Air Spaces in Patients Diagnosed with COVID-19 Pneumonitis- A Rare Complication


Abstract

Introduction: The outbreak of coronavirus disease 2019 (COVID-19) with its overwhelming morbidity and mortality has created a significant challenge for health systems worldwide. Although peripheral ground-glass opacities are the most frequent radiologic feature of COVID-19 described in the literature, late rare complications such as cavitations, pneumatocele, lung cyst, pneumothorax, empyema or hemothorax are occasionally reported.

Methods: We performed a retrospective study and described a group of eight patients, diagnosed with COVID-19, confirmed by the RT-PCR for SARS-CoV-2 and complicated with cystic air spaces. We have searched for studies describing air spaces in subjects with COVID-19 and analyzed the probable pathophysiology of air spaces development.

Results: Among 29 patients diagnosed with COVID-19 pneumonia complicated by air spaces, 19 (65.5%) received surgical intervention. Of note, 25 (86%) were males. Of the 19 interventions, 6 (20.6%) were exclusively chest drain insertions and the rest 13 (45%) required more advanced procedures like VATS or thoracotomy. Most patients did not have any risk factor for such a complication. Among the group- 18 (62%) had no history of smoking, 16 (55%) had no history of previous diseases and only 1 (3%) had the history of COPD. More than half of the patients (18- 62%) did not require mechanical ventilation during initial viral pneumonitis.

Conclusion: According to our observation and reviewed literature, not every pneumatocele or lung cyst requires surgical intervention the decision should be taken on the individual basis. Reasons for surgical intervention included non-resolving pneumothorax, superinfection of pneumatocele, non-responding to antibiotic therapy and hemothorax.

Keywords: COVID-19; Thoracotomy; Pneumatocele; World Health Organisation (WHO)

Abbreviations: ARDS- Acute Respiratory Distress Syndrome; CM-Centimeter; COPD- Chronic Obstructive Pulmonary Disease; COVID-19-Coronavirus Disease 2019; CPAP- Continuous Positive Airway Pressure; CRP- C-Reactive Protein; CT- Computed Tomography; CTPA- Computed Tomography Pulmonary Angiography; DIC- Disseminated Intravascular Coagulation; ESBL- Extended Spectrum Beta-Lactamase; HFO₂- High-Flow Oxygen Therapy; ICU- Intensive Care Unit; l/min- Liter Per Minute; LMWH- Low Molecular Weight Heparin; ML- Milliliter; NIC- Non-Invasive
Ventilation; NT-proBNP- N-Terminal Prohormone of Brain Natriuretic Peptide; RT-PCR- Reverse Transcription Polymerase Chain Reaction; Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); VATS- Video-Assisted Thoracic Surgery; VV-ECMO- Venous-Venous Extracorporeal Membrane Oxygenation; WHO- World Health Organisation

Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially reported to the World Health Organisation (WHO) on December 31st, 2019. As the cases of disease increased rapidly, WHO declared COVID-19 as a global pandemic [1]. Since then more than 489 million cases and more than 6 million deaths have been reported worldwide [2]. Mild to moderate cases with the clinical symptoms such as fever, dry cough, myalgia and fatigue could be community-managed. However, severe cases of viral pneumonia, which may be accompanied by Acute Respiratory Distress Syndrome (ARDS), require hospitalization and mechanical ventilation in the Intensive Care Unit (ICU) [1,3]. The most frequent radiological manifestations described in the literature are peripheral ground-glass opacities, interlobular septal and pleural thickening, crazy paving pattern and consolidations. Rare radiological presentations include: nodules, cystic changes, bronchiectasis, lymphadenopathy and pleural effusion [4]. Long-term severe thoracic complications, such as pneumatocele, lung cysts, pneumothorax, empyema or hemothorax were mostly described in the literature as case reports and case series [5-17]. We analyzed probable pathophysiology and outcome in patients with pneumatocele and lung cysts as pulmonary complication of COVID-19 supported by recent literature review.

Methods

From September 2020 to December 2021, a retrospective study was performed in patients admitted with a diagnosis of air space after SARS-CoV2 infection. Clinical and demographic variables were collected, including comorbidities, smoking history, laboratory results, infection and surgical history. We described 8 consecutive cases that exemplify uncommon complication of COVID-19 pneumonitis. Typical radiological manifestations like peripheral ground-

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Comorbidities</th>
<th>Smoking history</th>
<th>Complication</th>
<th>Diameter</th>
<th>Mechanical ventilation</th>
<th>Treatment</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>Male</td>
<td>none</td>
<td>&lt;2 pack years</td>
<td>Cyst with hemorrhage, pneumothorax</td>
<td>22 × 7,5 cm</td>
<td>no</td>
<td>VATS with cyst resection</td>
<td>Diffuse necrosis, hemorrhage and stromal damage, parietal pleura with stromal cell reactive metaplasia, organizing fibrin and multiple organizing thromboembolism</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>Male</td>
<td>hypertension, COPD, type 2 diabetes mellitus, atrial fibrillation, depression</td>
<td>yes</td>
<td>Superinfected air space</td>
<td>7 × 1,4 cm</td>
<td>no</td>
<td>Conservatively with antibiotics</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>Male</td>
<td>Hypertension, endoprothesoplasty of the right hip joint years ago</td>
<td>no</td>
<td>Air space</td>
<td>2,7 cm</td>
<td>Yes, +ECMO</td>
<td>Conservatively with antibiotics</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>Male</td>
<td>polytrauma</td>
<td>25 pack years</td>
<td>Superinfected cyst</td>
<td>14,1 × 8,3 cm and 4,3 × 2,7 cm</td>
<td>no</td>
<td>VATS with cyst resection</td>
<td>pus collection, cellular detritus and wall of the cyst with fibrosis, congestion, granulation tissue and purulent infiltrates</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>Male</td>
<td>none</td>
<td>1 pack year</td>
<td>Pneumatocele, pneumothorax, pleural effusion</td>
<td>14,5 × 5,5 cm -5,4 × 4,9 cm + pneumothorax 22-49 mm</td>
<td>no</td>
<td>VATS with pneumatocele resection secondary thoracotomy with decortication, air-leak</td>
<td>focal pleural congestion, oedema, granulation, fibrosis and active eosinophilic inflammation</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>Male</td>
<td>Hypertension, deep vein thrombosis</td>
<td>10 pack years</td>
<td>Cyst</td>
<td>40 × 30 mm</td>
<td>no</td>
<td>conservatively</td>
<td>none</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>Female</td>
<td>none</td>
<td>&lt;1 pack year</td>
<td>Pneumatocele</td>
<td>3,0 × 2,6 cm and 1,3 cm</td>
<td>no</td>
<td>conservatively</td>
<td>none</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>Male</td>
<td>Hypertension</td>
<td>40 pack years</td>
<td>Cyst, pneumatocele</td>
<td>7,5 × 4,4 cm and 3,5 × 1,9 cm</td>
<td>no</td>
<td>Right side thoracotomy, cyst excision</td>
<td>with focal organizing hemorrhages-forming cysts and surrounded by chronic inflammation and dust deposits</td>
</tr>
</tbody>
</table>

Table 1. Summary of our cases with the dimensions of pneumatocele.
glass opacities, interlobular septal and pleural thickening as well as consolidations have been described at the onset of the pandemic [3]. However, cystic abnormalities such as pneumatocele, cystic air spaces and cavitations were rarely reported. We have searched the PubMed for studies describing air spaces in subjects with COVID-19 using the free text term: “pneumatocele + lung cyst + COVID-19”. The search found 13 citations (Table 2). Together with our 8 cases, we analyzed the probable pathophysiology of air spaces development. Data collection was performed on January 12th, 2022. Our cases constituted 27.5% of the group. Our patients, during recovery from COVID-19 (4-6 weeks after first onset of the symptoms) presented with worsening of the clinical condition, which required further investigation. At date there is no dependable management algorithm for such pathology.

**Results**

Among these 29 patients diagnosed with COVID-19 pneumonia complicated by air spaces, 19 (65.5%) received surgical intervention. Of note, 25 (86%) were males. Of the 19 interventions, 6 (20.6%) were exclusively chest drain insertions and the rest 13 (45%) required more advanced

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<th>Mechanical ventilation</th>
<th>Treatment</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Mohsen et al. [5]</td>
<td>1</td>
<td>42</td>
<td>Male</td>
<td>none</td>
<td>-</td>
<td>Pneumatocele with fluid level, compression atelectasis, right side pneumothorax</td>
<td>no</td>
<td>VATS, deroofing</td>
<td>Fibroblast proliferation, intra-alveolar haemorrhage, prominent hyperplasia of pneumocytes</td>
</tr>
<tr>
<td>Kunadhariju et al. [6]</td>
<td>1</td>
<td>62</td>
<td>Male</td>
<td>Hyperlipidaemia, benign prostate hypertrophy, gastro-oesophageal reflux disease, anxiety, obstructive sleep apnoea</td>
<td>&lt;10 pack years</td>
<td>Multiple cystic changes</td>
<td>no</td>
<td>Antibiotics, fluconazole</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>68</td>
<td>Male</td>
<td>none</td>
<td></td>
<td>Pneumatocele, pneumothorax, pneumomediastinum, subcutaneous emphysema</td>
<td>no</td>
<td>Bilateral chest drains insertion</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>58</td>
<td>Female</td>
<td>hypertension</td>
<td></td>
<td>pneumothorax, pneumomediastinum, subcutaneous emphysema, pulmonary artery thrombosis</td>
<td>no</td>
<td>Pleural cavity decompression, anticoagulation</td>
<td>none</td>
</tr>
<tr>
<td>Castiglioni et al. [7]</td>
<td>1</td>
<td>55</td>
<td>Male</td>
<td>Hypertension, adipositas, impaired glucose tolerance</td>
<td>none</td>
<td>pneumatocele</td>
<td>yes</td>
<td>Left lateral muscle sparing thoracotomy with cyst resection</td>
<td>Pus collection, organizing pneumonia, squamous metaplasia and hemosiderin accumulation</td>
</tr>
<tr>
<td>Chang et al. [8]</td>
<td>1</td>
<td>35</td>
<td>Male</td>
<td>Pulmonary hypertension, right ventricle failure</td>
<td>none</td>
<td>Pneumatocele, recurrent right pneumothorax</td>
<td>yes</td>
<td>Left chest drainage insertion, right VATS converted to thoracotomy with right upper lobe pneumatocele resection, decortication, pericardial window</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>65</td>
<td>Male</td>
<td>none</td>
<td>none</td>
<td>bleb with alveolar leak</td>
<td>yes</td>
<td>Right VATS bleb resection</td>
<td>Organizing pneumonia, organizing phase of diffuse alveolar damage, fibrous pleuritis</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>60</td>
<td>Male</td>
<td>none</td>
<td>none</td>
<td>Pneumatocele, empyema,</td>
<td>no</td>
<td>Left robotic decortication, resection of pneumatocele, wedge resection of consolidated lung</td>
<td>Organizing pneumonia with chronic inflammation</td>
</tr>
</tbody>
</table>
procedures like VATS or thoracotomy. Most of the above described patients did not have any risk factor for such a complication. Among the group - 18 (62%) had no history of smoking, 16 (55%) had no history of previous diseases and only 1 (3%) had the history of COPD. More than half of the patients (18-62%) did not require mechanical ventilation during initial viral pneumonitis.

Discussion

According to the literature, including Fleishner Society Glossary [19], pneumatoceles are defined as thin-walled air-filled cysts in the lung interstitium. They often contain air-fluid level and may vary in size. Most cases of pneumatoceles are described in children or young adolescents. Pneumatocele can result from infection with Streptococcus pneumoniae, Staphylococcus aureus, Pneumocystis jiroveci, Pseudomonas aeruginosa, Klebsiella pneumoniae, adenovirus, Mycobacterium tuberculosis, Proteus mirabilis, Acinetobacter, Hemophilus influenzae B type, Bacteroid species, or noninfectious process like barotrauma from Continuous Positive Airway Pressure (CPAP) during mechanical ventilation. [20-22]. A lung cyst is described as a round parenchymal lucency with a well-defined interface with normal lung, surrounded by an epithelial or fibrous wall of variable thickness (<2mm). The both terms are used in the literature to described air spaces in COVID-19 patients.

The pathophysiology of these cystic lesions in COVID-19 is not well studied, although some potential mechanisms are described. Regarding recent literature, one theory explaining the process of the development of pneumatocele, according to Manenti et al. [23] is ischemia related. Inflammatory
Figure 1: A− Chest CT scan, axial view delineating extend of the lung cyst with air-fluid level B− Chest X-ray showing left side air cyst with air-fluid level.

Figure 2: A chest CT scan showing an oval air space.

Figure 3: An axial CT scan demonstrating a superinfected lung cyst in right apical segment.

Figure 4: (A,B) − A coronal chest CT scans demonstrating a complex structure of right-sided lung cyst (C) − An axial and (D) − sagittal chest CT scan showing left-sided pneumothorax (E) − An axial chest CT scan presenting air-fluid level in the lung cyst (F) − A chest X-ray showing thickening of the cyst wall and fluid level

Figure 5: An axial CT scan showing right sided pneumothorax, right sided pleural effusion and a pneumatocele.

Figure 6: An axial CT scan demonstrating a lung cyst in the left lung.
cells infiltration and exudate lead to occlusion of alveoli and respiratory bronchioles, causing a “ball-valve mechanism”-the air is allowed to enter the cystic space but not to leave it. Presence of microthrombi in pulmonary capillaries, which are affected by endothelitis, causes ischemia, necrosis and inflammation, which lead to alveolar wall damage and accumulation of air within the lung parenchyma. Consequently, the trapped air could disect the parenchymal tissue to the pleura or mediastinum- generating pneumothorax or pneumomediastinum or to the subpleural space, causing pneumatocele. In some of the pathological examinations of lung tissue (Table 1 and 2), diffuse necrosis, hemorrhage and thrombi are described. Nevertheless, most frequent findings are a wide range of lung interstitial inflammation with signs of organizing pneumonia, fibrosis and, in some cases, metaplasia, resulting in increased susceptibility of the lung parenchyma to damage. Supplementary factor is barotrauma, which increases intra-alveolar pressure and leads to alveolar wall rupture [5-7,21,23]. Continuous positive airway pressure during mechanical ventilation or non-invasive ventilation may cause injury, lung tissue disruption and enlargement of air space. However, more than 50% of the patients mentioned in our review required oxygen support without the necessity of invasive ventilation. Most pneumatoceles that are not COVID-19 related resolve within a few weeks to 12 months with no additional intervention. Probably uncomplicated pneumatocele (thin-walled, with no signs of progressive enlargement) in COVID-19 patients would also resolve spontaneously. The most frequent complications of pneumatocele described in the literature are rupture resulting in pneumothorax or pneumomediastinum, superinfection or haemothorax. Among patients described in the literature, diagnosed with COVID-19 pneumonia complicated by air spaces, after unsuccessful conservative treatment, surgical intervention was necessary. Part of the patients showed clinical and radiological improvement under conservative treatment and could be discharged. Hence, CT scanning should be repeated in patients with newly discovered pneumatocele after recovering from COVID-19, which may prevent to overlook further complications. Conservative management or surgical intervention in those complications should be decided during multidisciplinary discussion (thoracic surgeon, respiratory physician, intensive care specialist) taking into consideration the patient’s clinical status, radiological manifestation and expected outcome. Particular difficulties concern the proper interpretation of CT scans in patients with pneumatocele. The CT images are deceptively similar to pleural empyema. In these cases, a precise radiological diagnosis determines the appropriate surgical therapy and outcome of treatment.

Conclusions
The case series and systemic review of the literature provide a few learning points.
Not every infected pneumatocele or lung cyst requires surgical intervention.

Persistent air-leak, associated pneumothorax and haemothorax suggest more urgent surgical intervention.

Secondary infection of the pneumatocele not-responding to extended antibiotic therapy is a potential life threatening condition and should be considered for surgical resection. Prompt surgical approach may be lifesaving in patients in the critical clinical stage.

In patients with newly discovered pneumatocele after recovering from COVID-19, repeated imaging in 4-6 weeks may prevent further complications.

Second imaging in a prone position could help to distinguish a pneumothorax from a pneumatocele.

References