

Severe progression of idiopathic pulmonary fibrosis post-COVID-19 infection

Naomi Earl , Dillon Schoeneberg, Philip D Davidson

Respiratory Medicine, Tunbridge Wells Hospital, Tunbridge Wells, UK

Correspondence to
Dr Naomi Earl;
naomi.earl@nhs.net

Accepted 28 September 2021

SUMMARY

A 79-year-old woman presented with a week-long history of shortness of breath. She had a background of idiopathic pulmonary fibrosis (IPF) which was stable and had not required any antifibrotic treatment. A month prior to this presentation, she was admitted with COVID-19 pneumonia, with maximal oxygen requirement of 2 L, but was discharged without need for supplemental oxygen. On readmission, she was found to have severe, rapidly progressive pulmonary fibrosis. After all precipitating causes were ruled out, it was felt her recent COVID-19 infection was the exacerbating factor causing progression of pulmonary fibrosis. COVID-19 infection has been hypothesised to cause long term pulmonary fibrosis, but this is the first case highlighting COVID-19 infection as the causative agent exacerbating IPF.

BACKGROUND

At the time of writing, there have been 8 006 660 COVID-19 cases reported in the UK, with 160 824 associated deaths.¹

The spectrum of disease severity with COVID-19 infection is vast. The majority of patients that are hospitalised are with respiratory illness including pneumonia and ARDS. The acute manifestations of COVID-19 have been well documented, however, the long-term sequelae from acute COVID-19 remain speculative. There are many hypotheses around the development of long-term pulmonary fibrosis in this patient group and with it potentially a huge burden on future morbidity in our population.²

It is well documented that chronic lung disease, including idiopathic pulmonary fibrosis (IPF), is a risk factor for poorer prognosis in COVID-19 infection.³ Here, however, we present a case of rapidly progressive pulmonary fibrosis following COVID-19 infection. To our knowledge, there have been no published cases of this kind.

CASE PRESENTATION

A 79-year-old woman presented to the emergency department with a week-long history of worsening shortness of breath. One month prior to this, she had been an inpatient for 10 days being treated for COVID-19 pneumonia. For the first admission, she was managed with a 10-day course of dexamethasone, with a maximal oxygen requirement of 2 L via nasal cannula. Chest radiograph done during admission did not show clear progression of underlying pulmonary fibrosis, and CT imaging was not indicated. She clinically improved during this

admission and on discharge did not require oxygen, with saturations of 94% on room air.

Her medical history included IPF which had been diagnosed in February 2020. This had been managed at the local tertiary interstitial lung disease (ILD) unit and felt to be in early stage of IPF, radiographically and with only mild lung function impairment. She was considered to be stable with a forced vital capacity (FVC) of over 80%, not requiring any treatment/antifibrotic therapy, and with an exercise tolerance of 100 m. She underwent pulmonary function test in October 2020 which showed a normal FVC of 2.08 L (106.9% predicted) and forced expiratory volume in 1 s of 1.73 L (110.1% predicted), with a mildly reduced transfer factor for carbon monoxide (TLCO) of 3.56 mmol/min/KPa (58.3% predicted).

Other medical history of note included hypertension and hypercholesterolaemia. She was a never smoker and an independent and active woman.

On arrival to hospital, she was in type 1 respiratory failure, requiring 35% oxygen to maintain oxygen saturations above 92%.

INVESTIGATIONS

Chest X-ray showed features in keeping with worsening inflammation. Admission blood tests showed a white cell count (WCC) of $6.6 \times 10^9/L$, lymphocytes $1.28 \times 10^9/L$, neutrophils $4.54 \times 10^9/L$, C reactive protein (CRP) 45 mg/L, d dimer 243 ng/mL and a creatinine of 33 $\mu\text{mol/L}$. She was treated for possible superimposed infection with oral doxycycline, although this was clinically of low probability as she remained afebrile and no positive microbiology was obtained throughout her admission. This included repeat viral PCR swabs for COVID-19. She was never productive of sputum and given she remained afebrile no blood cultures were sent. There was also no evidence of her being at risk of aspiration. During admission, her WCC did not significantly rise, and her CRP fluctuated but did not rise above 65 mg/L, which was in keeping with an inflammatory picture. She was also commenced on 6 mg dexamethasone daily. Despite this, there was no clinical improvement. She was further investigated with a high-resolution CT scan and CT pulmonary angiogram which reported markedly progressive fibrotic changes with extensive interlobular septal thickening, honeycombing and traction bronchiectasis, predominantly in the lower lobes (figures 1 and 2). There was no evidence of pulmonary embolism but possible pulmonary artery hypertension. Echocardiogram showed a preserved left ventricular ejection fraction, and confirmed



© BMJ Publishing Group Limited 2021. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Earl N, Schoeneberg D, Davidson PD. *BMJ Case Rep* 2021;**14**:e244472. doi:10.1136/bcr-2021-244472

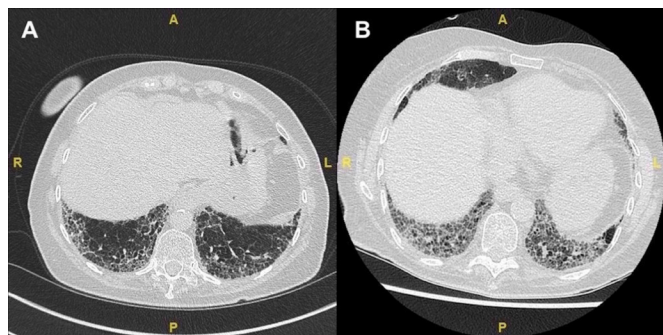


Figure 1 Axial sections from HRCT chest comparing (A) February 2020 (pre-COVID) showing mild peripheral fibrotic changes and (B) from February 2021 (post-COVID) showing markedly advanced progression of bibasal fibrosis, with interlobular septal thickening, honeycombing and traction bronchiectasis. HRCT, high-resolution CT.

pulmonary hypertension with pulmonary artery pressures raised at 55 mm Hg. There were no signs of connective tissue disease and her full autoimmune screen was negative. A bronchoscopy was considered to investigate further, but unfortunately the patient was too hypoxic for this to be done safely.

DIFFERENTIAL DIAGNOSIS

After ruling out infection and pulmonary embolus, her case was discussed with the local ILD tertiary centre. It was felt that her imaging was consistent with rapid progression of her IPF with the pattern still in keeping with usual interstitial pneumonia, consistent with the pre-existing diagnosis of IPF. With no other trigger found, it was felt this rapid progression of pulmonary fibrosis was in response to her recent COVID-19 infection.

TREATMENT

She was treated with high dose intravenous methylprednisolone over 3 days, followed by a subsequent tapering dose of oral prednisolone to treat any reversible inflammation. Unfortunately, she made no improvement clinically and required ongoing long term oxygen therapy. She was discharged on 10L/minute O₂.

OUTCOME AND FOLLOW-UP

She was discharged to a nursing home with palliative care input and long-term oxygen.

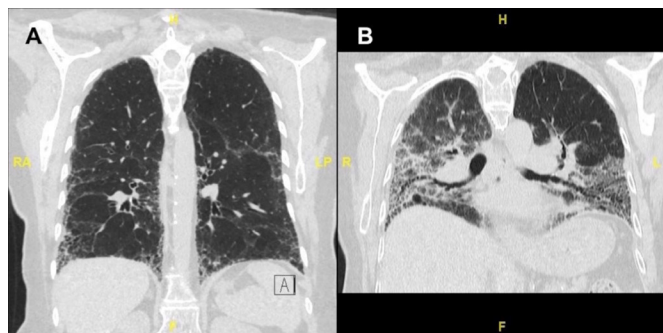


Figure 2 Coronal section from HRCT chest comparing (A) February 2020 (pre-COVID) and (B) from February 2021 (post-COVID) demonstrating the changes mentioned in figure 1, with additional note of reduced lung volumes in (B) secondary to advanced pulmonary fibrosis. HRCT, high-resolution CT.

DISCUSSION

Patients with pulmonary fibrosis are at higher risk of severe infection and mortality from COVID-19 compared with those without.⁴ Advanced fibrosis and poor lung function are associated with severe disease and poorer prognosis in the context of COVID-19 infection.⁵

The long-term sequelae of COVID-19 infection is an evolving and rapidly developing picture. Currently, there is little clinical data on the frequency and mechanism of post COVID-19 fibrosis. A study of patients 2–3 months after discharge from hospital with COVID-19 has seen CT changes keeping with fibrosis occurring at a similar rate as patients with severe acute respiratory syndrome (SARS), H1N1 and H7N9 pneumonias. Additionally, lung function testing abnormalities (largely reduced TLC) was reported in 25% of 55 patients, and ongoing symptoms of fatigue and dyspnoea are being observed.^{6,7} It is unclear what proportion of these changes represent new fibrosis or a late phase COVID-19 recovery. Parallels have been drawn with data from SARS and Middle East respiratory syndrome (MERS) pandemics, where patients were found to have restrictive lung disease and fibrotic CT changes on follow-up.^{5,8,9}

It is also known that other respiratory viruses can provoke progression of IPF including influenza A. The same pathophysiology has been seen in infection with tuberculosis also. Both of these conditions use the CD209L receptor, a C-type lectin also known as the L-SIGN receptor, as a portal of entry which is an alternative mediator of infection in COVID-19, implying possible similarities in pathogenesis.⁵

Pulmonary fibrosis following acute COVID-19 infection has been reported in small studies, mainly in intensive care unit (ICU) patients in the context of acute respiratory distress syndrome (ARDS).¹⁰ The severity of fibrosis correlates with advanced age, extent of comorbidity, severity of disease, length of ICU admission and need for mechanical ventilation.⁶ Similarly SARS patients admitted to ICU were found to have significantly lower FVC and TLC 6 months after discharge than those not requiring ICU.¹¹ However, post-ARDS fibrosis is described as being distinct from IPF—typically not progressing and having a recovery period of approximately 1 year.⁵

Our patient did not require more than 2L of oxygen for the duration of her first hospital admission. On the second admission, her extensive fibrotic changes were disproportionate to the severity of her recent COVID-19, thus, we feel this is not a case of fibrosis post COVID-19 infection but that the COVID-19 infection was the precipitating feature driving her progression of disease.

Our case we present poses a novel finding. There are currently no reported cases of COVID-19 infection causing a delayed rapid progression of IPF, as in this case. The hypothesis that patients with COVID-19 infection are at greater risk of then developing pulmonary fibrosis needs further prospective studies. Furthermore, COVID-19 exacerbating already established ILD needs further exploration and this case acts as a start to this discussion.

Contributors NE developed the concept of the report. All authors acquired and interpreted data for the report. NE and DS drafted the initial report. All authors reviewed and revised the report. PDD supervised the project.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Learning points

- ▶ Our case highlights COVID-19 as an exacerbating factor causing severe progression of idiopathic pulmonary fibrosis.
- ▶ In our case, steroids were of no benefit in management of severely progressive pulmonary fibrosis post COVID-19. Further research into the management of this is required.
- ▶ The long-term burden of pulmonary fibrosis in the context of COVID-19 needs further prospective studies to help establish this and to aid care of this cohort going forward.

Provenance and peer review Not commissioned; externally peer reviewed.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iD

Naomi Earl <http://orcid.org/0000-0002-4261-3900>

REFERENCES

- 1 UK Government. Coronavirus (Covid-19) in the UK, 2021. Available: <https://coronavirus.data.gov.uk/> [Accessed 29 Apr 2021].
- 2 Spagnolo P, Balestro E, Aliberti S, *et al.* Pulmonary fibrosis secondary to COVID-19: a call to arms? *Lancet Respir Med* 2020;8:750–2.
- 3 Çakır Edis E. Chronic pulmonary diseases and COVID-19. *Turk Thorax J* 2020;21:345–9.
- 4 Drake TM, Docherty AB, Harrison EM, *et al.* Outcome of hospitalization for COVID-19 in patients with interstitial lung disease. An international multicenter study. *Am J Respir Crit Care Med* 2020;202:1656–65.
- 5 Crisan-Dabija R, Pavel CA, Popa IV, *et al.* "A Chain Only as Strong as Its Weakest Link": An Up-to-Date Literature Review on the Bidirectional Interaction of Pulmonary Fibrosis and COVID-19. *J Proteome Res* 2020;19:4327–38.
- 6 Rai D, Sharma P, Kumar R. Post covid 19 pulmonary fibrosis- is it reversible? *Indian J Tuberc* 2020.
- 7 Zhao Y-M, Shang Y-M, Song W-B, *et al.* Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020;25:100463.
- 8 Ojo AS, Balogun SA, Williams OT, *et al.* Pulmonary fibrosis in COVID-19 survivors: predictive factors and risk reduction strategies. *Pulm Med* 2020;2020:6175964.
- 9 Zhang P, Li J, Liu H, *et al.* Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. *Bone Res* 2020;8:8.
- 10 Zhou S, Wang Y, Zhu T, *et al.* CT features of coronavirus disease 2019 (COVID-19) pneumonia in 62 patients in Wuhan, China. *AJR Am J Roentgenol* 2020;214:1287–94.
- 11 Hui DS, Joynt GM, Wong KT, *et al.* Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax* 2005;60:401–9.

Copyright 2021 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

Customer Service

If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow