Post-COVID-19 pulmonary fibrosis: A case series and review of literature

Deependra K. Rai¹, Subhash Kumar², Nishant Sahay³

Departments of ¹Pulmonary Medicine, ²Radiology, ³Anaesthesia, AIIMS, Patna, Bihar, India

Abstract
The most common lung problem faced by a post-COVID patient is lung fibrosis. Clinical recovery is generally complete in mild-to-moderately severe COVID-19 cases but a small proportion of patients with severe disease may go on to develop lung fibrosis. Patient groups at the highest risk to develop lung fibrosis are the elderly, especially those requiring ICU stay and mechanical ventilation. No definitive therapy for managing this pulmonary fibrosis exists as of date, even though various options are being explored. This case series highlights three cases of post-COVID lung fibrosis and reviews the existing literature.

Keywords: ARDS, antifibrotic, COVID-19, lung fibrosis

Introduction
A novel coronavirus producing the pandemic of a severe acute respiratory distress (SARS), first reported from China, but currently affecting most of the countries, has been termed as the SARS-CoV-2 and the disease termed as the coronavirus disease-2019 (COVID-19).[1] Since the COVID-19 outbreak there have been a growing number of patients worldwide, who have survived the initial disease but continue to be affected by a range of symptoms of the illness for a variably prolonged period even after they have been declared free of the virus with real-time polymerase chain reaction test (RT-PCR) for COVID-19. At present, management of these COVID-19 sequelae remains one of the most challenging aspects of this disease, and may range from mild symptoms such as fatigue and body aches to severe form of lung fibrosis which may require long term oxygen therapy. The authors, hereby report three cases of post-COVID-19 pulmonary fibrosis and provide a review of the literature.

Case Report

Case 1
An 84-year-old non-smoker, non-diabetic, SARS CoV-2 RT-PCR positive, man, without any comorbidities, was admitted with complaints of low-grade fever (100 F) and dry cough for the last 9 days, followed by breathlessness at rest for the last 2 days. His vitals were, heart rate (HR) of 96 beats/min, respiratory rate (RR) of 28/min, blood pressure (BP) of 142/86 mm Hg and O² saturation of 88% at room air. A plain radiograph showed extensive ground-glass opacification in both lungs with peripheral predominance [Figure 1a]. Hematological examination showed haemoglobin (Hb) 11.9 gm%, total leucocyte count (TLC) 8.38/mm³, platelets 290 thousand/microlitre, neutrophils 76.6% and lymphocytes 19.5%. All investigations have been summarised in Table 1. Patient was started on O₂ inhalation through nasal prong at a rate of 5 litres per minute, Inj Enoxaparin 0.6 ml s/c twice daily, Inj dexamethasone 6 mg once a day and Inj Remdesivir 200 mg on Day1 followed by 100 mg for 4 days. Patient was also given two units of convalescent plasma. On day 7, oxygen requirement increased up to 12 litres/minute but finally decreased from day 12 onwards. Patient had continued oxygen requirement to maintain O₂ saturation more than 90% even...
after day 28 of admission. HRCT chest was performed which showed multiple area of bronchiectasis, bronchiolectasis, coarse reticular opacities, emphysematous changes with architectural distortion and a fine honeycomb-like appearance [Figure 1b]. Provisional diagnosis of post-COVID fibrosis was made and discharged on oxygen, antibiotics, inhaled bronchodilator, low dose of prednisolone 30 mg once a day for a week and pulmonary rehabilitation. He was subsequently lost to follow-up.

**Case 2**

A 65-year-old non-smoker man, without any comorbidity, and SARS CoV-2 RT-PCR positive, presented with fever, dry cough, loss of appetite and dyspnoea for the last 5 days. On examination, he had HR of 102 beats per min, RR of 24 breaths per min, BP of 112/74 mm Hg and O2 saturation of 82% at room air. Blood investigations revealed Hb 14.0 gm%, TLC 9.50/mm³, neutrophils 67.3% and lymphocytes 19.6%. Other investigations are summarised in Table 1. A chest radiograph was near normal barring few areas of peripheral opacities in the left lung [Figure 2a]. He was managed conservatively with supplemental oxygen via nasal prongs, low molecular weight heparin (LMWH), dexamethasone and antipyretics. He improved symptomatically but complained of exertional dyspnea. He was able to maintain O2 saturation of 92% at room air which fell to 88% after walking about 100 meters. HRCT chest was performed which showed diffuse subtle resolving ground glass opacity and fine reticulations with antero-posterior and supero-inferior gradients, with few areas of consolidation and volume loss, ‘fine honeycombing’ especially in the left lung, the CTSS being 20/25 [Figure 2b]. The patient diagnosed to have post-COVID 19 pulmonary fibrosis and discharged on prednisolone 30 mg once a day, multivitamin tablet and pulmonary rehabilitation.

**Case 3**

A 36-year-old non-smoker, obese gentleman, SARS-CoV-2 RT-PCR positive, without any comorbidities, presented with fever and dry cough for the last 6 days followed by shortness of breath. His vitals were- HR 88/min, RR 30/min, BP 138/86 mm Hg and O2 saturation 84% at room air. Blood investigation showed Hb 14.3 gm%, TLC 12.83/mm³, neutrophils 91.7% and lymphocyte 6.9%. Other investigations are summarised in Table 1. A radiograph and HRCT were done at admission, which showed extensive homogeneous ground-glass opacification of both lungs with areas of sparing in the periphery and well as few small islands of lucencies [Figure 3a, b]. Patient was started on O2 inhalation through face mask at rate of 10 litres per minute, Inj. Piperacillin, Remdesivir, and Methyl prednisolone 40 mg twice a day and tablet paracetamol. Two unit of convalescent plasma was also transfused. Patient was transferred to the intensive care unit (ICU) on day 2 of admission after increased O2 requirement. He was started on high-flow nasal cannula with all supportive treatment. Patient gradually improved and was shifted to the ward after 21 days in ICU. At the time of discharge, patient was maintaining saturation of 94% at room air which decreased to 89% after exertion. His HRCT showed significant fibrotic changes with resolving ground-glass opacities [Figure 3c,d]. Patient was discharged on tab prednisolone 30 mg once a day for the 1st week then tapered to 20 mg OD and advised for pulmonary rehabilitation.

---

**Table 1: Summary table of laboratory findings of the three cases**

|                  | Case 1 | Case 2 | Case 3 |
|------------------|--------|--------|--------|
| Hb (g/dl)        | 11.9   | 14.0   | 14.3   |
| Total leucocyte  | 8.38   | 9.5    | 12.83  |
| Platelet         | 291    | 161    | 314    |
| Neutrophil (%)   | 76.8   | 67.3   | 91.7   |
| Lymphocyte       | 19.5   | 19.8   | 6.9    |
| ALT (U/L)        | 20.6   | 436.3  | 134.4  |
| AST (U/L)        | 12.6   | 183.8  | 90.8   |
| Blood urea (mg/dl)| 38.7  | 18.8   | 48.8   |
| Serum Creatinine | 0.74   | 0.47   | 0.62   |
| D-Dimer (mg/ml)  | 0.6    | 1.52   | 0.92   |
| LDH (U/L)        | 516.56 | 695.25 | 800    |
| Ferritin (ng/ml) | 284.84 | 485.26 | 500    |
| CRP (mg/L)       | 120.76 | 116.10 | 140    |
| Procalcitonin (ng/ml) | 0.31 | 3.91  | 0.36   |
| PT/APTT/INR      | 13.9/31.9/1.02 | N/A | 12.37/33.05/0.91 |

---

**Figure 1:** Imaging of 84 years old man (a) frontal chest radiograph at admission showing diffuse ground glass opacities in both lungs, more prominent in the periphery, with some apico-basal gradient; tiny ‘cysts’ or ‘hyperrlucent spaces’ are evident throughout the ground-glass areas (some of them have been marked with thin white arrows) (b) CT thorax, coronal reformatted image, showing extensive reticulations, architectural distortion, ectasis of bronchi and bronchioles and hyperlucency of intervening areas

**Figure 2:** A case of post COVID-19 pulmonary fibrosis is a 65 years old man (a) frontal chest radiograph showing few small peripheral opacities in the left lung (solid white oval) (b) Axial HRCT image showing extensive reticulations, especially in the periphery, prominent pulmonary vessels (thin black arrows), areas of volume loss with clustering of vessels (solid black circle), patchy consolidation (thin dashed black oval), and a fine ‘honeycomb’ appearance (thick dashed black oval)
development of lung fibrosis in COVID-19 is advanced age and this finding is same as in the Middle East Respiratory Syndrome (MERS) and the SARS-CoV1 coronavirus infections. In the present case series, two patients were elderly and this could be a cause for their severe illness with post-COVID pulmonary fibrosis.

Other risk factors include increased disease severity, presence of pre-existing comorbidities such as hypertension, diabetes, and coronary artery disease, and some laboratory features such as lymphopenia, leukocytosis, and an elevated serum lactate dehydrogenase (LDH) level. The serum LDH level, in particular, has been used clinically after acute lung injuries as a disease severity marker. It indicates lung parenchymal destruction and the levels correlates with mortality risk.

HRCT chest performed in our case series showed diffuse ground-glass opacity, reticular opacity, bronchiectasis and architectural distortion. As yet, we do not know the natural course of disease and nor do we have any guideline available which can tell us how to treat post-COVID fibrosis. In a study by Liu et al., HRCT was performed on the last day before discharge, and then after two and four weeks, the latter scans demonstrating the abnormalities (including focal/multiple GGO, consolidation, interlobular septal thickening, subpleural lines and irregular lines) to be gradually resolve =, and the lung lesions of about 64.7% cases were fully resolved at the 4-week follow-up study. Thus, the pulmonary damage induced by COVID-19 appears reversible to at least a group of patients.

The fibrotic disease associated with COVID-19 pneumonia has a spectrum varying from fibrosis associated with organising pneumonia to severe acute lung injury, in which there is evolution to widespread fibrotic change. This offers scope, at least theoretically, to use antifibrotic agents in some of the case. Existing antifibrotic therapies are exclusively used for idiopathic pulmonary fibrosis (IPF) but also in some cases of progressive pulmonary fibrotic disease in disorders other than IPF. Progression assessment in post-COVID fibrosis is also not defined to initiate antifibrotic therapy. Most of the experts believe that antifibrotics should be used in all symptomatic post-COVID fibrotic conditions. Both the commonly available antifibrotic drugs, pirfenidone and nintedanib have been shown to reduce the decline of lung function by approximately 50% in IPF.

Present evidence for these antifibrotic drugs in COVID induce fibrosis is limited and there is an unmet need of high-quality research to formulate recommendations in future. We need Longitudinal study with HRCT chest and PFT to defined the natural course of post-COVID fibrosis.

**Conclusion**

The most common lung problem faced by post-COVID patient is lung fibrosis. Considering the huge worldwide burden of COVID-19, even a small proportion of cases progressing to lung fibrosis is a real concern. Risk of fibrosis development is highest for the elderly patient with severe disease requiring ventilatory...
support. As of now, definitive and scientifically proven preventive or treatment options for this condition do not exist, even though extensive research is ongoing.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, **et al.** A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
2. Kahn NB, Ostergaard DJ, Graham R. AAFP constructs definitions related to primary care. Am Fam Physician 1994;50:1211-5.
3. Starfield B, Simpson L. Primary care as part of US health services reform. JAMA 1993;269:3136-9.
4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He ZX, **et al.** Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708‑20.
5. Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, **et al.** Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol 2020;92:491-4.
6. Xu J, Gonzalez ET, Iyer SS, Mac V, Mora AL, Sutliff RL, **et al.** Use of senescence-accelerated mouse model in bleomycin-induced lung injury suggests that bone marrow-derived cells can alter the outcome of lung injury in aged mice. J Gerontol A Biol Sci Med Sci 2009;64:731-9.
7. Das KM, Lee EY, Singh R, Enani MA, Al Dossari K, Van Gorkom K, **et al.** Follow-up chest radiographic findings in patients with MERS-CoV after recovery. Indian J Radiol Imaging 2017;27:342-9.
8. Liu X, Zhou H, Zhou Y, Wu X, Zhao Y, Lu Y, **et al.** Risk factors associated with disease severity and length of hospital stay in COVID-19 patients. J Infect 2020;81:e95-7.
9. Liu C, Ye L, Xia R, Zheng X, Yuan C, Wang Z, **et al.** Chest CT and clinical follow-up of discharged patients with COVID-19 in Wenzhou City, Zhejiang, China. Ann Am Thorac Soc 2020;17:1231-7.
10. Rai DK, Sharma P, Kumar R. Post covid 19 pulmonary fibrosis- Is it reversible? Indian J Tuberc 2020. doi: 10.1016/j.ijtb.2020.11.003.
11. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SL, Inoue Y, **et al.** Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381:1718-27.
12. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, **et al.** A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083-92.
13. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, **et al.** Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-82.
14. Raghu G, Wilson KC. COVID-19 interstitial pneumonia: Monitoring the clinical course in survivors. Lancet Respir Med 2020;8:839-42.