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COVID-19 and pirfenidone. A case report

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Abstract

Diagnosis and treatment of Idiopathic Pulmonary Fibrosis (IPF) has been greatly influenced by the COVID-19 pandemic. Not only has it impacted the prognosis of the Idiopathic Pulmonary Fibrosis, but also the approach to treating these patients. The aim of this study was to evaluate our patient who got infected with COVID-19 and after hospitalization the underling, not previously diagnosed idiopathic pulmonary fibrosis was suspected in this patient. Due to COVID-19 infection and suspected idiopathic pulmonary fibrosis the patient was administered Pirfenidon to treat the deep fibrotic changes. The case was studied during the period from November 2020 – July 2021 in "Vivamedi" hospital Tbilisi, Georgia. The systemic review was made using available literature from online libraries like PubMed, Google Scholar and UpToDate. The report was prepared after analysing all laboratory results and other radiological investigations that were performed during the course of treatment. The patient was treated mainly with Oxygen therapy, Pirfenidone and anticoagulants. The patient recovered from COVID-19 with minimal pulmonary fibrotic changes. The vitals of the patient were stabilised and the lab results returned to normal. The patient was discharged from the hospital after 10 days and fully recovered from the viral infection. The survival after COVID-19 pneumonia in a patient with newly diagnosed IPF under antifibrotic + treatment without serious deterioration is a novel case. Antifibrotics which are available or developing not only have a role in treating such cases but can also be valuable in treating severe COVID-19 in patients without IPF, and might also be helpful preventing pulmonary fibrosis after SARS-CoV-2 infection.

KEY WORDS: COVID-19; idiopathic pulmonary fibrosis; pirfenidone; co-existing

Introduction

Interstitial lung diseases (ILDs) comprise a wide spectrum of acute and chronic lung diseases that cause progressive fibrosis, scarring and the loss of the lung tissue, causing compromised blood oxygenation and respiratory function. The most common form is the idiopathic pulmonary fibrosis (IPF), which majorly affects the older population. It is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause. It is defined by the histopathologic and/or radiologic pattern of usual interstitial pneumonia. Viral infections can trigger acute exacerbations, with poor prognosis. ILD with COVID-19 infection is associated with higher rate of acute exacerbations of the disease, the impact was notably significant in males and younger patients. Also, COVID-19 patients with ILD have shown more severe clinical manifestations, including increased mortality than the ones without ILD. There are only a handful of recommendations for patients with IPF when they happen to get infected with COVID-19.

The aim of this study was to understand how COVID-19 affects a patient with suspected idiopathic pulmonary fibrosis and also the possibility of management of such patients with antifibrotics along with other conventional therapies. This case-report has a significant value, as the patient with newly contracted COVID-19 was diagnosed alongside with ILD. So, survival rate for such patient is near impossible but with the treatment with antifibrotic like pirfenidone, anticoagulants and supportive therapies, the patient survived and recovered the viral infection. Due to its rarity, we report this case and check all previous research on it.

Materials and methods

The research included a systemic review and a case of 66-year-old female patient. All the lab reports and test results were thoroughly studied. The literature review was made using the available literature on online libraries like PubMed, Google Scholar, Up-to-date and then the case report was prepared with the patient's anamnesis and the lab results before and after the treatment. The study carried on from November 2020 – July 2021.

Case report

The patient presented with the complains of a few days of sweating, chills, high temperature, dizziness, dry cough and breath insufficiency. RT-PCR was performed and the result came out to be positive for COVID-19. Treatment was started in the COVID special department as per the recommendations. It is also crucial to note that five years ago the patient was diagnosed with Diabetes mellitus. Her diabetes mellitus was managed poorly, as she reported her blood sugar level was almost always elevated. As she reported for the past five to six years, two three times a year she had febrile events with acute shortness of breath, which she treated symptomatically. According to the patient during the previous year she had two or three upper respiratory tract infection and all of them were complicated with severe shortness of breath, fevers and chills. Her family doctor considered above mentioned episodes as acute pneumonia, hence prescribed oral antibiotic treatments. Despite the fact that her fever chills and fatigue resolved, she still experienced shortness of breath that had been progressing for the past year.

Upon arrival the patient was in an acute (moderately severe) distress. She had fever 38ºC, sweating, chills, dry cough, increased respiratory rate 30-32, dyspnoea, blood pressure 135/75, heart rate 90 and oxygen saturation at 89-92% on room air. Upon examination, the patient was found to be well oriented in time and space and her speech was fluent. Bilateral dense vesicular sounds were heard on auscultation and the breath was weakened in the lower lobes of lung. Dry expiratory crackles could be heard, cardiac auscultation revealed dull rhythmic sounds. Patient had light acrocyanosis, otherwise skin inspection showed unremarkable results. The palpation of abdomen was painless, no organomegaly. There was no peripheral lymphadenopathy. CT examination demonstrated no deformity in the chest cavity or any mediastinal deviation. The trachea, main bronchus and the lobar bronchus were not obstructed but their walls were thickened and had dilations on the inner surface (bronchiectasis). Small paratracheal hypodense areas could be noted on the right side. There was reduced pneumatization of both lungs in a diffuse and uneven manner due to pneumofibrosis, more prominently seen in lower lobes. Calcifications of the paraseptal tissues could be seen. Additionally, ground-glass infiltrative changes were seen in both the lungs and rough fibrotic zones were expressed in areas of infiltration. IV contrast showed a more clearly enhanced picture. There was no pericardial or pleural effusion. See Fig.1.

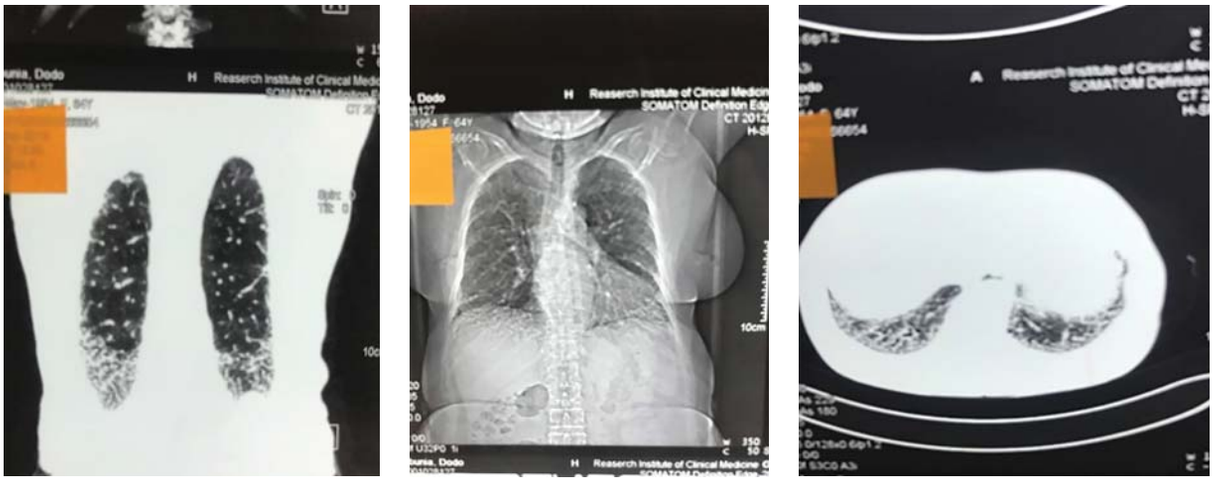

Fig. 1. *Photo from patient's medical history.*

CT data are consistent with the presence of interstitial pneumonia.

The main diagnosis was COVID-19 associated interstitial pneumonia (absorptive phase) and bilateral pneumofibrosis. The patient was treated with pirfenidone, oxygen supplementation and anticoagulants. The vitals were successfully stabilised and she was discharged within 10 days.

Discussion

Interstitial lung diseases are a heterogeneous group of disorders characterized by alveolar septal thickening, fibroblast proliferation, collagen deposition, and, if the process remains unchecked, pulmonary fibrosis. ILDs represent a large number of conditions that involve the parenchyma of the lung-the alveoli, the alveolar epithelium, the capillary endothelium, and the spaces between these structures, as well as the perivascular and lymphatic tissues.

ILDs have been difficult to classify because >200 known individual diseases are characterized by diffuse parenchymal lung involvement, either as the primary condition or as a significant part of a multiorgan process, as may occur in the connective tissue diseases (CTDs).

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonia.

Clinical Manifestations include exertional dyspnea, a nonproductive cough, and inspiratory crackles.

The HRCT lung scans typically show patchy, predominantly basilar, subpleural reticular opacities, often associated with traction bronchiectasis and honeycombing. Pulmonary function tests often reveal a restrictive pattern, a reduced DLCO, and arterial hypoxemia.

Histologic findings include interstitial inflammation, foci of proliferating fibroblasts, dense collagen fibrosis, and honeycomb changes [1,2].

Many patients with ILD are on immunosuppressive medications. It stands to reason that patients with ILD would have an increased rate of complications and death from COVID-19 [1,3,4]. Consequently, patients with idiopathic pulmonary fibrosis have poor clinical outcomes with COVID-19 disease.

The risk of serious disease and death in COVID-19 cases increases in people over age 65, in people who smoke or previously smoked, and in people with other serious medical disorders, such as Cancer, Chronic heart, lung, kidney, or liver disease, Diabetes, Stroke or cerebrovascular disease, Immunocompromising conditions, HIV infection, Tuberculosis, Sickle cell disease, Thalassemia, Dementia, Obesity, Pregnancy (up to 42 days after pregnancy), Some types of disabilities, Substance use disorders, Physical inactivity, Some mental health disorders such as depression and schizophrenia.

In addition to respiratory disease that can progress to acute respiratory distress syndrome (ARDS) and death, other serious complications include the following: Heart disorders including arrhythmias, cardiomyopathy, and acute cardiac injury, coagulation disorders including thromboembolism and pulmonary emboli, disseminated intravascular coagulation (DIC), hemorrhage, and arterial clot formation, Guillian-Barre syndrome (rare), sepsis, shock, and multiorgan failure [2,5,6].

Idiopathic pulmonary fibrosis (IPF) in the vast majority of cases affects the older population, in a progressive fibrosing manner, resulting in severe respiratory failure and death within 3-5 years [6].

Public health officials recommend that patients in the higher risk category should reduce the risk of being exposed to SARS-CoV-2 [7,8].

Patients with IPF, sarcoidosis, and other ILDs with known etiology, such as rheumatologic diseases with ILD involvement, could be at particular risk for SARS-CoV-2, since they tend to be older, have multiple comorbidities, and are often immunosuppressed by their disease or therapy. Currently, there is no reliable data regarding the incidence of COVID-19 in the field of ILDs.

Several media reported cases of pulmonary fibrosis resulting from COVID-19 disease. Most importantly, acute exacerbation leads to an in-hospital mortality of more than 50% with a mean survival time of only a few months [9].

Therefore, consideration of complications in IPF is of great importance for the may develop acute exacerbation such as pneumonia and progress to respiratory failure

and acute respiratory distress syndrome (ARDS), which requires life support with a mechanical ventilation.

Acute exacerbation of IPF and severe cases of COVID-19 show similar clinical profile as both affect the elderly, the ones suffering from diabetes, cigarette smoke exposure or ischemic heart disease. Among the underlying diseases, chronic respiratory comorbidities show more significant impact on the clinical picture of COVID-19. Thoracic malignancy and Chronic Obstructive Pulmonary Disease (COPD) are the risk factors for more severe manifestations and poor prognosis of COVID-19. As per studies, asthma does not possess any major risk for severity and susceptibility of COVID-19. There is very limited literature available on clinical course of COVID-19 in patients with ILD [10,11].

The exacerbated inflammatory state, associated with the fibrotic tissue stimulated by SARS-CoV-2, plays a key role in critical clinical cases. As the viral infection progresses to more severe stages, cytokine storm causes lung damage with extensive fibrosis and rapid onset of respiratory distress syndrome.

The possibility of shared mechanisms of fibrosis between ARDS cases and chronic ILDs raises the potential that therapies that treat ILDs could also be beneficial to COVID-19 associated lung disease [12,13]. In this regard, pirfenidone is being used in patients with COVID-19 in Wuhan, China (clinical trial.gov), and a prospective clinical trial with the other antifibrotic drug, nintedanib, is discussed [12], taken in consideration the shared pathogenetic and clinical similarities of COVID-19 and the fibrotic process.

Using antifibrotic agents, such as pirfenidone, can have therapeutic efficacy in addressing fatal lungs complications. Pirfenidone is a class of pleiotropic pyridine compounds with anti-inflammatory, anti-fibrotic and antioxidant properties.

Pirferidone and nintedanib are both pleiotropic anti-fibrotic agents and although both of the drugs are approved for the treatment of idiopathic pulmonary fibrosis (IPF) as a monotherapy [14], pirfenidone is the drug of choice in managing idiopathic pulmonary fibrosis (IPF). It was first approved in Japan for the treatment of patients with idiopathic pulmonary fibrosis after clinical trials, under the trade name of Pirespa by Shionogi, in 2008. Randomised controlled clinical trials and subsequent post hoc analyses have demonstrated that pirfenidone reduces lung function decline, decreases mortality and improves progression-free survival. Long-term extension trials, registries and real-world studies have also shown similar treatment effects with pirfenidone [3,10,15,16].

It is administered orally, 2-3 tablets three times a day, for at least 4 weeks. With a diversity of mechanisms of action reduces the inflammatory and fibrosis of the lung tissue. It downregulates the cytokines, including connective tissue growth factor (CTGF), transforming growth factor (TGF)-β1, tumour necrosis factor (TNF)-α and platelet-derived growth factors (PDGF). Also, pirfenidone is a reactive oxygen species (ROS) scavenger, as well as it suppresses the expression of ACE receptor, the major cellular

receptor for COVID-19. There are also some other features of pirfenidone, including antifibrotic effects and anti-apoptotic effects, which make it a suitable treatment for COVID-19. Moreover, employing a combined therapy of anti-inflammatories with antifibrotics, like pirfenidone could give additional clinical benefits.

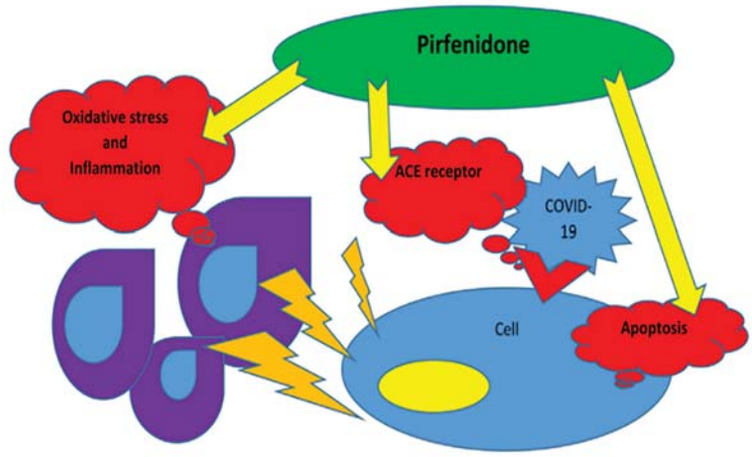

Fig. 2. *Pirfenidone inhibits apoptosis, down regulates the expression of ACE receptors, reduces inflammation through various mechanisms and ameliorates oxidative stress, thereby, protects pneumocytes from the invasion of COVUD-19 and the resulting cytokine storm.*

Pirfenidone has been shown to have a favourable safety profile and was generally well tolerated over the long term in clinical trials and real-world experience. However, side-effect management is critical to help some patients remain on treatment over the long term. The primary treatment-related adverse events associated with pirfenidone therapy are gastrointestinal upset, rash and photosensitivity. Gastrointestinal events may be mitigated by ensuring that pirfenidone is taken with food, while skin symptoms may be reduced by avoiding sun exposure and frequent use of sunblock [17].

There is description of case report about successful concomitant therapy with Pirfenidone and Nintedanib in idiopathic pulmonary fibrosis. They presented the first case of a Caucasian male patient with IPF treated with both pirfenidone and nintedanib following 2 years of treatment with pirfenidone monotherapy. Over a 24-month period, there was a clear decline in the patient's forced vital capacity from 3.5 liter before initiation of treatment to 2.5 liter after 24 months. Concomitant nintedanib treatment was initiated in March 2015. Lung function stabilized, and the two treatments were well tolerated. Treatment with pirfenidone and nintedanib has currently been ongoing for nearly 12 months. This was the first report of a successful long-term treatment with pirfenidone and nintedanib and suggested that in selected cases, concomitant anti-fibrotic therapy may represent a safe and therapeutically valuable escalation option after pirfenidone monotherapy [14].

Conclusion

The survival after COVID-19 pneumonia in a patient with a newly diagnosed, underlying IPF under antifibrotic treatment without serious deterioration is a novel case. The physicians today are facing the challenge to protect and treat the patients with ILD from COVID-19. Telemedicine has played a vital role in dealing with this pandemic. The case of our patient demonstrated that combining pirfenidone with the existing medications would not only cease the progression of the disease but also help with managing the residual pulmonary fibrotic damage in the post healing phase. With its pleotropic action mechanisms, pirfenidone can even be used to treat the COVID-19 patients without IPF. As, we know that in such pandemic situation we all are fond of treatment for COVID-19 and how we can stop it. In our case the patient was already suffering from symptoms of undiagnosed Idiopathic pulmonary fibrosis and the fibrotic changes were ongoing in her respiratory system. Additionally, to this chronic condition, the patient contracted COVID-19 infection and as a result her respiratory symptoms deteriorated rapidly [7,9,13]. The conjoined two chronic and acute fibrotic diseases made us to come to decision to start pirfenidone in this patient. 10 days after we started pirfenidone the patient's symptoms and laboratory results improved. After this she was discharged from the hospital. The patient was prescribed Pirferidone and recommended follow-up visit for 2 months. Follow-up pulmonary CT scan after 2 months revealed positive changes regarding fibrotic areas in the lung, as the intensity of fibrosis was decreased. So, we conclude that using Pirferidone in COVID-19 patients with high comorbidities like in the patients with suspected latent Interstitial Pulmonary fibrosis may lead to beneficial outcome, high survival rate and improved fibrotic areas in the lungs.

References

1. Podolanczuk AJ, Richeldi L. COVID-19 and interstitial lung disease: Keep them separate. 2020
2. https://www.merckmanuals.com/professional
3. Antoniou KM, Raghu G, Tzilas V, Bouro, D. Management of patients with interstitial lung disease in the midst of the COVID-19 pandemic. Respiration. 2020; 1
4. Ferrara F, Granata G, Pelliccia C, La Porta R, Vitiello A. The added value of pirfenidone to fight inflammation and fibrotic state induced by SARS-CoV-2. European Journal of Clinical Pharmacology. 2020; 76(11):1615-1618
5. Uzel FI, İliaz S, Karataş F, Çağlayan B. COVID-19 Pneumonia and Idiopathic Pulmonary Fibrosis: A Novel Combination. Turkish Thoracic Journal. 2020; 21(6):451
6. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ. American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018; 198(5):e44-68
7. British Thoracic Society Advice for Managing Interstitial Lung Disease Patients during COVID-19 pandemic. Available from: https://brit-thoracic.org.uk/media/455101/bts-management-advice-for-ild-patients-v10-23-march-2020.pdf
8. Halpin DM, Faner R, Sibila O, Badia JR, Agusti A. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? Lancet Respir Med. 2020; 8(5):436-8
9. Kreuter M, Polke M, Walsh SL, Krisam J, Collard HR, Chaudhuri N. Acute exacerbation of idiopathic pulmonary fibrosis: international survey and call for harmonisation. Eur Respir J. 2020; 55(4):1901760
10. Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, Agnew S. Outcome of hospitalization for COVID-19 in patients with interstitial lung disease. An international multicentre study. American journal of respiratory and critical care medicine. 2020; 202(12):1656-1665
11. Seifirad S. Pirfenidone: A novel hypothetical treatment for COVID-19. Medical hypotheses. 2020; 144:110005
12. Spagnolo P, Balestro E, Aliberti S, Cocconcelli E, Biondini D, Della Casa G. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Respir Med. 2020; 8(8):P750-52
13. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and

COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med. 2020; 8(8):P507-15

14. Hagmeyer L, Treml M, Priegnitz C, Randerath WJ. Successful Concomitant Therapy with Pirfenidone and Nintedanib in Idiopathic Pulmonary Fibrosis: A Case Report Respiration. 2016; n91(4):327-32
15. Behr J, Prasse A, Kreuter M, Johow J, Rabe KF, Bonella F. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. The Lancet Respiratory Medicine. 2021; 9(5):476-486
16. Lancaster LH, de Andrade JA, Zibrak JD, Padilla ML, Albera C, Nathan SD. Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. European respiratory review. 2017; 26(146)
17. Cottin V, Maher T. Long-term clinical and real-world experience with pirfenidone in the treatment of idiopathic pulmonary fibrosis. Eur Respir Rev. 2015; 24(135):58-64