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COVID-19 infection and nocardiosis causing the death of an adolescent with cystic fibrosis

To the Editor

At the start of the COVID-19 pandemic, individuals with cystic fibrosis (CF) and their families were encouraged to shield as it was feared SARS-CoV-2 infection would have devastating consequences. Over the subsequent two years, the low number of symptomatic infections and the small number of CF deaths has reassured patients, clinicians and authorities to relax restrictions. Children in the United Kingdom, including those with CF are now back in school with few restrictions. We report the distressing case of the death of an adolescent with CF who died following COVID-19 and *Nocardia farcinia* infection. We hope this case will highlight the continued risk to individuals with CF posed by COVID-19.

A 16-year-old boy with CF was hospitalised after a short history of pyrexia, breathlessness, cough and lethargy. He tested positive for SARS-CoV-2 on a PCR test two days earlier after being the household contact of a confirmed case. His CF diagnosis (homozygous Phe508del) was made in infancy due to failure to thrive. He had moderate bronchiectasis and chronic *Pseudomonas aeruginosa* infection. His lung function had deteriorated through adolescence but he had an excellent response to elexacaftor-tezacaftor-ivacaftor with FEV₁ increasing from 43% to 106% over six months.

On admission, he was tachycardic (149 beats/min), tachypnoeic (52 breaths/min), pyrexial (39.0°C) and hypoxic (requiring 8L/min oxygen to maintain SpO₂ ≥92%). He had increased work of breathing including tracheal tug and was struggling to speak in full sentences. Auscultation revealed coarse bilateral crackles and decreased air entry on the left posteriorly. Abdominal examination was normal. Investigations revealed neutrophilia (9.60x10⁹/L), lymphopenia (0.40x10⁹/L), elevated CRP (370mg/L) and hyponatraemia (127mEq/L). A repeat SARS-CoV-2 PCR was positive and chest radiography showed dense left lower lobe (LLL) opacification (Figure 1A). He was commenced on IV tobramycin, IV ceftazidime and IV dexamethasone. Tocilizumab was discussed but not started due to concerns regarding worsening pneumonia or sepsis.

Over the next 24 hours his work of breathing increased and he developed acute confusion which persisted despite management of his hypoxia with non-invasive ventilation. He was therefore intubated and underwent a brain magnetic resonance imaging (MRI) and computerised tomography (CT) pulmonary angiogram. The MRI did not show encephalitis, ischaemia, thrombus or haemorrhage. The CT revealed dense LLL consolidation but no necrosis or pulmonary embolus (Figure 1B). Over the next six days he remained intubated requiring increasing ventilatory support as well as nitric oxide, proning and insertion of a chest drain for pneumothorax. Serial lower airway samples isolated *Nocardia farcinia* prompting his antibiotic regimen to be changed to meropenem and co-trimoxazole. He had not previously isolated this organism. He intermittently required fluid boluses and inotropes for hypotension. Although they did not all occur simultaneously, he developed features of paediatric multisystem inflammatory syndrome (PIMS) including elevated ferritin (4977ng/mL), fibrinogen (>7g/L), lactate dehydrogenase (467U/L), N-terminal pro B-type

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natriuretic peptide (562ng/L), D-dimer (4977ng/mL) and Troponin I (185.5ng/L). His case was discussed with the regional PIMS multi-disciplinary team (MDT) who did not think any additional treatment should be started. On Day 12, due to continued instability and high ventilation requirements, he was transferred to another paediatric ICU for consideration of extracorporeal membranous oxygenation (ECMO) as an escalation of treatment and a possible bridge to transplant.

A further chest CT showed development of necrosis and cavitation in the LLL (Figure 1C) with persistence of the left pneumothorax. The ECMO MDT continued conventional ventilation and performed video-assisted thoracoscopic surgery with debridement and drainage of the left hemithorax. Linezolid was commenced. During the following five days he remained on high pressures and nitric oxide. He did not tolerate prone positioning due to cardiovascular instability. Despite sedation, he was able to open his eyes on command. His clinical condition then deteriorated over the following three days. He became unresponsive and his oxygen saturation and blood gases worsened. His CT head remained normal but CT chest (Figure 1D) again showed LLL necrosis. The ECMO MDT agreed additional treatment would be futile and care should be withdrawn. The family were in agreement and he died peacefully 20 days after admission to hospital, 22 days after testing positive for COVID-19.

Individuals with CF have not been as badly affected by COVID-19 as was first feared. As of January 2023, there had been 1,394 cases of COVID-19 reported to the UK CF Registry (approximately 13% of the UK CF population).[1] Seven percent were hospitalised and there had been ten deaths.[1] The mild illness experienced by most children with COVID-19, including those with respiratory disease has resulted in those with CF no longer being defined as clinically extremely vulnerable. As such, they do not have to shield and are attending school as normal. In contrast, adults with CF in the UK are still classed as extremely clinically vulnerable.

Necrotising pneumonia (NP) is a rare complication of community-acquired pneumonia. Parenchymal cell death caused by ischaemia and microbial toxins results in abscess formation, cavitation and in severe cases pulmonary gangrene. The high mortality relates to sepsis and respiratory failure. Although not common, there are several case series making the association between severe COVID-19 lung disease and the development of lung abscesses,[2] NP[3] and cavitation.[4] These cases are most commonly caused by *Staphylococcus aureus*, *Klebsiella pneumoniae* or *Pseudomonas aeruginosa*. [2–4] It is notable that the underlying pathology of COVID-19 pneumonitis and the parenchymal ischaemia of NP both include vasculitis and microthrombi. Nocardiosis is the term used to describe NP caused the *Nocardia* species.[5] These are a group of opportunistic, gram-positive, branching filamentous bacilli known cause a range of local and disseminated infections usually in immunocompromised hosts.[5] *Nocardia farcinia* is one of this group which has also been reported in individuals with CF.

To our knowledge this is the first published case of NP associated with COVID-19 in an individual with CF and the first associated with *Nocardia* infection. We suspect the combination of cystic fibrosis, COVID-19 pneumonitis and co-infection with *Nocardia farcinia* caused this young man's NP and ultimately his untimely death. We hope this case will highlight individuals with CF of all ages are at risk of severe COVID-19 infection.

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Conflict of Interest Statement

None of the authors have any conflicts of interest relevant to this manuscript.

Approvals

Ethical approval was not required by local policy

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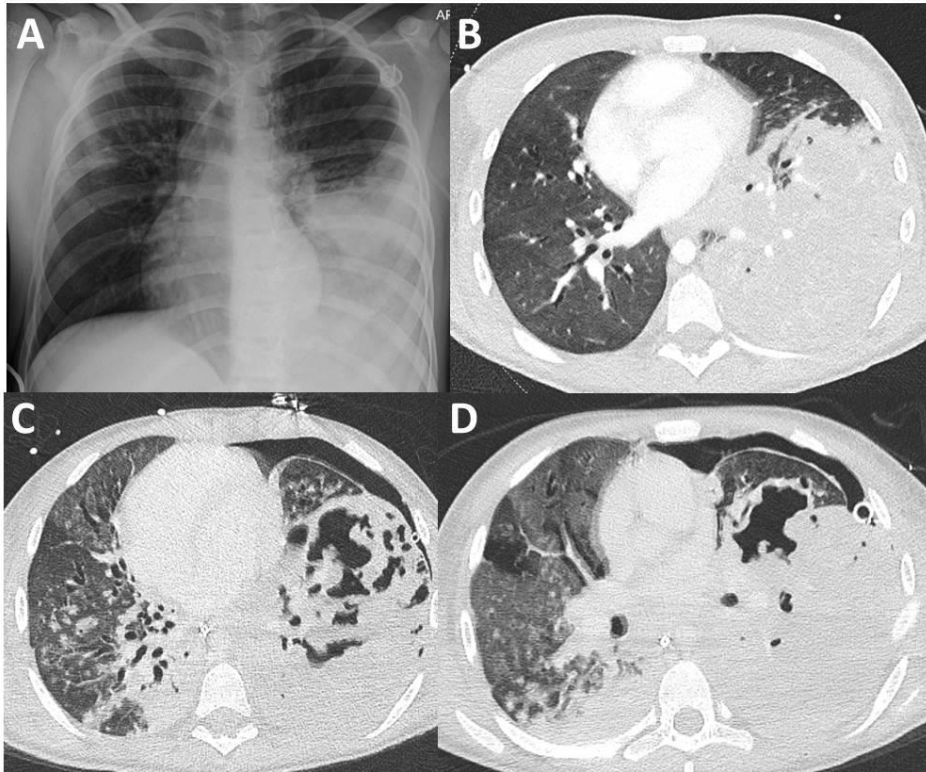


Figure 1. A: Chest x-ray on day 1 of admission showing left lower lobe consolidation. A totally implantable venous access device is also visible. B: High resolution CT chest on day 4 of admission showing dense consolidation of the left lower lobe with minimal aerated parenchyma. Right sided bronchiectasis also present. C&D: Repeat high resolution CT chest scans undertaken on days 13 and 19 showing left lower lobe necrosis and cavitation. A left sided pneumothorax is also seen (different size drains are seen on the two scans).