Spontaneous Air-leak Syndrome and COVID-19: A Multifaceted Challenge

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ABSTRACT

Spontaneous air-leak syndromes have emerged as rare but significant complication of Coronavirus disease-2019 (COVID-19) pneumonia in the last few months. This complication has been documented in both spontaneous and mechanically ventilated patients. Although few studies have used computed tomographic scans to confirm the diagnosis, this could be challenging in resource-limited setup. We present a series of 15 cases that highlight the clinical heterogeneity with respect to stage of illness, ventilatory status, and varied clinical scenarios at the time of development of these syndromes. All cases in our series were diagnosed clinically and confirmed by bedside chest X-ray and were managed promptly. Though mortality was not so infrequent in our experience, these air-leak syndromes were not directly attributed as cause of death in these patients. Therefore, high level of clinical suspicion and vigilance is necessary to identify and manage cases of air-leak syndrome.

Keywords: Air-leak syndrome, COVID-19, Pneumomediastinum, Pneumothorax, Subcutaneous emphysema.

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) has emerged as a multisystemic disorder over the last few months, leading to a myriad of complications. Pneumothorax and subcutaneous emphysema with or without pneumomediastinum have been reported in small number of patients with COVID-19, although the frequency and significance of this association remain uncertain. The incidence of spontaneous pneumomediastinum as reported varies from 1 to 1.1%. These pathologies were well-documented complications of severe acute respiratory syndrome coronavirus (SARS-CoV-1) and Middle East respiratory syndrome (MERS) and were indicative of severe disease with poor prognosis. The current literature comprises of case reports and retrospective cohort studies, all pointing toward clinical heterogeneity and indeterminate causal association of these complications in COVID-19 pneumonia. We hereby report the largest single-center case series of spontaneous pneumothorax and/or subcutaneous emphysema with or without mediastinal emphysema in both ventilated and nonventilated patients from a tertiary care intensive care unit in India over 4 months.

CASE DESCRIPTIONS

Cases 1–15

Out of the 15 patients documented in our series, nine were on invasive ventilation, five were on noninvasive ventilation (NIV), and one patient (Case 11) presented with spontaneous pneumothorax from home. This patient developed it as a sequela of COVID-19 pneumonia, 15 days after discharge. This patient came with breathlessness and was managed with intercostal drain (ICD) insertion. During his first admission in ICU, the patient was managed with high-flow nasal cannula. Patient had no apparent risk factors for spontaneous pneumothorax.

Out of the five patients on NIV, four developed subcutaneous emphysema and one developed pneumothorax requiring ICD insertion and rescue intubation with invasive mechanical ventilation (Case 2). Two of them also had evidence of pneumomediastinum

in the high-resolution computed tomography (HRCT) chest. All five patients were ventilated with a target minute ventilation of 10 to 15 mL/minute and positive end-expiratory pressure (PEEP) not exceeding 10 cm of H2O.

Out of the nine patients on invasive mechanical ventilation, four patients developed tension pneumothorax necessitating ICD insertion. Rest of the patients developed subcutaneous emphysema with evidence of mediastinal emphysema in only 3 cases in chest X-ray. HRCT thorax could not be done in these patients due to logistic reasons. All these patients were ventilated following lung-protective ventilation (LPV) strategy with the target of maintaining plateau pressure below 30 cm of H2O and tidal volume and PEEP not exceeding 6 mL/kg of IBW and 15 of H2O, respectively.

Most of the patients developed these complications in second week of illness and beyond but at different stages of illness, for example, one even in weaning phase (Case 10) and one patient while on extracorporeal life support (Case 13). Out of the 15 cases, only two had underlying lung condition which was chronic obstructive pulmonary disease (Case 1) and the other was interstitial lung disease (Case 6). None of the patient had any procedure (central venous cannulation/bronchoscopy/tracheostomy) done 24–48 hours prior to the development or detection of pneumothorax/subcutaneous emphysema. Eight out of nine intubated patients

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Table 1: Details of all 15 cases of pneumothorax

| Cases | Age/sex | Ventilation status/mode | Day of intubation (onset of illness) | Day of pneumothorax/SC emphysema | X-ray finding | ANC | ALCS | NLR at admission | Ferritin | D-dimer | IL-6 | Outcome |
|-------|---------|-------------------------|-------------------------------------|----------------------------------|---------------|-----|------|------------------|----------|---------|------|----------|
| 1     | 59/M    | Invasive CMV            | D11                                 | D17                              | Pneumothorax (L) | 16,553 | 160  | 48:1             | 33,511   | 8.22    | 1,487 | Death on D19 |
| 2     | 51/M    | Invasive NI PSV         | D14                                 | D14                              | Pneumothorax (L) | 20,640 | 731  | 12:1             | 511      | 8.45    | 1.45  | Death on D17 |
| 3     | 48/M    | Invasive CMV            | D16                                 | D19                              | Pneumothorax (R) | 27,081 | 300  | 17:1             | 609      | 1.36    | 1.06  | Death on D16 |
| 4     | 57/M    | Invasive CMV            | D10                                 | D17                              | Pneumothorax (R) | 30,827 | 280  | 15:1             | 816      | 1.1     | 1.8   | Death on D20 |
| 5     | 46/M    | Invasive NI PSV         | D2                                  | D21                              | SC and mediastinal emphysema | 15,842 | 448  | 7.1              | 4,115    | 0.96    | 0.96  | Death on D25 |
| 6     | 73/F    | Invasive CMV            | D5                                  | D12                              | SC emphysema     | 34,560 | 85   | 24:1             | 5,780    | 3.45    | 3.45  | Death on D26 |
| 7     | 71/M    | Invasive CMV            | D8                                  | D7                               | SC emphysema     | 34,032 | 110  | 31:1             | 2,913    | 0.59    | 0.59  | Death on D16 |
| 8     | 53/M    | Invasive CMV            | D28                                 | D11                              | SC emphysema     | 30,559 | 152  | 2:1              | 211      | 8.0     | 8.0   | Death on D18 |
| 9     | 56/M    | Invasive NI PSV         | D9                                  | D15                              | SC emphysema     | 25,906 | 363  | 23:1             | 2,446    | 3.69    | 3.69  | Death on D28 |
| 10    | 40/M    | Invasive CMV            | D18                                 | D35                              | SC emphysema     | 2,755  | 210  | 23:1             | 1,265    | 0.89    | 0.89  | Death on D50 |
| 11    | 61/M    | Spontaneous on room air at home | D12                                | D15                              | SC emphysema and mediastinal emphysema | 12,517 | 480  | 23:1             | 72,454   | 1.16    | 1.16  | Death on D26 |
| 12    | 73/M    | Invasive CMV            | D15                                 | D12                              | SC emphysema and mediastinal emphysema | 17,466 | 461  | 23:1             | 1,515    | 1.12    | 1.12  | Shifted to ward |
| 13    | 57/M    | Invasive ECMO/PCV       | D10                                 | D35                              | SC emphysema     | 35,514 | 36   | 23:1             | 2,180    | 4.94    | 4.94  | Shifted to ward |
| 14    | 42/M    | Invasive NI PSV         | D5                                  | D15                              | SC emphysema     | 17,242 | 380  | 11:1             | 3,017    | 23      | 23    | Shifted to ward |
| 15    | 41/F    | Invasive NI PSV         | D10                                 | D10                              | SC emphysema     | 18,050 |       |                 | 104      |         |      | Shifted to ward |

CMV, controlled mode of ventilation; NI PSV, noninvasive pressure support ventilation; SC emphysema, subcutaneous emphysema; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; NLR, neutrophil lymphocyte ratio; IL-6, interleukin 6

highest value of ANC, ferritin, D-dimer IL6, lowest value of ALC during the illness and at admission NLR taken into consideration
received prone ventilation. Hemodynamic instability was associated with all cases of pneumothorax along with hypoxemia and increased peak airway pressures that resolved after ICD placement. Rest of the cases were clinically identified by the presence of crepitus in neck region and later confirmed by chest radiograph and HRCT thorax whichever possible (Figs 1 and 2). Although the mortality was high in the patients in this series (13/15), the primary cause of death was not directly attributed to air-leak syndrome (Table 1).

**Discussion**

Pneumothorax, subcutaneous emphysema, and mediastinal emphysema are components of air-leak syndrome, documented to occur in acute respiratory distress syndrome (ARDS). Contribution of barotrauma, volutrauma, atelectrauma, and biotrauma has been implicated in pathological lung damages in ARDS patients on mechanical ventilation termed as ventilator-induced lung injury (VILI). Clinical and experimental data over the years have supported the use of LPV strategies to prevent VILI and therefore recommended in COVID-19-related ARDS.6 Our case series describes 15 cases of air-leak syndrome, out of which nine patients were on invasive mechanical ventilation. Although LPV was largely achieved, it was insufficient in preventing the development of air-leak syndrome in these patients. The insufficiency of LPV in preventing air-leak syndrome has also been documented in other studies,5 indicating that the pathological lung damages occurring in COVID-19 is much more complicated and multifactorial.

The consistent finding in most patients in this series is of laboratory parameters, suggesting a severe inflammatory state characterized by neutrophilia, lymphopenia, high neutrophil–lymphocyte ratio (NLR), and high inflammatory markers. Previous experience with SARS-CoV-1/ MERS showed that association of pneumothorax was consistent with higher neutrophil counts, more severe disease, and prolonged duration of lung inflammation.6 Earlier studies have attempted to explain pathological processes leading to air-leak syndromes that include consolidation, interstitial pneumonia, and in situ thrombosis leading to friable lung and pleura.6 These findings were demonstrated in our patients on X-ray. However, in situ thrombosis could not be confirmed in all but one patient. Although indirect evidence of thrombosis was suggested by elevated D-dimer levels. A few studies demonstrated the presence of bullae,6 subpleural blebs, ground-glass opacities (GGO),7 crazy paving patterns,6 and pneumatocele6 in HRCT thorax of patients presenting with air-leak syndrome (Fig. 1). Subpleural

Figs 1A to C: (A) Subcutaneous emphysema, pneumomediastinum, subpleural blebs, ground-glass opacities; (B) Ground-glass opacities only; (C) Subcutaneous emphysema, pneumomediastinum, subpleural blebs, ground-glass opacities, crazy paving, reverse halo sign
blebs, GGO, and crazy paving patterns could be demonstrated in HRCT thorax of our patients.

The occurrence of air-leak syndrome in spontaneously breathing patients raises further question on possible association of patient self-inflicted lung injury (P-SILI). Large swings in a minute ventilation could not be avoided, which may have put patients on NIV at risk of P-SILI. The possibility of P-SILI contributing to air-leak syndromes has also been suggested in other studies.9,10 Considering the possible factors putting patients at risk of air-leak syndromes, few probable preventive strategies could be to strictly maintain low driving pressure (plateau pressure—PEEP) and ultra-low tidal volume, prevent all possible patient ventilator asynchrony by maintaining appropriate sedation even in patients on NIV, and prevent cough as far as possible.

**Conclusion**

Our series presents a heterogeneous clinical scenario of air-leak syndrome. In a resource-limited setup where HRCT thorax is not possible in all patients, clinical diagnosis is paramount to identify air-leak syndrome. A high level of alertness, clinical suspicion, and prompt action are mandatory to prevent fatal consequences. Further randomized controlled studies are warranted for better understanding of pathogenesis of air-leak syndromes in COVID-19.

**Highlights**

This series highlights the heterogeneity of COVID-19-induced air-leak syndrome in terms of clinical presentation, day of illness from first symptom, mode of ventilation, and radiological features. However, the laboratory values in all our patients point toward a state of severe inflammatory response characterized by lymphopenia, high NLR, and higher value of other inflammatory markers. Further studies are required to understand the pathophysiology and predictors of air-leak syndrome associated with COVID-19 for better management of these patients.

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