

A Case of End-stage Post-Covid-19 Pulmonary Fibrosis in a Kenyan Hospital

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Abstract

Post-COVID-19 pulmonary fibrosis (PC19-PF) is one of the severe manifestations of the “long COVID syndrome,” with a prevalence of about 7%, and is characterized by the presence of persistent fibrotic lung changes (on a CT scan of the lungs) associated with impairment of pulmonary function. Some of the risk factors for PC19-PF include advanced age, the occurrence of acute respiratory distress syndrome (ARDS), the need for supplemental oxygen, mechanical ventilation, smoking, etc. Antifibrotic agents, e.g., pirfenidone and nintedanib, are increasingly being used in the management of PC19-PF with good outcomes, but larger studies on efficacy and benefit are needed. In this study, we present the case of a young woman in a rural Kenyan hospital found to have end-stage PC19-PF needing long-term oxygen therapy to highlight the reality of PC19-PF in the post-COVID-19 clinical era.

Keywords: post-COVID-19 pulmonary fibrosis, long COVID syndrome, pirfenidone, nintedanib, *cor pulmonale*, long-term oxygen therapy, Kenya.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic resulted in a growing number of survivors experiencing a wide range of symptoms long after they had recovered from the primary disease, i.e., the so-called “long COVID syndrome.” [1]. A 2022 meta-analysis and systematic review of long COVID syndrome showed an estimated global prevalence of 43%. [2]. Post-COVID-19 pulmonary fibrosis (PC19-PF) is one of the main presentations of long COVID syndrome [3]. It is characterized by the presence of persistent fibrotic lung changes (on a CT scan of the lungs) associated with impairment of pulmonary function during patient follow-up [4]. A recent systematic review showed a prevalence of PC19-PF of about 7% among the included studies, although this could be higher [5]. The risk factors for PC19-PF include advanced age, male gender, active smoking, a history of chronic alcoholism, diabetes, respiratory or cardiovascular diseases, the presence of acute respiratory distress syndrome (ARDS), the need for oxygen supplementation, prolonged ICU stay, mechanical ventilation, high levels of inflammatory markers, etc. [6]. The pathogenesis of PC19-PF involves an initial phase of lung injury followed by an acute inflammatory response and repair efforts. The acute inflammatory phase is characterized by elevated levels of pro-inflammatory cytokines (i.e., the cytokine storm). These cytokines, e.g., interleukin-6 (IL-6), interleukin-1 (IL-1), interleukin-17 (IL-17), and tumor necrosis factor-alpha (TNF- α), play a very significant role in lung damage, leading to ARDS [7]. The repair mechanisms primarily relate to the release of transforming growth factor (TGF- β 1) which causes angiogenesis, fibroblast activation, myofibroblast conversion, and collagen deposition and may lead to a restoration of normal lung architecture or lung fibrosis with the distortion of lung architecture and irreversible lung damage [8]. This progressively leads to respiratory failure, pulmonary hypertension, *cor pulmonale*, and eventual death. Patients with PC19-PF present with cough, dyspnea, exertional dyspnea, and poor saturation for at least 12 weeks after the diagnosis of COVID-19 [9]. Diagnostic tests include a pulmonary function test, which shows a restrictive pattern with reduced diffusion

capacity (also useful for screening at-risk patients) [10], and a CT scan (i.e., a high-resolution CT [HRCT] scan of the lungs, preferably). Typical features on an HRCT scan include predominantly ground glass, fibrotic, and mixed ground glass, and fibrotic changes predominantly in the lung bases [11]. The management of PC19-PF should be a multidisciplinary decision. Due to their antifibrotic effects and experience with use in idiopathic pulmonary fibrosis (IPF), pirfenidone and nintedanib are currently being used in multiple clinical trials for PC19-PF, already with promising outcomes [12]. Other therapies being investigated include anti-interleukin agents, immunosuppressants (e.g., mycophenolate mofetil [MMF]), and experimental compounds like sirolimus, saracatinib, buloxybutide, and resveratrol [13]. End-stage cases of PC19-PF (with pulmonary hypertension and cor pulmonale) should have individualized treatment decisions. These include pulmonary rehabilitation programs, long-term oxygen therapy, and lung transplantation, where possible [14, 15]. Similarities and differences between IPF and PC19-PF are well established. Nonetheless, the current status of the management of PC19-PF borrows a lot from the management of IPF [16].

Case Summary

Presenting illness and physical examination

A 43-year-old single mother of 3, a business lady from Mzee-Wanyama, Nakuru County, Kenya, presented to us for the first time in anasarca and profound hypoxia. This was preceded by a five-day history of a dry cough, right-sided pleuritic chest pains, and progressive dyspnea (presently at modified Medical Research Council dyspnea scale, grade 4). She had no night sweats, fevers, or weight loss. She had been diagnosed elsewhere with pulmonary fibrosis in August 2022 based on clinical features and a CT scan of the chest (see figure 1) and put on pirfenidone 267 mg thrice daily (she's been taking 250 mg thrice daily due to logistical challenges). She had a normal echocardiogram then. Importantly, she had a non-severe COVID-19 infection confirmed by a COVID-19 PCR assay of a nasal swab in December 2020 (during the first COVID-19 wave), which was marked by gastrointestinal, musculoskeletal, and flu-like symptoms. She also developed viral pneumonia-like symptoms during the second and third waves of COVID-19 and was treated at home in each case with supportive therapy. She was never vaccinated against COVID-19 due to her personal religious convictions. In July 2022, she developed recurrent and progressive dry cough and exertional dyspnea, leading to the diagnosis of pulmonary fibrosis in August 2022. From around December 2023 on, she developed recurrent hypoxia (oxygen saturation by pulse oximetry ranging between 80-88% in room air). A high-resolution CT scan of the chest done in January 2024 showed worsened bilateral bi-basal sub-pleural fibrosis. (see figure 2). She had no history of smoking, ethanol use, previous treatment for tuberculosis, or prolonged exposure to obvious inhalable environmental pollutants. Clinically, she was profoundly hypoxic with an oxygen saturation of 60-63% in room air, which normalized to 96-99% with supplemental oxygen at 4 L/min by nasal prongs. She was normotensive, afebrile, with grade 3 finger clubbing (see figure 3), and in obvious anasarca. She had coarse bilateral lung crackles with scattered wheezes, reduced air entry in the right lower lung zone, elevated jugular venous pressure to about 12 cm, a right parasternal heave, normal S1 and S2 heart sounds with a loud P2, and a grade 4/6 tricuspid regurgitation murmur. She was in sinus rhythm. She had a tender, pulsatile hepatomegaly with a liver span of about 16 cm, moderate ascites, but a non-tender abdomen. The rest of the exam was unremarkable.

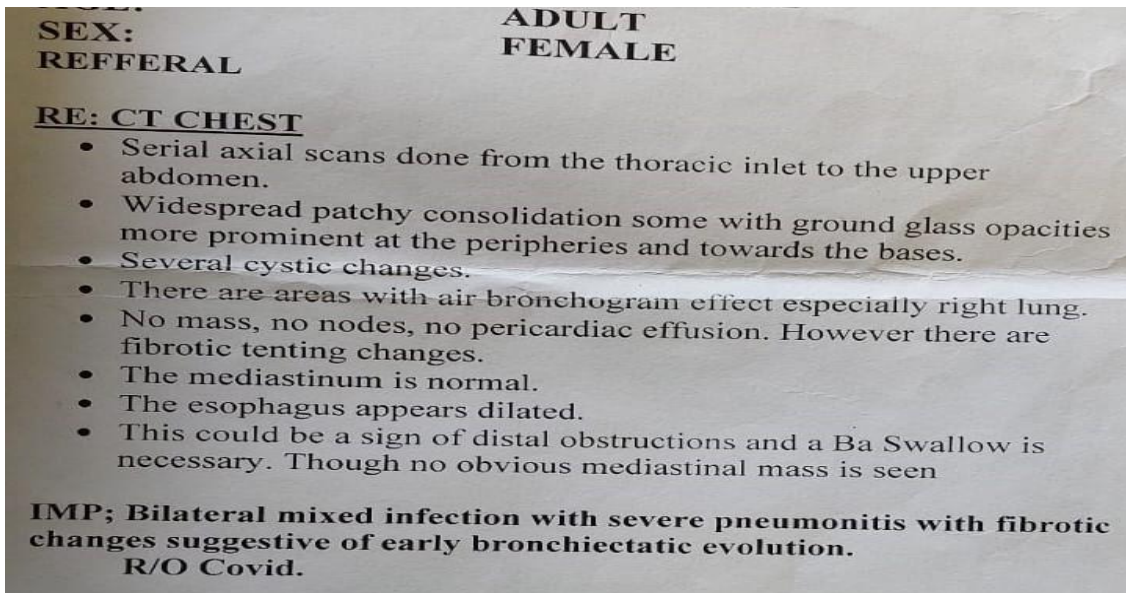


Figure 1: A CT chest report in August 2022 showing features of pulmonary fibrosis. (CT scan images are not available.)

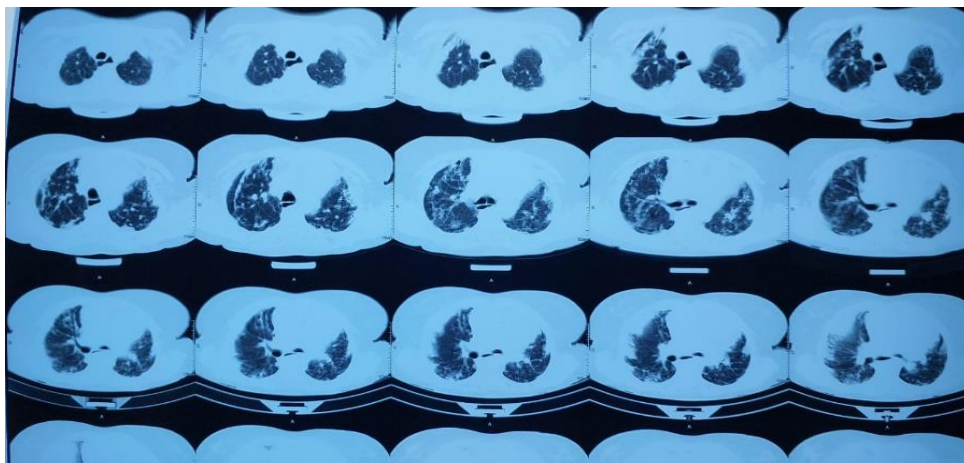


Figure 2: HRCT of the lungs showing significant bilateral subpleural fibrosis involving both lungs and most marked in the lung bases.



Figure 3: Finger clubbing grade 3: -the nails take an obvious curvature and appear as biconvex laterally.

Grading of finger clubbing: -

Grade 1: The nail bed becomes soft. Grade 2: There are changes in the angle of the nail fold with loss of Schamroth window.

Grade 3: The nail takes on a more obvious curve.

Grade 4: The end of the finger becomes thicker (club-like).

Diagnostic work-up

A complete blood count was normal with a hemoglobin of 16 g/dL (we'll monitor for hypoxia-induced secondary polycythemia). A CXR showed bilateral reticular infiltrates predominantly in the bases of the lungs and right mid- and lower-lobe consolidation. See figure 4. An EKG showed a normal sinus rhythm, a right-axis deviation, a right ventricular strain pattern, and P-pulmonale (right atrial enlargement). A point-of-care cardiac ultrasound showed severely dilated right atrium and ventricle with severe tricuspid regurgitation, severely reduced right ventricular systolic function, a reversed Bernheim effect, and an estimated left ventricular systolic function of about 55%. Sputum induction for acid fast bacilli was unsuccessful. An attempted pulmonary function test as well as a 6-minute walking test were impossible to perform due to severe exertional dyspnea but will be tried in her subsequent clinic visits.

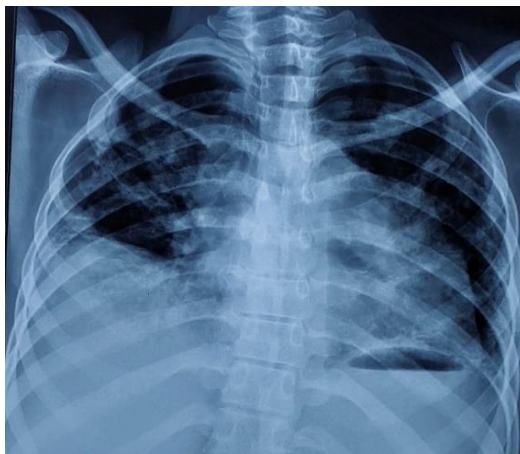


Figure 4: A CXR showing bilateral reticular infiltrates predominantly in the bases of the lungs and right mid- and lower-lobe consolidation.

Diagnosis, Management, and Follow-up

We assessed her to have post-Covid-19 severe (end-stage) pulmonary fibrosis complicated with severe pulmonary hypertension (WHO Group 3), currently in severe *cor pulmonale* and hypoxia. Her current decompensated status was precipitated by community-acquired pneumonia against a background of progressive pulmonary fibrosis. We managed her with supplemental oxygen, diuresis with furosemide and spironolactone, antibiotics (intravenous ceftriaxone and azithromycin, then oral co-amoxiclav), anticoagulation with warfarin, sildenafil for the pulmonary hypertension, pirfenidone at 250 mg thrice daily (only pirfenidone 200 mg tablets available locally), pneumococcal vaccination with PVC-13 (she'll also be given PPSV-23 later), chest physiotherapy with incentive spirometry, and other supportive care. We discussed with her and her family the advanced nature of the disease and the need for long-term oxygen therapy (LTOT) and a referral to a pulmonologist for evaluation for possible candidacy for a lung transplant in the future. We secured her an oxygen concentrator for home use by nasal prongs and discharged her one week later. We'll follow her up in the medical clinic.

Discussion

Our patient developed pulmonary fibrosis about two years after her first confirmed COVID-19 infection, on the background of two more viral pneumonia-like illnesses occurring during the second and third waves of COVID-19 in Kenya. The latter two could also have been due to the COVID-19 infection. She had no plausible alternative risk factors for pulmonary fibrosis. She was never vaccinated against COVID-19 due to personal convictions. Cases of PC19-PF have increasingly been reported in the literature from about two years since the onset of COVID-19, although CT scan evidence of lung fibrosis may appear much earlier in some patients [17]. A population-based study in Korea demonstrated that vaccination against COVID-19 decreased the incidence of post-COVID-19 interstitial lung disease (which includes PC19-PF), i.e., an incidence of 0.8 vs. 1.83 per 1000 person-years between the vaccination cohort and the controls, respectively [18]. Despite our patient being on pirfenidone 250 mg thrice daily since August 2022 (when the pulmonary fibrosis was first demonstrated on a CT scan), she has had progressive worsening of the

pulmonary fibrosis until she's currently oxygen-dependent. It is possible that she started the pirfenidone when the fibrosis was already advanced or that she was not compliant with the medication due to cost issues. Besides, the ideal dosage of pirfenidone is 2400 mg/day [19], although some studies have suggested a similar benefit profile with lower dosages of ≤ 1200 mg/day [20]. Our patient has been unable to escalate the dose of pirfenidone from 750 mg/day to 2400 mg/day (or >1200 mg/day) due to its expensive retail price. Some studies have demonstrated that early treatment with pirfenidone in patients with post-COVID-19 pneumonia may reduce the risk of developing pulmonary fibrosis [21], while also improving lung functions in patients with established fibrosis [12]. Larger randomized clinical trials are needed to unequivocally settle the benefit question of pirfenidone in PC19-PF. For our patient, we have elected to keep her on pirfenidone as we have no other alternative. She is currently in end-stage pulmonary fibrosis with severe *cor pulmonale*, needing long-term oxygen therapy and rationalized supportive care for her WHO Group 3 pulmonary hypertension as per standard guidelines [22]. She will be evaluated by a multidisciplinary team for candidacy for a lung transplant [15], although this option is prohibitively expensive and currently unavailable in Kenya.

Conclusion

PC19-PF is increasingly becoming a medical reality of the post-COVID-19 era and is associated with a significant limitation of cardiopulmonary function in affected patients. Early diagnosis and use of antifibrotic agents like pirfenidone and nintedanib may reduce the rate of progression of pulmonary fibrosis, but more studies are needed to fully elicit their effectiveness in PC19-PF. Patients with PC19-PF need to be managed by a multidisciplinary team to realistically rationalize their treatment goals.

Acknowledgement

The author acknowledges Mr. Seth Manera, Dr. Collins P. Malalu, and the nursing staff in the female ward of St. Joseph Rift Valley Hospital, Gilgil, for their help with managing this patient.

Informed Consent

Informed consent was obtained from the patient to publish this case study.

Funding

The author has no funding sources to declare.

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