Subcutaneous and mediastinal emphysema, uncommon complications of COVID-19 ARDS: a case series

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Abstract: Coronavirus disease 2019 (COVID-19) adult respiratory distress syndrome (C-ARDS) has led to ventilator related complications such as ventilator associated events (VAE), venous thromboembolic events (VTE), barotrauma, and ultimately profound diffuse pulmonary fibrosis. Barotrauma is one such complication, with reports of spontaneous pneumothorax (PTX) and pneumomediastinum. We present a case series of four patients with severe C-ARDS, complicated by subcutaneous emphysema and mediastinal emphysema with and without pneumothroracies, which required supportive care, except one patient with PTX. Of the four patients only one patient was discharged alive. C-ARDS can induce lung injury, resulting in subcutaneous and mediastinal emphysema, which may not represent a PTX as etiology. The exact mechanism of subcutaneous emphysema and mediastinal emphysema without pneumothoracies in the setting of severe C-ARDS has not been clearly elucidated. Two plausible mechanisms may be related to the "Macklin effect" *vs.* type I and II pneumocyte breakdown when infected by COVID-19. Strategies used to minimize worsening of subcutaneous and mediastinal emphysema with and without pneumothoracies, may be to minimize positive end-expiratory pressure (PEEP), continue to maintain a lung protective strategy (LPS), while utilizing a higher fraction of inspired oxygen (FiO_2) concentration. In the majority of cases, supportive care is usually required, unless PTX presents or tension pneumomediastinum develops, at which time treatment with a thoracostomy tube placement may be necessary or cardiothoracic surgery consultation may be warranted, to perform "gills" procedure.

Keywords: Coronavirus disease 2019 adult respiratory distress syndrome (C-ARDS); subcutaneous mediastinal emphysema; mechanical ventilation (MV); pneumothorax (PTX)

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Introduction

We report four patients, average age of 52.8±2.2 years (*Table 1*), all diagnosed with coronavirus disease 2019 (COVID-19) pneumonia, noted to have markedly elevated D-dimer levels (>20 mcg/mL) with negative procalcitonin levels (<1.0 ng/mL). All patients adhered to lung protective strategy (LPS) mechanical ventilation (MV), targeting plateau pressure (Pplat) of ≤30 cmH_2O and driving pressure (ΔP) of ≤15 cmH_2O. We present the following article in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/jeccm-20-149).

Case presentation

Despite these protective strategies, extensive pneumomediastinum

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Table 1 C-ARDS case series characteristics and therapies

Characteristics and therapies	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	54	52	50	55
Gender	Female	Male	Female	Female
IDBW (kg)	55	67	55	66
COVID-19 positive	Yes	Yes	Yes	Yes
History lung disease	No	No	Yes (asthma)	No
Respiratory rate	30	28	34	14
D-dimer (mcg/mL)	>20	>20	>20	>20
Procalcitonin (ng/mL)	Not drawn	0.28	0.49	0.97
Venous thromboembolism	No	No	Yes (DVT)	Yes (DVT)
Therapeutic anticoagulation	Yes (enoxaparin)	Yes (enoxaparin)	Yes (heparin gtt)	Yes (heparin gtt)
Ejection fraction (%)	55–60	Not performed	65–70	60–65
PASP (mmHg)	38	Not performed	50	41
Discharge destination	Died	Died	Died	LTACH
COVID-19 therapies				
Azithromycin	Yes	Yes	No	No
Remdesivir	No	Yes	Yes	No
Tocilizumab	No	Yes	Yes	Yes
Steroids	Yes	Yes	Yes	Yes
Convalescent plasma	No	Yes	Yes	No
Systemic antibiotics	Yes	Yes	Yes	Yes
Prone	Yes	Yes	Yes	Yes
Paralyzed	Yes	Yes	Yes	Yes
Inhaled epoprostenol	Yes	Yes	Yes	Yes
ECMO	No	Yes	No	No
Radiologic findings				
CXR	Yes	Yes	Yes	Yes
CT	No	No	Yes	Yes
PTX	No	No	No	Yes
Subcutaneous emphysema	Yes	Yes	Yes	Yes
MV characteristics				
Ventilator mode	APRV/PRVC	PRVC	AC	APRV/PRVC
Initial tidal volume (mL)	400	500	340	500
Initial PEEP (cmH_2O)	14	14	16	14
Tidal volume after subcutaneous emphysema or PTX (mL)	300	470	340	500
PEEP after subcutaneous emphysema or PTX (cmH_2O)	10	8	8	5

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics and therapies	Patient 1	Patient 2	Patient 3	Patient 4
P-high (cm)	35	N/A	N/A	37
Peak (cmH_2O)	38	38	39	58
Plateau (cmH_2O)	29	31	37	30
FiO_2	0.65	1.0	0.8	0.5
ΔP (cmH_2O)	20	23	31	20
PaO_2/FiO_2 (mmHg)	103	81	84	76
SpO_2 (%)	95	93	94	88
ICU metrics				
Ventilator days	20	39	31	50
Days proned	19	10	17	21
Ventilator day of pneumomediastinum	14	5	3	30
Tracheostomy	No	Yes	No	Yes

COVID-19, coronavirus disease 2019; C-ARDS, COVID-19 adult respiratory distress syndrome; IDBW, ideal body weight; PASP, pulmonary artery systolic pressure; ECMO, extracorporeal membrane oxygenation; CXR, chest X-ray; CT, computerized tomography; PTX, pneumothorax; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; FiO_2, fractional inspired oxygen; ΔP, driving pressure; PaO_2, partial pressure of oxygen in arterial blood; SpO_2, saturation of peripheral oxygenation; ICU, intensive care unit; DVT, deep vein thrombosis; gtt, infusion; LTACH, long term acute care hospital; mL, milliliter; APRV, airway pressure release ventilation; PRVC, pressure regulated volume control; AC, assist control.

in all four patients was noted on either chest X-ray (CXR) or computerized tomography (CT) of the chest, with one patient noted to have small apical pneumothorax (PTX) bilaterally (*Figures 1*,*2*). Retrospective review of all charts revealed pneumomediastinum and or PTX occurred as early as MV day 3 and as late as day 30. All except patient 3 did not have a preexisting lung condition, of which patient 3 had a history of asthma. Three of the four patients had mild to moderate pulmonary hypertension, with preserved left and right systolic function. Due to rapidly worsening COVID-19 adult respiratory distress syndrome (C-ARDS), difficulty maintaining LPS was documented in the chart, with ΔP's ≥ 20 cmH_2O and Pplat's ≥ 30 in three out of four patients. Strategies to continue to adhere to LPS standards and ΔP's <15 were attempted, in addition to decreasing positive end-expiratory pressure (PEEP) in all four patients (*Table 1*). All patients were proned, paralyzed, trialed on inhaled epoprostenol, received systemic steroids, systemic antibiotics, therapeutic anticoagulation and one or more of the following COVID-19 antiviral or immune modulator therapies: azithromycin, remdesivir, tocilizumab or convalescent plasma. Patients received variable ventilator modes between assist control (AC), pressure regulated volume control (PRVC) and airway pressure release ventilation (APRV). Average ventilator days for four patients was 13±12 days, with two of the four patients undergoing tracheostomy.

Three of the four patients died within the hospitalization, with one patient transferring to long-term acute care facility. The Institutional Review Board (IRB) approved this study and waived the need for consent from individual patients owing to the retrospective nature of the study (IRB ID: STUDY0003052). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013).

Discussion

Patients undergoing MV are at risk for ventilator-induced lung injury (VILI), such as barotrauma, volutrauma, atelectrauma, ergotrauma and biotrauma (1,2). The latter is less understood, in relationship to COVID-19 infection, as profound cytokines release syndrome may further elevate interleukin-6 (IL-6) levels (1,3). Regardless

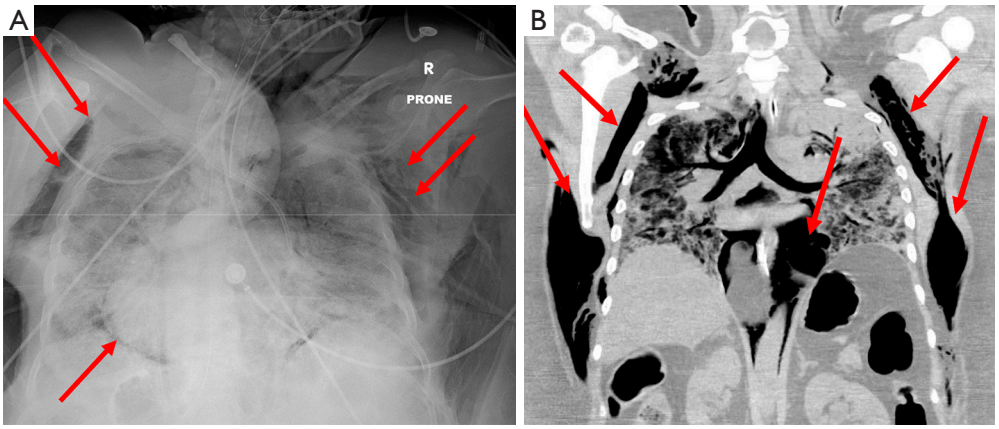

Figure 1 Patient 3 demonstrating extensive subcutaneous emphysema. (A) CXR, extensive subcutaneous emphysema, depicted by red arrows. (B) CT chest (coronal view) extensive subcutaneous emphysema, depicted by red arrows. CXR, chest X-ray; CT, computerized tomography.

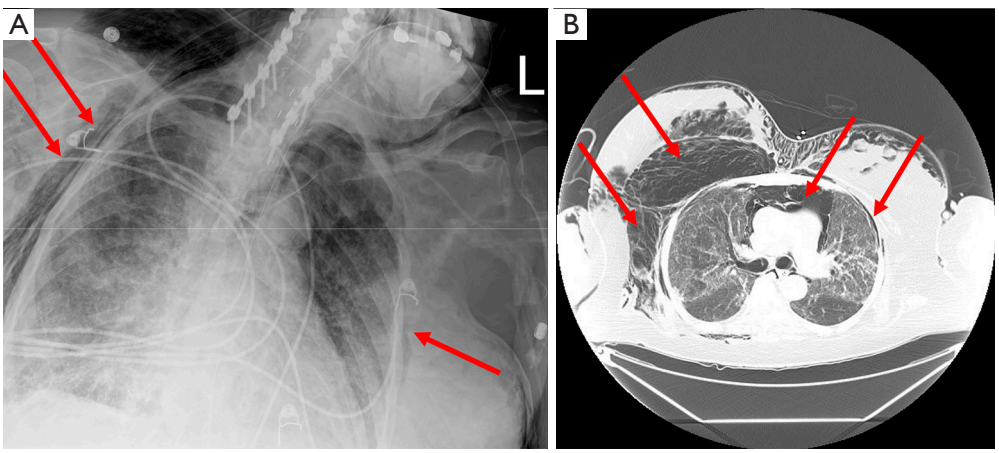

Figure 2 Patient 4 demonstrating extensive subcutaneous emphysema. (A) CXR, extensive subcutaneous emphysema, depicted by red arrows. (B) CT chest extensive subcutaneous emphysema, depicted by red arrows. Additionally, small apical PTX noted on (A). CXR, chest X-ray; CT, computerized tomography; PTX, pneumothorax.

of the exact mechanism of VILI, multiple clinical trials have demonstrated that injured lungs should undergo the following ventilator management strategies to decrease mortality and morbidity: LPSs to include targeting low tidal volume ventilation (LTVV) [tidal volume (VT) 4–8 mL/kg ideal body weight (IDBW), Pplat ≤30 cmH_2O and ΔP ≤15] (4-6). Despite adhering to these guidelines VILI still may occur, resulting in increased mortality, secondary complications of MV, such as PTX, pneumomediastinum, pneumoperitoneum and subcutaneous emphysema (7,8).

Pneumomediastinum is defined as the abnormal presence gas within the mediastinum. This phenomenon was first described by Laennec *et al*. in 1819 and the occurrence of a spontaneous pneumomediastinum by Hamman in 1939 (9). Macklin identified mechanism by which air can dissect by itself via artificial channels, along sheaths of the pulmonary vessels, leading to pneumomediastinum, as demonstrated in experiments in cats and other animals, labeled as the "Macklin effect" (10). Macklin's research further identified that by overinflating alveoli, would cause small ruptures in the alveoli floor, leading to air dissecting along pulmonary vessels, leading to pulmonary interstitial emphysema into the mediastinum. Mechanistically, this would be similar to MV utilizing positive pressure, leading to VILI. Other

reports of etiology of spontaneous pneumomediastinum, may be related to type I and II pneumocyte breakdown when infected by virus (11).

Reported incidence of barotrauma, defined as PTX, pneumomediastinum, pneumoperitoneum or subcutaneous emphysema, in mechanically ventilated ARDS patients can be as high as 2.9% (12). At our institution, our rate of barotrauma in C-ARDS is 1.3%, with a mortality of 75% among this small cohort, suggesting pneumomediastinum may be a predictor of poor outcome.

Risk of developing pneumomediastinum while mechanically ventilated has been primarily related to risk factors for barotrauma and high airway pressures (12). All of our patients had elevated airway pressures and ΔPs, which could have led to development of pneumomediastinum. Although this was mitigated by limiting pressures via PRVC, APRV or AC, one would expect that as compliance worsens, the risk of barotrauma increases, as regional lung tissue is exposed to ventilator forces, in non-dependent and dependent areas at differing phases of ventilation (13). Further review of COVID-19 therapies including steroids, has not shown to contribute to increased risk of VILI, in context of wide use of steroids, since results of the RECOVERY trial report benefit (14,15).

Management of pneumomediastinum can vary, depending on whether hemodynamic embarrassment is occurring, or worsening ventilation or oxygenation is present. For initial evaluation, CXR is diagnostic for extensive pneumomediastinum, but may only identify 75% of cases, whereas CT identifies 100% of cases, often limited by stability of patient to leave intensive care unit (ICU) (16). Once pneumomediastinum is identified, determination of cause, as related to PTX, upper airway injury, tracheobronchial disruption, or esophageal injury exists. If only pneumomediastinum without above complicating features, the clinician may opt to invoke continued conservative therapy, by limiting PEEP as able, utilizing LPS and targeting Pplat ≤30 cmH_2O and ΔP <15.

If conservative therapy fails and inability to ventilate patient or hypotension develops, due to extensive subcutaneous pneumomediastinum and potentially tension pneumomediastinum physiology, consultation of cardiothoracic surgeon may be warranted, to perform "gills" procedure (17). "Gills" procedure may improve ability to ventilate, by relieving tension pneumomediastinum and relieve tension pneumopericardium.

Our four patients were managed conservatively, with LPS, targeting Pplat ≤30 cmH_2O, ΔP <15 cmH_2O and lower PEEP, as tolerated. Only in 1 patient was a possible source of pneumomediastinum identified, which was thought to be related to the endotracheal tube manipulation, all other patients were likely related to combination of barotrauma, breakdown of type I and II pneumocytes and the Macklin effect.

Subcutaneous and mediastinal emphysema is an uncommon finding associated with C-ARDS and is likely related to the combination of barotrauma the "Macklin effect" and breakdown of type I and II pneumocytes related to COVID-19 infection. Conservative management of subcutaneous and mediastinal emphysema is usually all that is required, unless tension pneumomediastinum occurs, or PTX is present.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at http://dx.doi.org/10.21037/jeccm-20-149

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jeccm-20-149). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). The Institutional Review Board of Washington Hospital Center of Washington DC, approved this study and waived the need for informed consent from individual patients owing to the retrospective nature of the study (IRB ID: STUDY0003052). Additionally, all patients are deceased, and all exhaustive attempts have been made to contact the family and they were not accessible. Any potential patient's identifiers have been removed from the description/images and this paper has been anonymized not to cause any harm to the patient or the family. We believe our case would be a great teaching

case for the clinicians.

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