Alveolar Air Leak Syndrome a Potential Complication of COVID-19-ARDS - Single Center Retrospective Analysis

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Abstract

Background: Alveolar air leak comprising of pneumothorax, pneumomediastinum, and subcutaneous emphysema in the ongoing COVID 19 pneumonia have been increasingly reported in literature. These air leaks were also recognized in the severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and H1N1 viral pandemics. Here we review the incidence and outcomes of alveolar air leaks over 400 patients admitted to our tertiary care institution for moderate-severe COVID-19 pneumonia.

Methods: We performed a retrospective audit of moderate to severe COVID-19 cases admitted to our hospital. Patients who were recognized as either a spontaneous pneumothorax, pneumomediastinum, pneumopericardium and subcutaneous emphysema were identified. Their clinical features and characteristics were thoroughly documented and clinical outcomes were gathered. Each case has been presented as a brief synopsis.

Results: During the audit period, we reviewed over 670 patients, out of these 419 patients required intensive care for moderate to severe disease. 10 patients developed Pneumothorax, pneumomediastinum, pneumopericardium and/or subcutaneous emphysema - referred to as Alveolar Air leak syndrome; The incidence of alveolar air leak was found to be 2.39%. 6 patients did not survive the resultant complication.

Conclusion: Spontaneous alveolar air leaks are a rare but definite complication of COVID-19 viral pneumonia and may occur in the absence of mechanical ventilation. ICU Clinicians must be alert about the diagnosis and treatment of this complication.

Background

The novel coronavirus nCoV-19 (SARS-CoV-2), responsible for the coronavirus disease-19 (COVID-19), first seen in the Hubei province, China, on December 31, 2019 has rapidly spread globally with more than 30.6 million cases and 950 000 deaths. Similar to the etiological agents in previous human coronavirus outbreaks (severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)), SARS-CoV-2 primarily affects the respiratory system.

In the course of managing sick COVID-19 patients we noticed a high number of patients with...
pneumothorax, pneumomediastinum, and pneumopericardium, even in absence of mechanical ventilation.

Alveolar Air leak comprising Pneumothorax, pneumomediastinum and subcutaneous emphysema have been known complications of organizing pneumonias\(^2\). These complications have been observed in the context of COVID-19 pandemic also. The exact mechanism and management guideline has not been established yet. We aim to demonstrate few cases of “Alveolar Air leak Syndrome” which could enable researchers new insight of this complication and possible preventive or management strategy.

Here we review the incidence and outcomes of 10 cases with alveolar air leaks either pneumothorax / Pneumomediastinum / Pneumopericardium or Subcutaneous Emphysema in moderate to severe COVID-19 patients admitted to our institution.

### Methods

We conducted a retrospective review of patients admitted with moderate to severe COVID-19 disease at our tertiary hospital between June 1 and 25th September 2020. During this period we managed 670 patients with COVID-19. There were 419 cases with moderate to severe disease as per the Indian Council of medical research guidelines. Their diagnosis was based on rapid antigen testing (RAT) or polymerase chain reaction (PCR) testing of nasopharyngeal swab sampling. All patients had a routine chest X-ray on admission. The presence of Alveolar air leak – Pneumothorax/pneumomediastinum/pneumopericardium/subcutaneous emphysema was based on an audit of clinical documentation and chest radiographic imaging. Patients who had an air leak at any time during their management course were thoroughly reviewed. Baseline laboratory parameters including inflammatory markers C-reactive protein (CRP), lactate dehydrogenase (LDH), Ferritin, D-dimer, Interlukin-6 were documented for each patient. The incidence of pulmonary leaks in COVID-19 patients was then calculated.

### Results

During the audit period, we reviewed over 670 patients, admitted with confirmed COVID-19 pneumonia. Out of these 419 patients required intensive care for moderate to severe disease. Ten patients developed Pneumothorax / pneumomediastinum / pneumopericardium or subcutaneous emphysema - referred as Air leak syndrome; the incidence of alveolar air leak was found to be 2.39%. The characteristics of these patients are summarized in Tables 1 and 2.

### Case 1

A 46-year-old male with a background of Diabetes presented

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Table 1: Demographics and clinical characteristics for patients with COVID-19 and Pulmonary air leak

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender/age</th>
<th>Comorbidities</th>
<th>Radiological image</th>
<th>Time to onset</th>
<th>Predominant Oxygenation method</th>
<th>Max PEEP (Cm H2O)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/46</td>
<td>Diabetes</td>
<td>Pneumothorax</td>
<td>8 days</td>
<td>Non invasive ventilation</td>
<td>8</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>F/62</td>
<td>Hypertension</td>
<td>Pneumomediastinum</td>
<td>14 days</td>
<td>Non invasive ventilation</td>
<td>8</td>
<td>Discharged</td>
</tr>
<tr>
<td>3</td>
<td>M/60</td>
<td>None</td>
<td>Pneumomediastinum</td>
<td>15 days</td>
<td>High flow nasal cannula</td>
<td>6</td>
<td>Discharged</td>
</tr>
<tr>
<td>4</td>
<td>M/61</td>
<td>Diabetes</td>
<td>Pneumomediastinum</td>
<td>16 days</td>
<td>Mechanical ventilation</td>
<td>10</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>M/64</td>
<td>Hypertension/COPD</td>
<td>Pneumomediastinum</td>
<td>2 days</td>
<td>Non invasive ventilation</td>
<td>6</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>F/63</td>
<td>Diabetes</td>
<td>Pneumomediastinum</td>
<td>17 days</td>
<td>Non invasive ventilation</td>
<td>6</td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>M/37</td>
<td>None</td>
<td>Pneumomediastinum</td>
<td>21 days</td>
<td>Non invasive ventilation</td>
<td>8</td>
<td>Discharged</td>
</tr>
<tr>
<td>8</td>
<td>M/70</td>
<td>Diabetes</td>
<td>Pneumomediastinum</td>
<td>16 days</td>
<td>Non invasive ventilation</td>
<td>8</td>
<td>Died</td>
</tr>
<tr>
<td>9</td>
<td>M/81</td>
<td>Diabetes</td>
<td>Pneumomediastinum</td>
<td>8 days</td>
<td>Non invasive ventilation</td>
<td>6</td>
<td>Died</td>
</tr>
<tr>
<td>10</td>
<td>M/54</td>
<td>None</td>
<td>Pneumomediastinum</td>
<td>24 days</td>
<td>High flow nasal cannula</td>
<td>6</td>
<td>Discharged</td>
</tr>
</tbody>
</table>

Table 2: Baseline inflammatory markers in patients with COVID-19 and pulmonary air leak

<table>
<thead>
<tr>
<th>Case</th>
<th>CRP (mg/L)</th>
<th>LDH (IU/L)</th>
<th>Ferritin (ng/ml)</th>
<th>IL-6 (pg/ml)</th>
<th>D-Dimer ng/ml</th>
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<tbody>
<tr>
<td>1</td>
<td>90</td>
<td>661</td>
<td>347</td>
<td>395</td>
<td>5200</td>
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<tr>
<td>2</td>
<td>91.3</td>
<td>559</td>
<td>347</td>
<td>53.22</td>
<td>292</td>
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<tr>
<td>3</td>
<td>65</td>
<td>1054</td>
<td>462</td>
<td>26.42</td>
<td>5220</td>
</tr>
<tr>
<td>4</td>
<td>131</td>
<td>429</td>
<td>186</td>
<td>57.3</td>
<td>5250</td>
</tr>
<tr>
<td>5</td>
<td>13.65</td>
<td>1086</td>
<td>618</td>
<td>22.70</td>
<td>819</td>
</tr>
<tr>
<td>6</td>
<td>20.2</td>
<td>742</td>
<td>682</td>
<td>120</td>
<td>400</td>
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<tr>
<td>7</td>
<td>89.4</td>
<td>750</td>
<td>415</td>
<td>48.40</td>
<td>378</td>
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<tr>
<td>8</td>
<td>54</td>
<td>428</td>
<td>728</td>
<td>58.15</td>
<td>314</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>621</td>
<td>377</td>
<td>1117</td>
<td>271</td>
</tr>
<tr>
<td>10</td>
<td>6.3</td>
<td>621</td>
<td>1117</td>
<td>2585</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1: CT Pulmonary angiogram: large Pneumomediastinum

Fig. 2: CT Thorax: Pneumomediastinum

Fig. 3: CT Thorax: small Pneumomediastinum
with a week’s history of fever followed by breathlessness. He required oxygen supplementation with nasal cannula eventually needing noninvasive ventilation.

He received broad spectrum antibiotics, corticosteroids, low molecular weight heparin, Remdesivir, convalescent plasma and off label Tocilizumab. A week later, the patient developed worsening hypoxia, A CT Pulmonary angiogram was done to rule out possible Pulmonary Embolism but demonstrated a large Pneumomediastinum (Figure 1). Patient developed intractable respiratory failure and died despite providing resuscitative measures.

**Case 2**

A 62-year-old hypertensive female presented with 5 days history of fever followed by breathlessness. She required oxygen supplementation with high concentration mask.

She received broad spectrum antibiotics, corticosteroids, Remdesivir, convalescent plasma and low molecular weight heparin. Patient was being weaned off oxygen when she developed acute chest pain and breathlessness. A CT scan of thorax was done along with cardiac investigation. The CT Thorax showed Pneumomediastinum (Figure 2). Positive pressure ventilation was avoided, and patient was managed conservatively. She was discharged after a week with complete resolution.

**Case 3**

A 60-year-old male was referred to our Hospital as difficult to wean off oxygen, after being managed with broad spectrum antibiotics, corticosteroids, anticoagulants, Remdesivir. A CT scan of thorax was done which showed a small Pneumomediastinum (Figure 3). Patient was managed conservatively on high flow nasal cannula and recovered after a long course of Hospitalization.

**Case 4**

A 61-year-old Diabetic male presented with a history of fever followed by breathlessness. He required oxygen supplementation with non invasive ventilation. He received broad spectrum antibiotics, corticosteroids, Remdesivir, DVT prophylaxis and convalescent plasma.

Patient had a stormy stay in the hospital eventually needing mechanical ventilation. An HRCT Thorax was done which showed an extensive Pneumomediastinum and subcutaneous emphysema (Figure 4). Patient developed multiorgan failure and died despite providing resuscitative measures.

**Case 5**

A 64-year-old male with a background of Chronic Obstructive Pulmonary Disease and Diabetes presented typical symptoms. He developed type II respiratory failure requiring Bilevel Positive Pressure support with an IPAP of 16 and EPAP of 6 cm of water.

Two days later he developed acute hypoxia, a chest X-ray was done which showed a right sided Pneumothorax (Figure 5). An intercostal chest drain had to be inserted. He had to be intubated and put into mechanical ventilation. Patient developed multiorgan respiratory failure and died despite providing resuscitative measures.

**Case 6**

A 63-year-old female with a background of Diabetes was referred to our center as a case of severe hypoxia. A chest X-ray was done which showed a left Pneumothorax (Figure 6). An intercostal chest drain had to be inserted. He had to be intubated and put into mechanical ventilation. Patient developed multiorgan respiratory failure and died despite providing resuscitative measures.
Case 9

An 81-year-old retired Physician male presented with a history of acute decompensation following fever. He required oxygen supplementation with non invasive ventilation. He received broad spectrum antibiotics, corticosteroids, Remdesivir and convalescent plasma.

Patient had a stormy stay in the hospital eventually needing mechanical ventilation for refractory respiratory failure. He was ventilated as per ARDS-Net protocol and needed PEEP below 10 cm of water. Just a day after intubation, he developed massive subcutaneous emphysema (Figure 9). An HRCT Thorax was done which showed an extensive Pneumomediastinum with small pneumothorax and subcutaneous emphysema. Patient developed multiorgan failure and died despite providing resuscitative measures.

Case 10

A 54 -year-old male admitted as case of severe COVID Pneumonia and ARDS. He had a long course In the ICU and was discharged after 3 weeks with significant recovery. He returned within few hours to the emergency with acute left sided chest pain. A CT Thorax done, showed left sided pneumothorax (Figure 10). An emergent Chest drain was done and patient was managed for a week more in the ICU. He was discharged in stable condition after a good recovery.

Discussion

Patients with COVID-19 disease can progress to severe Pneumonia and acute respiratory distress syndrome (ARDS). Their infection is characterized radiologically by ground glass opacities mostly peripherally placed progressing into consolidations and then in later stages to Organizing pneumonia/fibrosis. Organizing pneumonia (OP) first described by Davison and Epler et al in the 1980s is a clinicopathologic pattern of lung injury characterized by the filling of alveoli and alveolar ducts with spindle-shaped fibroblasts and myofibroblasts that later form granulation tissue.

Organizing pneumonias and its histological variant, acute fibrinous organizing pneumonia (AFOP) were commonly recognized during the severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and H1N1 viral pandemics. Alveolar air leak comprising of pneumothorax, pneumomediastinum, and subcutaneous emphysema have been presenting feature of Organizing pneumonia. A similar spectrum of complications is being observed in patients with COVID 19 infections as per many reports published world over. Aioddi et al reported a couple of persistent pneumothorax in COVID-19 pneumonia patients while on mechanical ventilation. There are also case reports wherein patients have developed Pneumothorax/ Pneumomediastinum/subcutaneous emphysema when spontaneously breathing or not on mechanical ventilation.

In this case series we observed that Ten patients with COVID-19 pneumonia developed air leaks out of four hundred odd cases with moderate and severe disease; the incidence of 2.39% is much higher than what has been recently reported in the literature.

Although over 30 million confirmed cases of COVID-19 worldwide, patient management recommendations are not very clear. It was widely known that respiratory failure in patients with COVID-19 infection was due to pneumonia progressing to ARDS; hence many moderate to severely ill patients receive noninvasive and invasive ventilation with high positive end-expiratory pressure (PEEP). High-flow oxygen therapy may be a safer alternative to avoid the potential complications of positive pressure ventilation in these types of patients.

In several COVID-19-ARDS cases, severe hypoxemia along with preserved lung compliance was observed, prompting to Atypical ARDS Syndrome and micro-vascular obstructive thrombo-inflammatory syndrome hypothesis. Our observations of air leaks without an obvious barotrauma supports emerging theories of lung damage in SARS Co-V2 infection.

In infections like COVID-19, the virus can infect both type I and II pneumocytes which results in the breakdown of alveolar membrane integrity. Viral infections can cause an increase of alveolar pressure due to violent coughing and eventually causing alveolar damage. Selective overdistention of the alveoli owing to mucus impaction, inflammation
and consolidative phase of COVID-19 pneumonia can lead to alveolar rupture.

The mechanism of alveolar leak in organizing pneumonia is a ball valve effect by localized plugs of fibrous tissue in bronchiolar lumen causing alveolar hyperinflation and resultant rupture. Another possible triggering mechanism is severe coughing seen commonly in patients with COVID-19 disease. Coughing may increase the leakage of air out of the alveoli by leading to sudden lengthening followed by shortening of the pulmonic vessels, associated bronchus during respiration, further moving the “train of bubbles” into the vascular sheaths.

COVID-ARDS healing with organizing pneumonia might be a possible pathological condition underlying alveolar leak and we suspect this mechanism to be playing the key role in alveolar air leaks. There is need for more research to determine the pathological mechanism of hypoxemia in COVID-19 patient to enable better ventilation strategies.

After the RECOVERY trial role of steroids in management of COVID-ARDS has been established with mortality benefits. This finding would tilt the mechanism of the disease in the favour of organizing pneumonia, which responds well to steroid treatment.

We also observed rise in inflammatory markers like CRP, LDH, Ferritin, D-dimer, and IL-6 levels in almost all patients in our study. However, there was no correlation with mortality or alveolar leak syndrome to the level of inflammatory markers. Patients in our study did not have a consistent trend of high inflammatory parameters unlike those seen in recently published works.

In conclusion, pneumothorax and pneumomediastinum, Pneumopericardium or subcutaneous emphysema are possible complications of COVID-19 pneumonia, causing acute decompensation that can worsen the prognosis of patients.

**Learning Points**

1. **Pneumomediastinum, pneumopericardium, pneumothorax or subcutaneous emphysema may be a possible cause of sudden deterioration in COVID-19 patients.**

2. **COVID-pneumonia—ARDS—Acute fibrinous Organizing pneumonia might be a most likely course of disease, although it needs further biopsy/autopsy studies and research.**

3. Avoiding any kind of high PEEP and use of HFNO or other high-low oxygen devices might prevent alveolar-air-leaks and may improve the outcome in COVID-ARDS.

**References**