Development of bullous lung disease in a patient with severe COVID-19 pneumonitis

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SUMMARY
A 60-year-old man presented with sudden onset right-sided chest pain and gradually worsening shortness of breath on exertion. Eleven days earlier, he had an admission with COVID-19 pneumonitis requiring 8 days of continuous positive airway pressure. He was tachypnoeic with a respiratory rate of 24 breaths/min, oxygen saturations on room air of 91%. Examination revealed reduced air entry and a resonant percussion note over the right hemithorax. Chest radiograph suggested a complex right pneumothorax; however, a CT chest was notable for widespread right-sided bullous lung disease. After a day of observation on a COVID-19 ward (and a repeat radiograph with a stable appearance), he was discharged with a 2-week follow-up with the respiratory team, safety netting advice and ambulatory oxygen. This case suggests that bullous lung disease may be a complication of severe COVID-19 pneumonitis.

BACKGROUND
As the peak of COVID-19 passes in many countries around the world, clinicians are slowly returning to a state of normalcy with routine outpatient services reopening and medical admissions reflecting a broader case mix. One aspect of the pandemic that clinicians need to be aware is the possible sequelae of both COVID-19 and the interventions used to treat COVID-19-related pneumonitis (namely, invasive and non-invasive ventilation).

This case describes a patient with COVID-19 pneumonitis, with no history of chronic lung disease or smoking, who had been treated with continuous positive airway pressure (CPAP) during admission and discharged. Unilateral severe bullous disease, pneumatocele and secondary pneumothorax developed, leading to readmission within 2 weeks of discharge. Although this patient previously had a video-assisted thoracoscopic (VATS) procedure for a unilateral pleural effusion (7 years prior to this illness), his pre-COVID-19 radiographs were normal with no suggestion of chronic lung disease or bullae. With the degree of respiratory illness induced by SARS-CoV-2, clinicians need to be conscious of possible risks of readmission with bullous lung disease and/or pneumothoraces.

CASE PRESENTATION
A 60-year-old man with no significant cigarette smoking history self-presented to the urgent care centre and was triaged to the emergency department with sudden onset right-sided pleuritic chest pain and shortness of breath. He had previously been admitted for 11 days due to COVID-19 pneumonitis with initial treatment including intravenous ceftriaxone (for 5 days) and titrated oxygen therapy. Due to worsening type 1 respiratory failure, CPAP was required for 8 days. Medical history included alcohol excess, hypertension and high cholesterol. There was no history of cigarette smoking (the patient did use chewing tobacco for 10 years in his youth and stopped at age 40). There was no recreational drug use or family history of chronic lung disease. Notably, this patient previously had a VATS procedure for a right-sided unilateral pleural effusion (7 years prior to this illness); however, his pre-COVID-19 radiographs were completely normal with no suggestion of chronic lung disease nor bullae.

On presentation, he was afebrile and tachypnoeic with a respiratory rate of 24 breaths/min, oxygen saturations on room air of 91% (increased to 96% on 2 L/min nasal cannula), blood pressure of 141/69 mm Hg with a pulse rate of 79 beats/min. On examination, the patient appeared comfortable, speaking in full sentences with no respiratory distress. Trachea was central and there were no distended neck veins. Examination was notable for reduced air entry on the right hemithorax and a resonant percussion note. Auscultation also revealed crackles over the left hemithorax. He had no signs or symptoms of a Deep Vein Thrombosis (DVT).

INVESTIGATIONS
Full blood count showed haemoglobin was 136 g/L, white cell count was 6.2×10^9, lymphocytes were 1.0×10^9 and platelets were 140×10^9. Liver function tests showed a resolution of a transaminitis which was noted on his previous admission with COVID-19. Renal function was within normal range and his C-reactive protein was 6.7 mg/L. These blood results were consistent with the known diagnosis of COVID-19 and made a superimposed bacterial infection unlikely.

The patient was haemodynamically stable throughout the admission and would maintain oxygen saturations of 96% with a respiratory rate of 16 while at rest. However, his oxygen saturation would drop to 88% even walking short distances. An arterial blood gas taken on room air showed ongoing hypoxaemia with a pAO2 of 8.55 kPa, pH of 7.409, pACO2 of 5.17 kPa and bicarbonate was 24.5 mmol/L. Alpha-1-antitrypsin was mildly elevated at 2.2 ruling out alpha-1 antitrypsin deficiency.

DIFFERENTIAL DIAGNOSIS
Pleuritic chest pain in a patient with COVID-19 can be attributable to disease progression; however, the

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The unilateral nature in this case requires exclusion of complications such as pulmonary embolism and pneumothorax. Although it is well reported that patients with severe COVID-19 disease are at increased risk of pulmonary embolism, given that the patient had been previously discharged with prophylaxis for venous thromboembolic disease and had a clear alternative cause of his symptoms, D-dimer was not sent and no contrast arterial phase scan was performed during CT. In this case, chest radiograph (figure 1) showed a possible complex, right-sided pneumothorax. As the patient was stable and had large new bullae on the right lung, a CT (figure 2) was performed within 1 hour of presentation reporting that the suspected pneumothorax was attributed to large bullae and no pneumothorax was present. Four weeks earlier (figure 1), there were no bullous changes noted on radiography. In addition, this patient had a normal baseline chest radiograph in 2015.

In general, bullae can occur as a primary disease, secondary to emphysema or fibrosis, and/or patients can have a genetic predisposition to them. In this patient, there was additional diagnostic complexity as disease was unilateral and had progressed very rapidly. Primary bullous lung disease (also known as vanishing lung syndrome) is common in young, male smokers and involves the displacement of normal lung tissue with giant bullae in a short period of time. Bullae in the context of otherwise normal lungs is termed bullous lung disease.

Given his normal pre-COVID radiographs and his lack of smoking history, chronic emphysema was unlikely. There had been no suggestion of any familial disorders but a late presentation of alpha-1-antitrypsin deficiency was considered given his previous transaminitis. However, there was no evidence of alpha-1 antitrypsin deficiency on serum testing.

On previous workup for a unilateral right pleural effusion, 5 years earlier, tuberculosis and fungal infection were excluded with cultures. Pleural biopsy and fluid cytology showed acute chronic inflammation with no malignant cells nor other abnormalities. In summary, other than severe COVID-19, investigation did not reveal any other underlying disease that could trigger a rapid deterioration of the lung parenchyma.

During his previous admission with severe COVID-19 pneumonitis, the patient underwent 8 days of CPAP. Patients requiring CPAP for COVID-19 pneumonitis can require high positive end expiratory pressures to recruit inflamed and often fluid-filled airways. It is also possible that destruction of the lung tissue secondary to COVID-19 pneumonitis resulted in pressure-induced expansion of the airspaces during CPAP. Although there is a well-established link between positive pressure ventilation and pneumothoraces, there is no proven link between CPAP and the development of bullous lung disease.

In the absence of any other underlying disease being discovered, the working diagnosis was COVID-19 pneumonitis-induced bullous disease.

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**Figure 1**  X-ray chest performed on 27 April 2020 showing bilateral, predominantly middle and lower lung zone air space shadowing which is more confluent in the right lower lung zone, indicative of COVID-19 infection. No evidence of bullous disease or pneumothorax was evident.

**Figure 2**  (A, B) High-resolution CT chest. Coronal and axial images of the chest showing that there is extensive right-sided bullous disease with significant parenchymal changes, likely related to post CPAP changes and/or COVID-19 pneumonitis-related scarring. The presumed right pneumothorax suggested on previous radiograph represented a large bulla on this CT examination.
Bullae and secondary pneumothorax are also need to be considered, as they can be part of the differential diagnosis in a patient who presents with breathlessness after completing treatment for COVID-19 pneumonitis. However, there is no known link between CPAP and the development of new bullous lung disease.

Prior studies of patients who have survived influenza A infection have shown a small percentage who go on to develop small bullous cysts on follow-up chest CT imaging. Moreover, severe Acute Respiratory Distress Syndrome (ARDS) of any cause may result in bullae formation in the lung. Although there have been case reports of recurrent pneumothoraces associated with H1N1 infection, there have been no case reports of the development of symptomatic bullous lung disease complicating H1N1-induced pneumonia.

In addition, this case also demonstrates the importance of obtaining CT imaging of the chest when the initial radiograph suggests a complicated pneumothorax. This will prevent any ill-advised attempts at chest drain insertion which could be complicated by insertion of drainage catheter into a bulla causing a continuous air leak. In this case, the CT scan was suggestive of widespread bullous disease and the patient was managed conservatively. In summary, the development of pneumothoraces and bullous lung disease may be an important cause of morbidity in a subset of patients treated for COVID-19 and should be part of the differential diagnosis in a patient who presents with breathlessness after completing treatment for COVID-19 pneumonitis.

OUTCOME AND FOLLOW-UP
The patient’s CT scan (Figure 3) had highlighted several potential indications for bullectomy including compressed pulmonary parenchyma and involvement of more than one-third of the hemithorax. The patient was discussed with the cardiothoracic surgical team shortly after admission, and as he was stable, it was decided that inpatient treatment was not needed at this time and he could be followed up as an outpatient. A repeat chest radiograph was performed prior to discharge which showed no significant worsening. The patient was given a 2-week follow-up in the ambulatory care unit and 6-week follow-up in respiratory clinic for a repeat CT scan of the chest and pulmonary function tests.

DISCUSSION
This case illustrated one of the possible sequelae of COVID-19 in a patient treated with CPAP. As patients convalesce and recover from severe COVID-19 pneumonitis, clinicians should consider the possibility of bullous lung disease and secondary pneumothorax in patients who present with pleuritic pain and shortness of breath. As COVID-19 has developed, clinicians have become aware of the significant interval change in the lungs in short duration of 4 weeks.

CT imaging is essential in the case of radiographically presumed complex pneumothoraces to prevent erroneous drain insertion into a bulla.

The respiratory sequelae of COVID-19 infection are unknown, thus a high degree of suspicion should be maintained in searching for causes of chronic lung disease in patients who have recovered from the infection and represent.

Bullous lung disease (with or without pneumothorax) should be part of the differential diagnosis in a patient who represents with breathlessness after completing treatment for COVID-19 pneumonitis.

Management for this patient was largely supportive, including the organisation of ambulatory oxygen therapy. The patient was also discharged with ongoing tinzaparin and antiembolism stockings as his mobility was reduced.

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Correction notice This article has been corrected since it was published Online. The author’s name “Dr Rebecca Phillips” has been added to the author byline in this article. The contribution section has also been updated.

Contributors SB admitted the patient on medical take and wrote and edited the majority of the article. AT and RP looked after the patient on the ward and wrote the first draft of some of the article. ASa is a consultant radiologist who reviewed images initially and contributed to radiological description. ASi is the lead consultant in charge of the patients care during both admissions and reviewed article drafts before submission.

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