Spontaneous pneumomediastinum, pneumothorax and subcutaneous emphysema in COVID-19 pneumonia: a rare case and literature review

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SUMMARY
Spontaneous pneumomediastinum (SPM) and pneumothorax (PNX) unrelated to positive pressure ventilation has been recently reported as an unusual complication in cases of severe COVID-19 pneumonia. The presumed pathophysiological mechanism is diffuse alveolar injury leading to alveolar rupture and air leak. We present a case of COVID-19 pneumonia complicated on day 13 post admission by SPM, PNX and subcutaneous emphysema in a patient with no identifiable risk factors for such complication. The patient received medical treatment for his COVID-19 infection without the use of an invasive or non-invasive ventilator. Moreover, he is a non-smoker with no lung comorbidities and never reported a cough. He was eventually discharged home in stable condition. A comprehensive literature review revealed 15 cases of SPM developing in patients with COVID-19 pneumonia.

BACKGROUND
By the end of 2019, several cases of pneumonia with unknown aetiology were reported in Wuhan, China.1–4 Most cases progressed to acute respiratory distress syndrome (ARDS).2 Later on, a novel coronavirus was identified, which was named SARS-CoV-2 and the disease implicated by the virus as ‘COVID-19’. Despite travel restrictions and quarantine measures, the number of COVID-19 cases continued to rise worldwide, leading to declaration of a COVID-19 pandemic on 11 March 2020. The intrusive nature of COVID-19 has left the physicians to deal with some of its untoward complications.

Here, we present a rare case of SARS-CoV-2 pneumonia complicated by spontaneous pneumomediastinum (SPM), pneumothorax (PNX) and subcutaneous emphysema (SCE) without the use of an invasive or non-invasive positive pressure ventilator. Despite the potential for a worse outcome, the patient fortunately survived and had a good clinical outcome. After an extensive literature review, we identified 15 cases in the literature that developed SPM with COVID-19 and most had a favourable clinical outcome with close observation and conservative management.

CASE PRESENTATION
A 63-year-old man with a medical history of hypertension and type 2 diabetes mellitus presented to the emergency department with 2 days of worsening non-exertional shortness of breath associated with fever and fatigue. The patient was exposed to positive patients with COVID-19 at work. He then developed upper respiratory tract symptoms and was tested positive 8 days before presentation. He denied cough, chest pain, nausea, vomiting or headaches. He does not consume alcohol, smoke tobacco or use recreational drugs.

On arrival, the physical examination revealed a calm patient with no apparent respiratory distress. His oxygen saturation was 88%–90% on room air, which improved to 96% on a non-rebreather mask at 15 L/min. His respiratory rate was 24 breaths/min, temperature was 37.1°C, pulse 98 bpm and blood pressure 111/61 mm Hg. Examination of the lungs revealed bilateral ronchi; otherwise, the rest of his physical examination was benign.

His initial chest X-ray showed bilateral infiltrates and widening of the mediastinum (figure 1). Therefore, a chest CT was obtained, which showed an extensive bilateral peripheral ground-glass infiltrates, but no mediastinal pathology was noted (figure 2). Laboratory studies were remarkable for normal white cell count 8.1×109/L with a neutrophil count of 90% and lymphocyte count of 5%. His sodium was 132 mmol/L. Arterial blood gas on non-rebreather mask at 15 L/min showed a pH of 7.5, pCO2 of 27.5, pO2 of 180.6 and HCO3 of 21. Reverse transcriptase PCR of COVID-19 was positive. His D-dimer was initially 2276 ng/mL, ferritin 3110 ng/mL, lactate dehydrogenase (LDH) 804 U/L and C reactive protein 6.8 mg/dL. The patient completed a course of ceftriaxone, azithromycin, dexamethasone sodium phosphate, and then methylprednisolone 50 mg and remdesivir.

Throughout hospitalisation, the patient was on supplemental oxygen and underwent frequent self-proning. At no point he required the use of any positive pressure oxygen devices. On hospital day 13, he developed hypothermia, hypotension and elevated lactic acid. Physical examination was pertinent for a crepitus sensation in the neck and an audible crunching sound on cardiac auscultation. His pO2/FiO2 ratio decreased to 116. Repeat CT scan of the chest showed extensive pneumomediastinum (PM) with mass effect on the anterior cardiac border associated with biapical pneumothoraces with persistent ground-glass opacity (figure 3). Additionally, SCE extending superiorly to the base of the bilateral neck, anteriorly to the right chest...
OUTCOME AND FOLLOW-UP
During the following 1 month, the patient showed tremendous clinical improvement. He underwent extensive physical rehabilitation and responded well. His oxygen requirements transitioned to room air. His SCE resolved and the follow-up chest radiography showed a complete resolution of the PNX and significant improvement of the PM (figure 4).

DISCUSSION
SARS-CoV-2 is a positive-stranded RNA virus with a crown-like appearance. It shares 89% of the nucleotide sequence found in the bat SARS-like isolate CoVZXC21 and 82% with the human SARS-CoV. Transmission is from human to human with droplet transmission representing the most common form, although aerosol transmission has also been suggested. Contact with contaminated objects is another source of transmission. The incubation period ranges from 2 to 14 days and symptoms can include fever, malaise, dry cough, dyspnoea, sore throat, nasal congestion, headache, muscle pain, loss of taste and/or smell, diarrhoea and vomiting. Most cases are mild, while others can progress to pneumonia, sepsis, ARDS and/or multiorgan failure.

The virus enters the cells through the Angiotensin-Converting Enzyme 2 (ACE2) receptor, which is extensively expressed in the alveolar cells of the lungs. AN excessive host immune response can be triggered, leading to extensive tissue damage. Interleukin (IL)-6 is considered a main trigger of such an immune response. Another factor is the release of IL-1B, which causes extensive inflammation and eventual fibrosis of the lung. The most frequent radiographical finding is ground-glass opacities occurring in the intermediate/late phase and reticular alterations occurring in the early phase. Distribution is usually bilateral, peripheral and with middle/lower predominance. Consolidation gradually occurs over time.

An uncommon presentation of COVID-19 is the occurrence of SPM, PNX and SCE.

PM, also known as mediastinal emphysema, is the presence of air tracking along the mediastinum. It can be spontaneous (SPM) or traumatic. Mechanical ventilation causing barotrauma, blunt or penetrating trauma to the chest or iatrogenic injury (eg, thoracic surgery) are examples of traumatic PM. SPM can be primary, in which no underlying lung disease is present, or secondary, in which an underlying lung or airway disease that predisposes to air leak is present. Examples of secondary SPM include asthma or cystic fibrosis. PM can also be classified into benign or malignant PM, which can be fatal. Benign forms can turn malignant when, for example, the pressure in the mediastinum rises rapidly and there is no escape route to the neck or retroperitoneum, or air escapes into the bilateral pleural cavities causing bilateral PNX, which can turn into a tension PNX, especially with the presence of cough. Malignant PM can result in mechanical obstruction, which will interfere with the heart and the blood vessels, causing a decrease in circulation.

PM is considered a rare occurrence, with the incidence being 1/25 000 in ages between 5 and 34 years. The majority are men, representing 76% of the cases, and it is more frequent in children (1/800 to 1/15 500). One explanation is that children have loose mediastinal tissue compared with adults who have fibroed sheath, making air migration difficult.

The pathophysiology of SPM is based on the Macklin phenomenon, which describes the occurrence of a large pressure gradient between the marginal alveoli and the lung interstitium, resulting in air leak to the surrounding bronchovascular sheath.
marginal alveoli have their bases in the bronchi, bronchioles, blood vessels and pleura, separated by a connective tissue sheath or the interstitium. This type of alveoli can let air escape into the connective tissue sheath, which can result in pulmonary interstitial emphysema, leading to PM. The other partitional alveoli have pores between the adjacent alveoli, causing air to pass to the adjoining ones, preventing such occurrence.

One mechanism is an increase in intrathoracic pressure, resulting in an increase in intra-alveolar pressure and overinflation of the alveoli without corresponding expansion of the vascular lumen. This will result in a pressure gradient that can rupture the marginal alveoli, leading to air leaking to the interstitium which can track along the perivascular and peribronchial sheath to the hilum of the lung and then to the low pressure mediastinum. Examples of such mechanisms include cough, vomiting, sneezing, defecation or asthma exacerbation.

The second mechanism is caused by a reduction in the calibre of the pulmonary vessels, without a corresponding diminution of the alveolar pressure. This will increase the pressure gradient causing air leak to the sheath. Examples include forced expiration against obstruction which will dam the blood back to the venous side decreasing the vascular calibre, but the alveolar end-expiratory pressure is higher than normal. This can increase the pressure gradient, resulting in air leak and PM.

Both mechanisms can occur simultaneously in which the alveoli is overdistended while the blood calibre is decreased. This will increase the pressure gradient significantly, inducing air leak more easily. An example of such occurrence is when men escaping from a submarine ascend to the surface and hold their breath. This will lessen the pressure on the chest and permit the expansion of the alveoli without equalising its pressure with that on the chest. Holding the breath will stagnate the venous blood therefore, lessening the pulmonary vessel calibre. This will increase the alveolar gradient significantly, inducing PM. Scuba diving is another example that can cause PM. As divers descend, the lung volume decreases and air in the lungs become compressed, resulting in pulmonary oedema and haemorrhage. When divers ascend, the transalveolar pressure increases, resulting in overexpansion of the alveoli and alveolar rupture. Air will then leak along the connective tissue sheath to the lung hilum, causing PM. Risk of occurrence is increased when divers hold their breath as they ascend or in those with obstructive lung disease.

Figure 3 Chest CT showing COVID-19 pneumonia on day 13 post admission. Note the extensive pneumomediastinum with mass effect on the anterior cardiac border. Additionally, there is extensive subcutaneous emphysema extending superiorly to the base of the bilateral neck, anteriorly to the right chest wall and posteriorly to the bilateral scapula. There is mild biapical pneumothorax, right greater than left.

Figure 4 A follow-up chest CT scan 3 weeks after the appearance of the extensive pneumomediastinum. There is interval improvement of the pneumomediastinum as well as complete resolution of the pneumothoraces. Moreover, the subcutaneous emphysema has significantly improved.
## Table 1: Literature review of cases of spontaneous pneumomediastinum developing in patients with COVID-1950–60

<table>
<thead>
<tr>
<th>Date of publishing</th>
<th>Author/country</th>
<th>Cases (n)</th>
<th>Age</th>
<th>Gender</th>
<th>Comorbidities and smoking</th>
<th>Received non-invasive ventilator</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2020</td>
<td>Wang et al.,50 China</td>
<td>1</td>
<td>36</td>
<td>Female</td>
<td>None</td>
<td>Yes</td>
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<td>Conservative</td>
<td>Expired</td>
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<td>April 2020</td>
<td>Wang et al.,51 China</td>
<td>1</td>
<td>62</td>
<td>Male</td>
<td>None</td>
<td>Yes</td>
<td>Spontaneous pneumothorax, pneumomediastinum and subcutaneous emphysema</td>
<td>Conservative</td>
<td>Recovered</td>
</tr>
<tr>
<td>March 2020</td>
<td>Zhou et al.,52 China</td>
<td>1</td>
<td>38</td>
<td>Male</td>
<td>None</td>
<td>No</td>
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</tr>
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<td>May 2020</td>
<td>Mohan et al.,53 USA</td>
<td>1</td>
<td>49</td>
<td>Male</td>
<td>Hypertension and type 2 diabetes</td>
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<td>June 2020</td>
<td>Romano et al.,54 Italy</td>
<td>2</td>
<td>30</td>
<td>Male</td>
<td>Unknown</td>
<td>Unknown</td>
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<td>Recovered</td>
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<tr>
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<td>38</td>
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<td>June 2020</td>
<td>Murillo Brito et al.,56 Spain</td>
<td>1</td>
<td>58</td>
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<tr>
<td>June 2020</td>
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<td>2</td>
<td>78</td>
<td>Female</td>
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<td></td>
<td></td>
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<td>No</td>
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<td>恢复</td>
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<tr>
<td>June 2020</td>
<td>López Vega et al.,68 Spain</td>
<td>3</td>
<td>84</td>
<td>Female</td>
<td>Prosthetic valve replacement, renal failure, heart failure, hypertension and hypercholesterolemia</td>
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<td>Right partial hydropneumothorax, left full hydropneumothorax and pneumomediastinum</td>
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<tr>
<td></td>
<td></td>
<td>67</td>
<td>67</td>
<td>Male</td>
<td>None</td>
<td>No</td>
<td>Bilateral apical pneumothorax and pneumomediastinum</td>
<td>保守治疗</td>
<td>恢复</td>
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<td></td>
<td></td>
<td>73</td>
<td>73</td>
<td>Male</td>
<td>Basal cell epithelioma, obstructive sleep apnea, obesity and depression</td>
<td>Yes</td>
<td>Pneumomediastinum</td>
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<tr>
<td>May 2020</td>
<td>Kolani et al.,69 Morocco</td>
<td>1</td>
<td>23</td>
<td>Female</td>
<td>None</td>
<td>No</td>
<td>Pneumomediastinum</td>
<td>保守治疗</td>
<td>恢复</td>
</tr>
<tr>
<td>May 2020</td>
<td>Lei et al.,70 China</td>
<td>1</td>
<td>64</td>
<td>Male</td>
<td>None</td>
<td>Unknown</td>
<td>Spontaneous pneumomediastinum</td>
<td>保守治疗</td>
<td>恢复</td>
</tr>
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</table>
Other predisposing factors of SPM include tobacco or marijuana smoking, illicit drug use (such as heroin, cocaine or nitrous oxide)\(^{23-25}\), interstitial lung disease, lung infections and vigorous Valsalva manoeuvres.\(^{26}\)

SPM was first described in 1819 by Laennec\(^{26}\) and was further characterised in 1939 by Hamman\(^{27}\) who reported a case series of patients presenting with SPM and SCE. Hamman then described the mediastinal crunching sound heard during auscultation over the cardiac apex and the left sternal border that is synchronous with the heartbeat, which is named the Hamman’s sign.\(^{28}\) Additionally, Muller noted the bubbling crepitations that occur with heart beat and the disappearance of the cardiac dullness.\(^{29}\) Common presenting symptoms include chest pain (60%–100%), dyspnoea (75%), coughing spells (80%), neck pain (36%) or dysphagia, but some cases have no complaints or provoking factors.\(^{30,31}\)

In most cases, the pressure in the mediastinum is relieved by tracking of air to the subcutaneous tissue, resulting in SCE which is detected in 70% of patients with PM.\(^{32}\) The most common site is at the root of the neck, resulting in crepitations. This is because the visceral layer of the deep cervical fascia is continuous with the mediastinum. Free air can also spread to the face, limbs, abdomen and perineum because of the connection among the facial planes. The occurrence of SCE can result in marked relief of the patient’s symptoms.\(^{17}\) Air can also track to the pericardial tissue causing pneumopericardium,\(^{32,33}\) or to the spinal canal causing pneumorrachis\(^{32,34}\) or to the pleural cavities causing PNX.\(^{35}\)

Several cases of upper and lower lung infections have been reported to cause air leak, leading to SPM or PNX. These include fungal pneumonia,\(^{36}\) Mycoplasma pneumoniae,\(^{37}\) staphylococcal pneumonia,\(^{38}\) bronchiolitis obliterans organising pneumonia\(^{39}\) and critical pertussis.\(^{40}\) In HIV infection, Pneumocystis carinii pneumonia and tuberculosis has been reported to cause PNX.\(^{41}\) Viral respiratory infections can rarely cause SPM, PNX and SCE. It has been reported with cytomegalovirus pneumonia,\(^{42}\) measles pneumonia\(^{43}\) and influenza infections.\(^{17,44-48}\) The pathophysiological reasons discussed in those cases follow the Macklin phenomenon. In case of influenza, the cough leads to increased alveolar pressure and eventual rupture. In case of measles, the airway obstruction from secretions or enlarged lymph nodes result in hyperinflation of the alveoli, increasing the pressure gradient.

A retrospective analysis of SARS-CoV database identified 13 patients who developed SPM with or without PNX and SCE at a mean of 19.6±4.6 days from symptom onset.\(^{49}\) No patient had isolated PNX and all were unrelated to the use of invasive or non-invasive positive pressure ventilation. Four patients died, two of them after intubation. Others who survived took a median of 28 days to resolve completely. Analysis showed that high peak serum LDH, which might signify cellular damage, was associated with the development of SPM. The authors postulate that severe diffuse alveolar damage is the cause of the alveolar rupture that results in interstitial emphysema and air tracking along the bronchoalveolar sheath to the mediastinum. Viral load was not related to its development, suggesting that other mechanisms behind viral-induced cytolysis might be important in the pathogenesis of alveolar damage (eg, immunological injury).

Our review of literature has identified 15 cases of SPM developing in patients with COVID-19 (table 1).\(^{50-60}\) These cases illustrate the severity of COVID-19 and its spontaneous complications. Six of these cases were associated with PNX. Another six cases were associated with SCE and one with pneumopericardium. Such complication was identified in some patients during initial presentation to the hospital, while others developed it during the course of the hospitalisation. Our patient developed SPM, PNX and SCE on day 13 of the hospitalisation. Similar to our case, seven of these cases did not use any sort of invasive or non-invasive positive pressure ventilator before the development of the SPM. This suggests that other processes related to COVID-19 might be the mechanism of air leak that progress to SPM, PNX and/or SCE. This suggestion is even supported by the absence of smoking history in all of these patients and the absence of significant comorbidities that can predispose to air leak. Our patient has a history of hypertension and diabetes with no history of lung disease or smoking. Studies suggest that a dysregulation of the immune response seen with SARS-CoV-2, SARS-CoV or MERS-CoV could be a cause of the significant lung injury causing an ARDS pattern.\(^{61,62}\) Fox et al\(^{61}\) published a case series of COVID-19 autopsies and found that the dominant process in all cases was the diffuse alveolar damage with a mononuclear response around thrombosed small vessels. They suggest that the maladaptive immune response plays a significant role in severe COVID-19. This may suggest that the mechanism of air leak seen with COVID-19 could be related to the significant alveolar damage, which make the alveolar wall more prone to rupture. The rupture could be exacerbated by cough or anything that increases the alveolar pressure. In our hospital, we identified eight patients who developed air leak after the application of an invasive or non-invasive positive pressure ventilator. This is the only patient who did not receive such positive pressure oxygenation and did not complain of a cough. This suggests that patients with COVID-19 are at high risk of developing air leaks that can precipitate with anything that increases the alveolar pressure. Therefore, care should be taken to mitigate reasons of increased alveolar pressure such as cough and positive pressure ventilators based on the Macklin phenomenon.

Fortunately, our patient recovered and his follow-up CT scan showed significant improvement. He had no complications during the follow-up period. Additionally, most of the cases identified during the literature review showed spontaneous resolution with conservative management. Eleven patients recovered
and had a favourable clinical course, whereas four patients expired, resulting in a mortality rate of 26%, based on available literature. Therefore, SPM is mostly a self-limiting benign condition and treatment is mainly conservative with bed rest, analgesia and oxygen therapy. However, in all cases, close monitoring is pertinent and any precipitating factors should be identified and managed to avoid potential serious complications. High serum LDH might signify an elevated risk of SPM in patients with COVID-19. Early imaging with chest CT scan has a significant role in prompt diagnosis and determining the reason of respiratory compromise and the pulmonary complications associated with COVID-19. SPM and PNX should be considered in the differential diagnosis of worsening disease in patients with COVID-19. Further research with a larger number of cases is needed in this area.

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