Case Report

COVID-19 lung lesion treated with pirfenidone and effective rehabilitation: A Case Report

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Abstract

SARS-CoV-2 leads to an inflammatory and fibrotic state in the lungs which can be the cause of death and even in those who survive cause a functional limitation.

A male patient of 28 years with COVID-19 was treated with nitazoxanide 500 mg 6 hourly, ibuprofen 500 mg 8 hourly, levofloxacin 500 mg and vitamin D 4,000 IU 24 hourly, and pirfenidone (K-LP) 1,200 mg 12 hourly. The patient was ventilated and extubated after 13 days in the intensive care unit. He was then immersed in a strict rehabilitation programme based on re-teaching the diaphragmatic respiratory pattern.

Pirfenidone at a dose of 1,200 mg twice a day could be considered as a valid option to reduce lung fibrosis caused by the SARS-CoV-2 virus. To ensure optimal recovery, pulmonary rehabilitation therapy should be added to the management.

Keywords: *case report, COVID-19, lung fibrosis, pirfenidone, rehabilitation.*

Introduction

One condition associated with coronavirus disease (COVID-19) severity is hyper-inflammation, a phenomenon observed in patients who are unable to control the infection and its consequences in the early stages because of therapeutic limitations, delayed medical care, or biological idiosyncrasies. In any case, the Th1 profile inflammatory response exacerbation is manifest, with limited possibilities for resolution.[1]

Pirfenidone (5-methyl-1-phenyl-2-1H–pyridone), a small synthetic molecule with a molecular weight of 185.2 kDa, is an anti-inflammatory and anti-fibrotic drug approved for the treatment of idiopathic pulmonary fibrosis.[2] Pirfenidone treatment might protect patients infected with

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SARS-CoV-2 from acute respiratory distress syndrome (ARDS) and other morbidities related to inflammation in general, thereby improving patient outcomes and reducing post-COVID fibrotic sequelae. Pirfenidone can mitigate fibroblast proliferation and cut the production of proteins and cytokines associated with fibrosis. It also mitigates the increase in biosynthesis and accumulation of extracellular matrix in response to cytokines and growth factors such as transforming growth factor beta and platelet-derived growth factor.[3] This article reports a successful evolution of a critical patient with COVID-19 who recovered lung function after receiving pirfenidone followed by a rehabilitation programme.

Case report

A man aged 28 years developed dyspnea, backache, tiredness and sleepiness, and O_2 desaturation on November 17th, 2020. qPCR test done on the same day confirmed a COVID-19 diagnosis. The patient was admitted to hospital on 18th November and prescribed 500 mg of nitazoxanide 6 hourly, 500 mg of ibuprofen 8 hourly, 500 mg of levofloxacin and 4,000 IU of vitamin D every 24 hours, and 1,200 mg of pirfenidone (K-LP) every 12 hours for seven days. Since pirfenidone is a drug for the treatment of idiopathic pulmonary fibrosis, the patient signed an ethical clearance for its use in this circumstance.

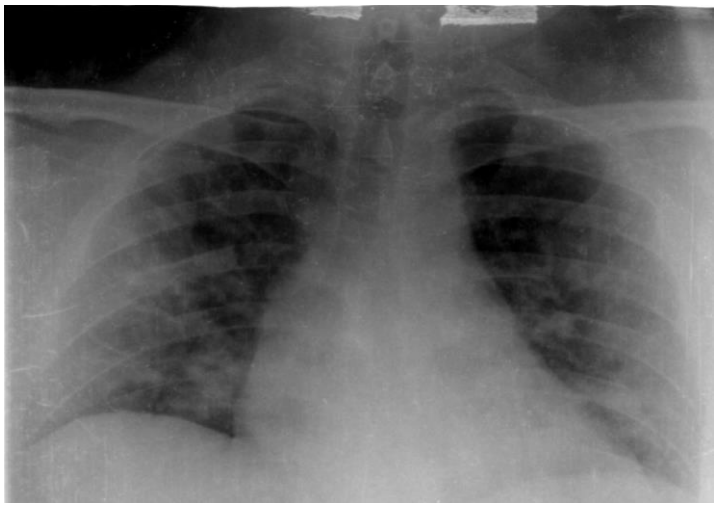

Figure 1: Initial Chest-X ray

On November 18th the patient became delirious. Laboratory tests taken at home showed erythrocytes 6.2 x 10^6/µl, Hb: 18.1 g/dl, platelets: 260,000/µl, leucocytes: 9800/µl, lymphocytes: 1666/µl, glucose: 167 md/dl, cholesterol: 132 md/dl, triglycerides: 210 md/dl. His O2 saturation dropped to 84% and the chest radiography (Figure 1) and computed tomography (CT) of the thorax showing major changes in the lungs (Figure 2).

The patient's condition deteriorated while using an O_2 concentrator set at 5 L/min, with his heart rate (HR) reaching 85 bpm and a more severe deterioration of O_2 to 79%. When the patient was hospitalized on November 18th, his D-dimer was 9,862 ng/mL and ferritin, 575.9 ng/mL. On November 21st he was in haemodynamic failure with severe ARDS requiring propofol, dexmedetomidine, buprenorphine, cisatracurium, and amines. His blood pressure was 81/78 mmHg and HR was 70 bpm. He was placed in the prone position with the following ventilator conditions: mode Assist/Control with a tidal volume of 480 mL, a respiratory rate of 28 per min, a positive end-expiratory pressure of 12 cmH_2O, a fraction of inspired oxygen (FiO_2) of 100, an inspiratory/expiratory rate of 1.18, a P_{PLAT} of 37 mmHg, and a SAT O_2 of 93%. The patient received pirfenidone until November 23rd. On November 27th the amines were stopped, and the

patient extubated on November 30th. The control chest radiogram was taken on December 17th (Figure 3). There were no adverse events using pirfenidone at the recommended dose.

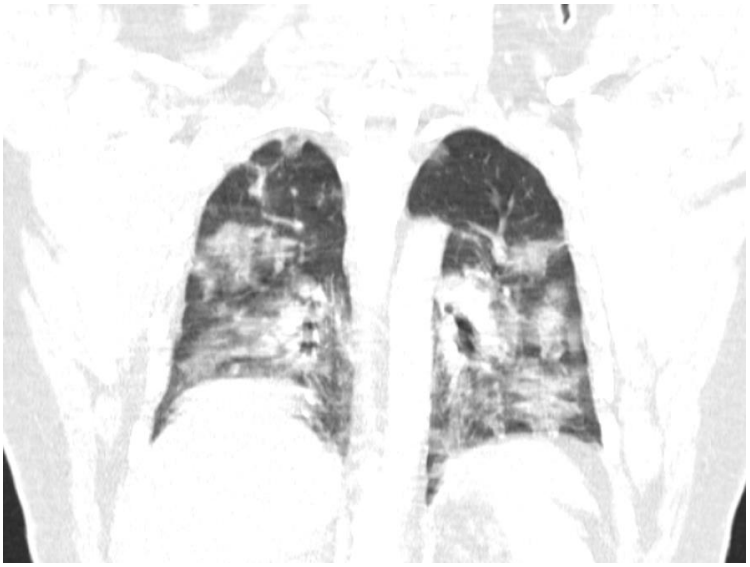

Figure 2: Initial computed tomography of the thorax

The patient was immersed in a strict rehabilitation program based on re-teaching the diaphragmatic respiratory pattern. Once the patient understood and controlled this pattern, he proceeded to free breathing exercises and then to exercises with resistance, with a combination of gaiters and resistance bands on 4 extremities. He received incentive volume spirometry and inspiratory muscle training with POWERbreathe black to recapture strength, endurance, and power of the wasted muscles. As the patient progressed through rehabilitation, interval training with a bicycle, stairs, and steps were introduced. The patient continued to be monitored and the chest CT scan taken a year and a half later shows healthy lungs without fibrosis (Figure 4).

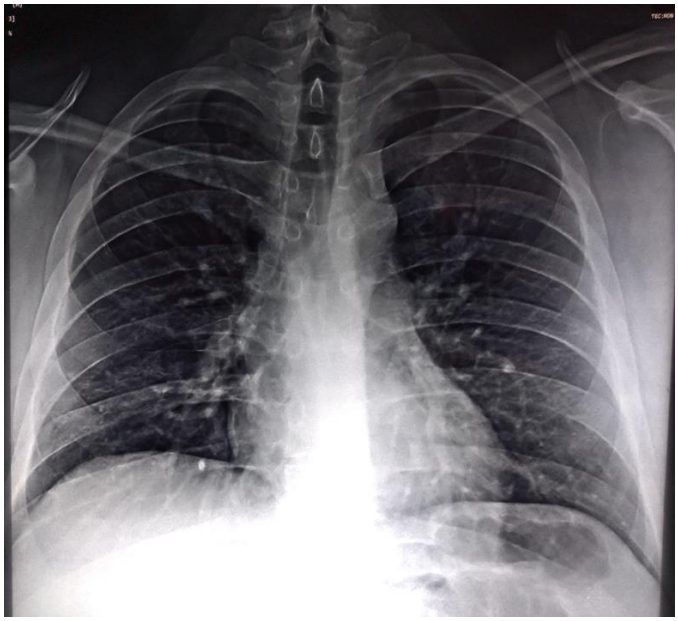

Figure 3: CXR taken 2 weeks post extubation

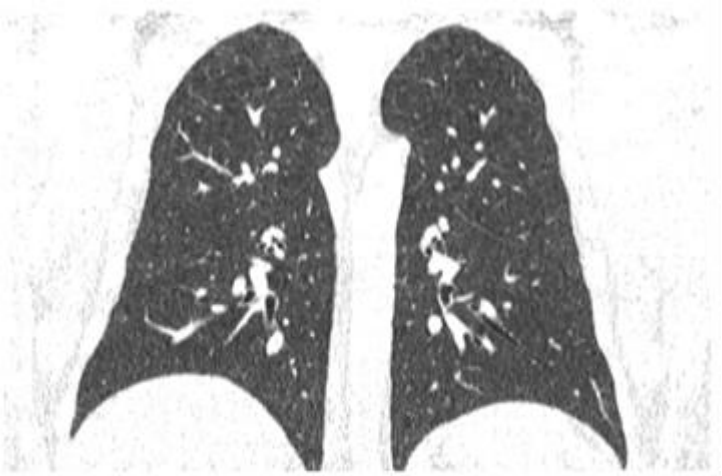

Figure 4. Up-dated (June 22, 2022) computed tomography of the thorax

Discussion

Lung function impairment persists in critical patients with COVID-19 even several months after discharge from the intensive care unit.[4] Cytokine storm, multiorgan failure and particularly, ARDS are the leading causes of mortality and morbidity in patients with COVID-19. Pirfenidone can inhibit apoptosis, downregulate the expression of angiotensin-converting enzyme (ACE) receptors, decrease inflammation, and ameliorate oxidative stress, hence protecting pneumocytes and other cells from simultaneous COVID-19 invasion and cytokine storm.[5]

From the scientific literature and epidemiological results and considering the pathophysiological, biological, and molecular characteristics of SARS-CoV-2, an antifibrotic drug such as pirfenidone as a monotherapy or in combination with anti-inflammatory drugs can be effective therapeutically to avoid serious complications during viral infections. The same approach can also work as post infection therapy in patients with residual pulmonary fibrotic damage. Moreover, management of inflammation and fibrotic status with a combination therapy of pirfenidone and IL-6 or IL-1 inhibitors can represent a pharmacological synergy with added value.[6]

This case report discusses the radiographical changes in a patient receiving pirfenidone for 6 days with apparent remission of fibrosis. The role of this antifibrotic drug in patients with ongoing SARS-CoV-2 infection or in patients with residual pulmonary fibrosis is still unclear. The scientific rationale for initiating, continuing, or discontinuing therapy has been poorly defined to date. In addition, information on clinical experiences of treating COVID-19 with pirfenidone is sparse, including a case report after steroid failure and a narrative experience with 7 patients without acute exacerbations, higher frequency of side effects, or antifibrotic treatment withdrawal.[7] The combination of pirfenidone and melatonin has been reported as reducing SARS-CoV-2 viral infection.[8] Also, researchers have suggested the therapeutic value of pirfenidone and nintedanib for use in SARS-CoV-2–induced pulmonary fibrosis.[9] Recently, 82.6% survival was

reported in 23 COVID-19 patients (12 women and 11 men; mean age 44.5 ± 17.1 years) treated with pirfenidone, nitazoxanide and colchicine in a rural setting.[10]

To date, the therapeutic efficacy of pirfenidone in SARS-CoV-2–induced fibrosis is still being investigated in clinical trials. However, some studies have shown the efficacy of antifibrotics for patients with pathogenic profibrotic pathways caused by inflammatory dysregulation, which may have similarities to those caused by SARS-CoV-2 infection.[11]

ACE receptors are the main receptor for the SARS-CoV-2 virus in humans. Surprisingly, pirfenidone has been shown to inhibit the AT1R/p38 MAPK pathway, ACE receptor expression, Type 1 angiotensin II receptor expression, and angiotensin II itself, which strongly increases the hepatic X receptor-α expression. Another important issue to consider is the possibility of low cost production of this drug.[12]

CT visualization of the lungs a week after presentation and one year and seven months later with tomographic demonstration of a significant recovery is a significant finding in this patient. As also shown by other authors, this case illustrates the importance of using rehabilitation with patients with COVID-19, because, despite having had a severe lung injury, this patient had a satisfactory recovery. Using a multidisciplinary team to treat all patients affected by COVID-19 is recommended.

The apparent success in managing COVID with pirfenidone should be taken with caution, because there are multiple factors that may have contributed to the recovery of the patient. One limitation of this case report is the existence of multiple variables that can induce confusion and a mistake in the supposition of the clinical benefits of using pirfenidone against the fibrosis caused by the SARS-CoV-2 virus.

Based on clinical and radiological evolution in the patient presented in this case report, it could be hypothesized that pirfenidone at a dose of 1,200 mg twice a day could be considered as a valid option, alone or combined with other antifibrotic drugs, to diminish the lung fibrosis caused by the SARS-CoV-2 virus. The case also demonstrates the possibility of satisfactory recovery of respiratory function by adding a rehabilitation programme. The timeline of this case is shown in Figure 5

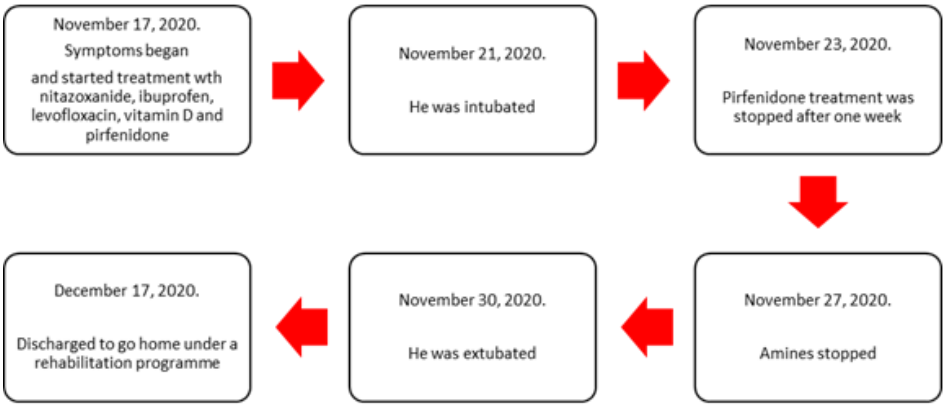

Figure 5: Timeline of events

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Ethics statement: The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his names and initials will not be published, and due efforts will be made to conceal his identity, and anonymity can be guaranteed.
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