray at presentation showing a large right pneumothorax, with the majority of the right lung collapsed. There is mild to moderate mediastinal shift to the left. Both lungs show evidence of bilateral airspace/interstitial disease (right).



254 **Figure 2:** Follow up chest x-ray on day 4 showing an unresolved right pneumothorax (20-30%) and ill-
255 defined pulmonary opacities throughout both lungs, deduced to be bilateral interstitial disease. A round
256 lesion with central air-fluid levels formed within the right mid lung and was speculated to be a
257 pneumatocele.

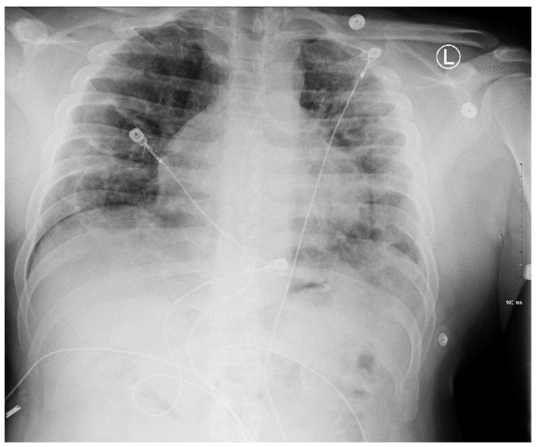


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Figure 3: Noncontrast CT scans showing resolution of the pneumothorax. Laterally in right upper lobe, there is oval-shaped lucent lesion measuring 7 cm (AP) x 4.6 cm (transverse) x 2.5 cm (cc). Wall is thin and barely perceptible. Inner margin of the cavity is smooth. There is an internal air-fluid level. It is difficult to tell if this collection is tracking along the minor fissure. Numerous scattered ground-glass pulmonary opacities are present throughout each lung.