

Case report

Broadening the differential: pneumomediastinum and COVID-19 infection

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SUMMARY

The novel coronavirus (COVID-19) has emerged as a new pathogen responsible for an atypical viral pneumonia, with severe cases progressing to an acute respiratory distress syndrome. In our practice, we have observed patients admitted with COVID-19 pneumonia developing worsening hypoxaemic respiratory failure prompting the need for urgent endotracheal intubation. Here, we present a case of a patient admitted with severe COVID-19 pneumonia who required continuous positive airway pressure support following acute deterioration. However, with the patient requiring an increasing fraction of inspired oxygen (FiO₂), a prompt CT pulmonary angiogram scan was performed to exclude an acute pulmonary embolism. Surprisingly, this revealed a pneumomediastinum. Following a brief admission to the intensive care unit, the patient made a full recovery and was discharged 18 days post admission.

BACKGROUND

The spectrum of COVID-19 infection ranges from mild to severe disease. Of the eight million cases diagnosed worldwide,¹ an estimated 5% are critically unwell.² Cases of hospitalised COVID-19 pneumonia can be complicated by hypoxaemic respiratory failure, a common reason for admission to intensive care unit (ICU). These patients develop an acute respiratory distress syndrome (ARDS) with deterioration often attributed to worsening disease or the so-called 'cytokine storm'.³

However, worsening respiratory failure in patients with COVID-19 pneumonia may have aetiology other than ARDS. A study from Wuhan analysing the characteristics of COVID-19 pneumonia found that 1% of patients had a pneumothorax on chest imaging.⁴ There is also increasing recognition that pulmonary embolism (PE) is a major cause of acute deterioration, with elevated hypercoagulability profiles observed in patients with COVID-19 with acute respiratory failure.^{5,6} Furthermore, superimposed bacterial infection has been attributed as the cause of mortality for 50% of patients who have died with COVID-19.⁷

Our case highlights several learning points which readers may find interesting. First, it emphasises the importance of 'thinking outside the box'. Respiratory deterioration may not always be due to PE or worsening infection; uncommon diagnoses such as pneumomediastinum should be considered. Second, it highlights the importance of thorough scrutiny of chest radiographs. In considering only certain

pathologies, less common diagnoses may be missed, even if their radiographic findings are self-evident! We feel this is something that doctors and medical students in training can empathise with. Third, it is uncommon to see an adult case of a pneumomediastinum, in the absence of trauma or prolonged mechanical ventilation. There are only a handful of reports of pneumomediastinum associated with COVID-19 currently in the literature.⁸⁻¹⁰

CASE PRESENTATION

A 56-year-old man presented to the Emergency Department with a 14-day history of a non-productive cough, dyspnoea and fever. His medical history included type 2 diabetes mellitus, hypertension and seasonal asthma. Social history elicited the patient was a non-smoker and did not consume alcohol. The patient's regular medications included oral antihyperglycaemic agents, an ACE inhibitor and when required, a salbutamol inhaler.

Physical examination revealed the patient was in respiratory distress, with an oxygen saturation (SpO₂) of 88% on room air and a respiratory rate of 40 breaths/min. He was feverish at 37.9°C, with a blood pressure of 151/78 mm Hg and pulse of 103 beats/min. Auscultation of the chest did not reveal any added sounds. Remainder of the clinical examination was unremarkable.

Laboratory blood tests on admission revealed a normal white cell count of $8.4 \times 10^9/L$ ($4.0-10.0 \times 10^9/L$), elevated ferritin at 512 µg/L (30-400 µg/L) and lactate dehydrogenase (LDH) of 348 U/L (0-249 U/L). His D-dimer was raised at 1.16 mg/L fibrinogen equivalent units (FEU) (<0.50 mg/L FEU) with a C-reactive protein (CRP) of 146 mg/L (<5 mg/L). Serum troponin T level was normal. Of note, there was no lymphopenia on admission.

An admission chest X-ray (figure 1) displaying bibasal opacities suspicious for COVID-19 infection was confirmed with subsequent positive reverse-transcriptase PCR testing. Despite conflicting evidence for the efficacy of non-invasive ventilation (NIV) in type 1 respiratory failure not attributed to acute cardiogenic pulmonary oedema,¹¹ based on both national and local guidance,¹² the patient was started on continuous positive airway pressure (CPAP) support after failure on supplemental oxygen therapy. The patient received antibiotic cover with coamoxiclav and clarithromycin.

Following less than 12 hours of CPAP support, the patient was de-escalated to non-invasive supplemental oxygen. Over the next 3 days, the patient improved clinically with reducing oxygen



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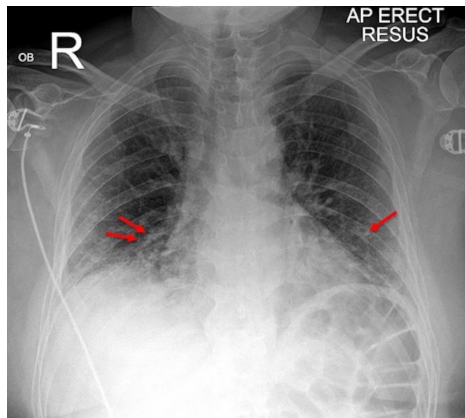


Figure 1 Admission chest X-ray. Subtle bibasal opacities and air bronchograms (more prominent R>L) (see red arrows).

requirements (FiO₂ of 24%) and downtrending laboratory inflammatory markers (CRP falling to 75 mg/L).

On day 5 of admission, the patient showed signs of acute respiratory distress requiring increasing supplemental oxygen therapy at 10–15 L/min to maintain SpO₂ above 90%. This also coincided with worsening blood tests; a lymphocyte count of 0.6×10⁹/L, LDH of 521 U/L, D-dimer of 2.42 mg/L FEU and a CRP of 137 mg/L. A repeat chest X-ray (figure 2) was interpreted and reported as showing no interval change when compared with admission (figure 1). Subsequently, the patient was restarted on CPAP support with antibiotic therapy escalated to piperacillin–tazobactam.

Over the next 48 hours, while on CPAP, the patient continued to have an increasing oxygen requirement (FiO₂ rising from 35% to 60%). A decision was made to perform a CT pulmonary angiogram (CTPA) to investigate for an acute PE as a cause of the patient’s worsening hypoxia. While the CTPA showed no PE, it did reveal to our surprise a moderate pneumomediastinum (figures 3 and 4).

Following further episodes of marked desaturations (SpO₂ below 75%) and increasing oxygen requirements (to an FiO₂ of 100%), the patient was admitted to ICU for high-dependency monitoring. Over this 24 hours ICU admission, the patient did not require endotracheal intubation and was managed on CPAP with low-pressure settings.

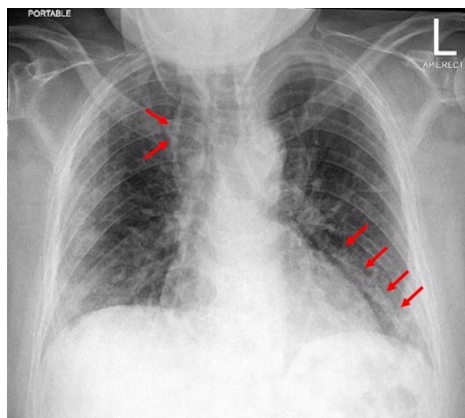


Figure 2 Repeat chest X-ray at day 5. Curvilinear opacities seen along superior mediastinum and heart border, suggestive of extraluminal air (see red arrows).



Figure 3 Coronal cross section of CT pulmonary angiogram showing a pneumomediastinum (see red arrows).

INVESTIGATIONS

The admission chest X-ray (figure 1) showed subtle bibasal air space opacities consistent with COVID-19 pneumonia. When the patient deteriorated on day 5, a repeat chest radiograph was initially reported as being unchanged from admission (figure 2). On further scrutiny of the scan post CTPA, this did show curvilinear lucencies around the mediastinum and heart border, suggesting extraluminal air in the mediastinum and pericardium. This finding was missed by the medical team and radiology.

With the presumption that we did not see any obvious X-ray findings to explain the ongoing hypoxia, a decision was made to proceed to CTPA. This showed no intraluminal filling defects however revealed a moderate pneumomediastinum without a pneumopericardium (figures 3 and 4). A transthoracic echocardiogram demonstrated a normal left ventricular ejection fraction with no evidence of pericardial effusion or tamponade.

DIFFERENTIAL DIAGNOSIS

Patients with COVID-19 pneumonia can become progressively hypoxic coinciding with worsening biochemical (as in our case) and prognostic markers, that is, D-dimer. Chest X-rays typically show worsening consolidation and/or an ARDS picture; this was not the case with the repeat chest X-ray for our patient. On the presumption, there was no obvious radiographic abnormality to explain the worsening hypoxia and the raised D-dimer, it was appropriate to investigate for a PE. This is in concordance with the advice from the European Society of Radiology and the European Society of Thoracic Imaging, who advocate the use of

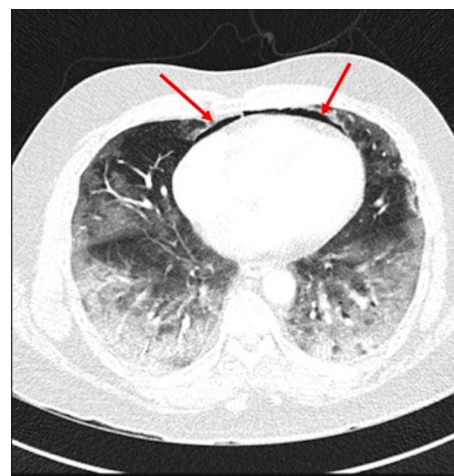


Figure 4 Axial cross section of CT pulmonary angiogram showing a pneumomediastinum (see red arrows). Note the patchy opacities and the linear scarring of both lungs due to COVID-19.

CT imaging in the diagnosis of PE in patients with COVID-19 pneumonia with limited disease extent, requiring supplemental oxygen therapy.¹³ Cross-sectional imaging also has the added advantage of revealing pathologies which are either poorly visualised on a chest X-ray or missed, which in our case revealed a pneumomediastinum.

TREATMENT

Following discussion with the thoracic surgery team, it was advised that the pneumomediastinum should be managed conservatively. Following a slow wean off CPAP and supplemental oxygen therapy, the patient was discharged in good health. The total length of admission was 18 days.

OUTCOME AND FOLLOW-UP

A repeat CT thorax was performed 6 weeks post discharge which showed a complete resolution of the pneumomediastinum.

DISCUSSION

Patients with COVID-19 infection can develop an atypical-like pneumonia with bilateral ground glass opacities seen on chest radiograph.⁴ The disease can be further complicated by a 'cytokine storm', a systemic inflammatory response characterised by the release of proinflammatory markers, specifically tumour necrosis factor, interleukin 6 (IL-6) and IL-1 β .^{3 14} This can exacerbate symptoms, potentially leading to fatal multiorgan failure. This explains the pattern of the sudden acute respiratory deterioration seen in some patients, requiring need for endotracheal intubation.

Our case highlights the importance of considering other causes of an acute respiratory deterioration in a patient with COVID-19 pneumonia. In a study by Chen et al,⁴ they analysed chest imaging of 99 patients with COVID-19 and found 1 patient to have a pneumothorax. This is further supported by a case report from China describing a patient with COVID-19 pneumonia deteriorating suddenly with CT imaging showing a pneumothorax and pneumomediastinum.⁸ Furthermore, a recent case report published in the *Lancet* also described a patient with COVID-19 developing a pneumomediastinum at day 11 of symptoms,⁹ with a similar association described in a recent BMJ case report.¹⁰

Pneumomediastinum describes the presence of gas in the mediastinal cavity. It can either be spontaneous, with no identifiable aetiology or secondary to a precipitating factor.¹⁵ Suggested pathophysiology for pneumomediastinum is the presence of a pressure gradient between the alveoli and lung interstitium leading to alveolar rupture and tracking of air into the mediastinum. This is known as the 'Macklin effect'.¹⁶ The mechanisms thought to create this gradient is an increase in intra-alveolar pressure, seen in coughing or a decrease in pressure in the perialveolar interstitium, seen in extreme respiratory effort.¹⁵ Macklin and Macklin¹⁶ further suggested that inflammatory diseases can also predispose alveolar leakage. Symptoms of respiratory distress coupled with the alveolar damage in COVID-19 make pneumomediastinum a potential complication of the disease.¹⁷

In our case, the patient had no history of trauma or recent instrumentation. Patients with pneumomediastinum most commonly have problem of chest pain followed by dyspnoea¹⁸; the former which was absent in our case. Our patient had underlying asthma, which is a very small risk factor pneumomediastinum. The CT chest did not reveal any perforated hollow viscus or oesophageal rupture to explain the aetiology. Typically, with these patients, there is a preceding history of vomiting or

retching which our patient did not have problem of. Although reported in the literature, it is uncommon for NIV, particularly for short periods, to cause pneumomediastinum (and is more likely to be seen with mechanical ventilation).¹⁹ Indeed, there is a direct correlation between positive airway pressure and the incidence of pneumomediastinum.²⁰ The inspiratory positive airway pressure (IPAP) required to deliver the same tidal volume in NIV is less than that required in invasive mechanical ventilation. Furthermore, in mechanical ventilation, higher IPAP will lead to elevation of the alveolar pressure, ultimately increasing the differential between the alveolar and interstitial pressure, termed the transalveolar pressure, and the threshold for alveolar rupture.²¹ In essence, pulmonary barotrauma is observed at a far higher incidence with mechanical ventilation. Therefore, it is unlikely that barotrauma secondary to CPAP was the sole cause of the pneumomediastinum in our case, especially in view of the patient only receiving 12 hours of CPAP prior to clinical improvement over the next 3 days. Indeed, the repeat chest X-ray (figure 2) which showed mediastinal air was performed when CPAP was restarted on day 5. We cannot term the patient's pneumomediastinum as spontaneous; it occurred in the context of lung injury. However, it highlights the likelihood of COVID-19 infection playing a significant contributory role in its development. Emerging literature certainly supports this hypothesis.⁸⁻¹⁰

It is unclear exactly what the underlying pathophysiology is. We suspect the diffuse alveolar damage seen in severe COVID-19 pneumonia contributes to alveoli rupture. This can lead to dissection of air along bronchovascular bundles into the hila and eventually the mediastinum.²⁰ It is suggested that the development of pneumomediastinum in COVID-19 may signify worsening disease which would be consistent with the patient's deterioration seen on day 5 of admission.^{9 10}

The case also highlights how findings can so easily be missed especially when the said diagnosis is not habitual. A chest radiograph can show findings suggestive of pneumomediastinum in up to 90% of cases.²² In our case, as we were considering other differential diagnoses, we overlooked subtle findings on chest X-ray, which were later confirmed on the CTPA. This emphasises the importance of having a systematic approach to interpreting chest X-rays to avoid missing diagnoses.

Learning points

- ▶ 'Think outside the box'. Respiratory deterioration may not always be due to pulmonary embolism (PE) or worsening infection; uncommon diagnoses such as pneumomediastinum should be considered.
- ▶ Have a low threshold for cross-sectional CT imaging in patients with COVID-19 with increasing oxygen requirements.
- ▶ Adult cases of pneumomediastinum are uncommon in the absence of trauma or prolonged mechanical ventilation. It may signify worsening disease in COVID-19 infection.
- ▶ Most importantly, create a systematic approach when interpreting chest-X rays to avoid missing self-evident diagnoses.

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Reminder of important clinical lesson

published. RP: agreement to be 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.

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