

Case Report

Pulmonary Fibrosis: The Dead End of COVID-19 - Short Review with a Case

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ABSTRACT

As, COVID-19 still continues to spread over the world and new complications are emerging as a sequelae of the disease. Pulmonary Fibrosis is one such devastating complication following COVID-19 infection. Much more clinical research is required in identifying patients at the early stage who are at risk of developing pulmonary fibrosis as a result of COVID-19, and more trials are required for a potential treatment option. Co-morbid conditions, severe form of disease and prolonged ICU stay, mechanical ventilation are such risk factors trailing the disease to fibrosing stage. Early identification and effective treatment is required in such patients to prevent such morbid outcomes.

KEYWORDS: Pulmonary Fibrosis, D Dimer, Post COVID Fibrosis, Inflammatory Markers, SARS-COV-2, Lung Transplant

INTRODUCTION

The world has been battling a pandemic of a novel Coronavirus named SARS-COV 2 and witnessing the frantic dance of COVID-19 in the year 2020-21 and much more to be seen in the time ahead. Despite being a respiratory infection, COVID-19 has been proven to complicate by affecting other systems and has poor prognosis in patients having associate co-morbid conditions.^{1,2}

Epidemiological and Clinical research has concluded that most of the COVID – 19 patients elicit a milder form and good response to recommended medical treatment, resulting in recovery. The ICU admission rate stood around 5.0% and Invasive Ventilation was required for 2.3% of them, out of which the mortality rate was around 1.4%.³

CT Scan is widely used as a diagnostic tool for evaluating extent and type of lung involvement. Common features in CT Scan includes Ground Glass Opacities^{4, 5} characteristic crazy paving pattern and consolidation.⁶

Emerging data shows that 17% of patients diagnosed with COVID – 19 have developed Pulmonary Fibrosis as a complication⁷. It is still not clear that whether these early signs pointing towards Pulmonary Fibrosis in COVID-19 will progress into Interstitial form or will get completely absorbed⁸.

The host immune response varies according to Gender and age, while severity increases with associated risk factors such as Type II Diabetes mellitus, Hypertension and Cardiovascular disease⁹. These factors are responsible for marked discrepancy in the clinical course of COVID-19 disease in every infected patients.^{10,11,12} Role of Infective markers is also vital as inflammatory process in lungs is a complex cascade of events consisting of inflammatory mediators such as Chemokines and Cytokines which will stimulate alveolar macrophages and will ultimately cause unregulated Immune System.¹³ Looking to all

COVID-19 has been termed as a complex immuno-thrombo-inflammatory disease.¹⁴ Fibrosis is the end result of pulmonary inflammation. Inflammation is more likely to occur as a sequel in Moderate to severe COVID – 19, where extent of lung damage is higher, inflammatory markers are alarmingly raised and patient has pre-existing co-morbidities.¹⁵

In spite knowing the basic pathological process of COVID-19 and its sequel, in terms of Pulmonary Fibrosis, the treating physicians are still lacking in terms of proper identification and

stratification of patients who are at risk of developing pulmonary fibrosis. The present short review will flash some light on pathophysiology and treatment of this devastating sequelae of COVID-19 along with a case.

CASE REPORT

A 65-Year-Old male presented in Pacific Medical College and Hospital with cough and difficulty in breathing since 10 days. He was a known case of Hypertension (7 Years) and Type – 2 Diabetes Mellitus (15 Years).

INITIAL LAB WORKUP

- Hb – 11.0 gm% (13.5-18 gm %)
 - TLC – 11,800 /mm³(4000-11000 /mm³)
 - CRP – 3.23 mg/L (<5 mg/L)
 - Ferritin – 259.8 ng/mL (30-400 ng/mL)
 - D Dimer – 3980 ngFEU/ml (<710 ng FEU/mL)
 - IL-6 – 9.0 pg/ml (<7 pg/mL)
- Admission CT scan (Fig.1) showed Ground Glass opacities and Interstitial Septal Thickening and a severity score of 15/25

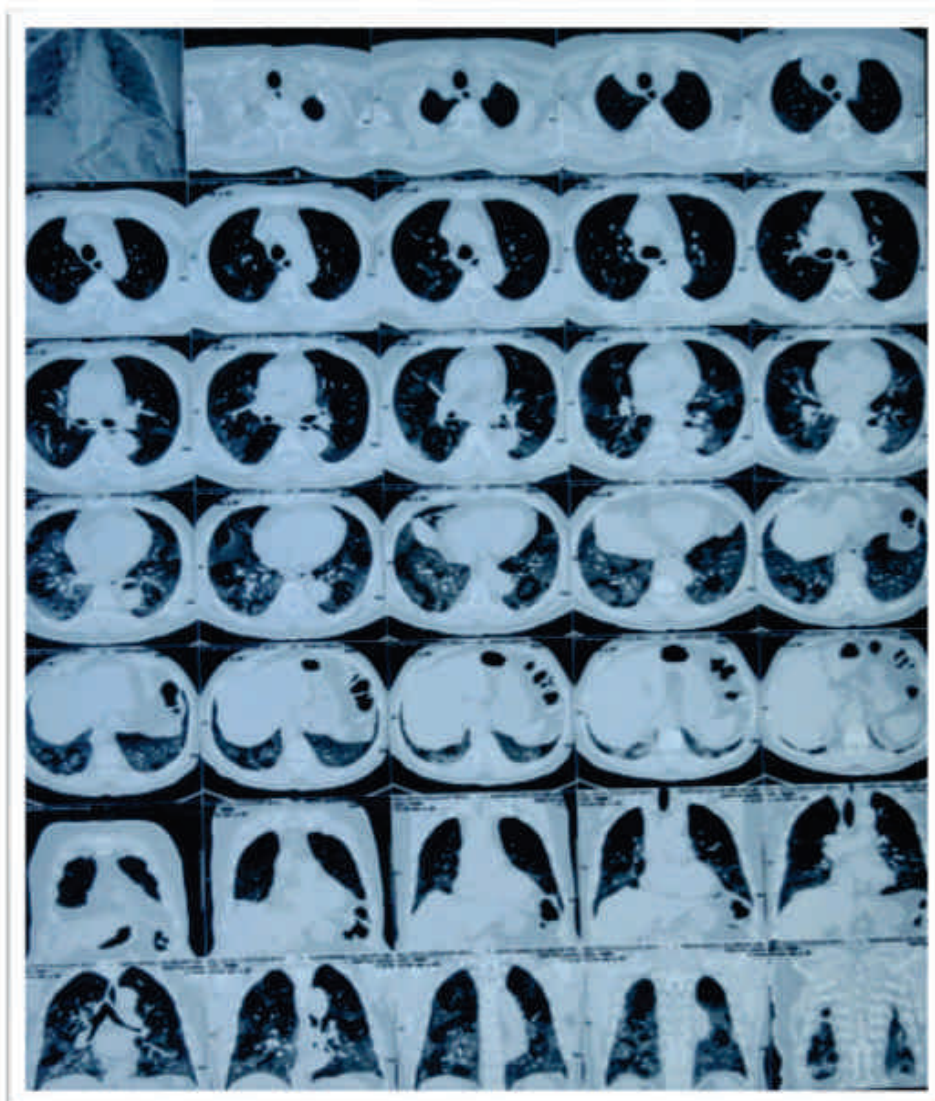


Figure 1: Admission CT Scan with CT Score 15/25

Patient had a month long stay in the ICU but did not require any mechanical ventilation. He was kept on Non-Invasive Ventilation through BiPAP mask, and intermittently on NRBM mask.

Patient was given IV Antivirals (Remdesivir), IV Corticosteroids (Methylprednisolone), S/C Low Molecular Weight Heparin (Enoxaparin) and appropriate Antibiotics with Oral Pirfenidone for anti-fibrotic treatment.

After being shifted to ward from ICU a repeat CT scan (Fig 2.) showed widespread fibrotic changes in the lung. There was significant reticulation and patchy areas of consolidation in both lungs, mainly in the peripheries with relatively sparing lung apices along with bronchiolar and vascular dilatation. Keeping with post COVID status and distribution of fibrosis, these features favored fibrosing stage of disease process (Moderate). His CT Scoring was 13/25.

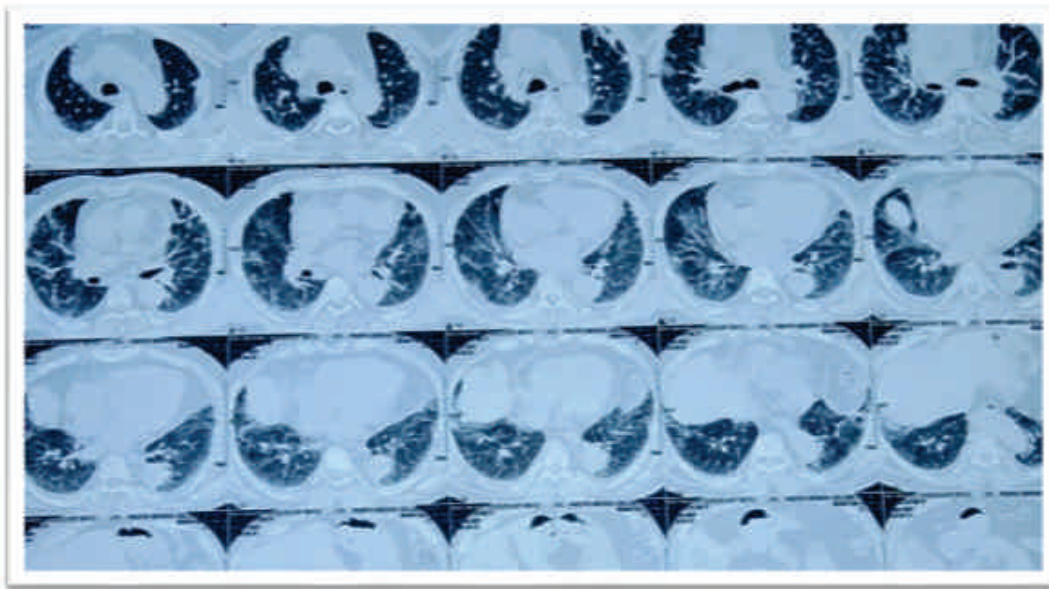


Figure 2: Discharge CT Scan with CT Score 13/25

Patient was in a high-risk category and developed Pulmonary Fibrosis as a terminal complication. Patient was discharged with O₂ support at home after 34 days of hospital stay.

His Pirfenidone was continued at home along with anti-coagulation cover. His lab workup at time of discharge showed high D - Dimer (3876 ngFEU/ml) and almost normal inflammatory markers.

This is a classical case of COVID -19, with risk of advancing age and pre-existing Hypertension and Type 2 Diabetes Mellitus, landing in Pulmonary Fibrosis. The only laboratory correlation that existed was significantly higher D – Dimer even at the end of 1 month with normal levels of other inflammatory markers.

It is extremely difficult to predict the risk of development of pulmonary fibrosis because of limited understanding of the pathophysiology and marked variations observed in disease progression and its complications.

RISK FACTORS

There are possible risk factors which can enforce the danger of complicating the disease to the stage of fibrosis -

1. AGE

- It is said to be an incredibly significant risk factor. The risk of Pulmonary fibrosis increases with advancing age. This has also been observed during the MERS outbreak.¹⁶

2. DISEASE SEVERITY

- Duration of disease along with severity are important determinants for the development of Pulmonary fibrosis in post COVID-19 Pneumonia. Study in patients with COVID-19 pneumonia in Wuhan showed that Pulmonary Fibrosis was observed in 4% of patients, who had the duration of disease of <1 Week. While 61% of patients had lung fibrosis with disease duration of >3 Weeks.¹⁷

3. PRE-EXISTING CO-MORBID CONDITIONS

- Co-morbid conditions also increase the risk of disease severity. Pre-existing Diabetes, Coronary Artery Disease, Hypertension etc. in all these conditions the clinical course of the disease is quite severe. According to WHO around 14% of COVID-19 patients have a severe form of the disease.¹⁸

4. DURATION OF ICU STAY AND VENTILATORY SUPPORT

- If the patient has a severe form of the disease, there are ample chances of prolonged hospitalisation, especially ICU stay and use of mechanical ventilation. The longer the ICU stay the severe the disease becomes. The mechanical ventilation comes with its own complication such as Ventilator Associated Lung Injury. Risk of mortality is significantly higher in such patients and those who

have survived are at risk of developing Pulmonary Fibrosis.¹⁹

5. CHRONIC SMOKING

- Smokers have an increased likelihood of developing severe form of the disease (1.4 times) and they are twice more likely to require ICU admissions and mechanical ventilation. They are more at risk of higher mortality as compared to non-smokers.^{20,21}

6. CHRONIC ALCOHOLISM

- WHO and National Institute on Alcohol Abuse and Alcoholism (NIAAA) have warned people to avoid excessive alcohol consumption, stating that habit can increase the severity and susceptibility of COVID-19 and increases the risk of complications.²²

The best way to predict development of Pulmonary Fibrosis is by HRCT Scanning of Thorax. To identify prediction of Pulmonary Fibrosis development by CT Scan imaging, Minhua et al. studied 32 patients with confirmed COVID – 19 rtPCR status and divided them into two groups according to the evidence of Fibrosis on their latest CT Imaging. These CT Findings showed that 14 patients developed Fibrosis while 18 patients had a clear CT scan. The fibrotic group of patients were older in age and the median levels of their Infective markers were also raised significantly compared to the non-Fibrotic group. Conclusion was made that Fibrosis was more likely to develop in patients with severely clinical conditions, especially with high inflammatory indicators.¹⁵

Based on these risk factors described above there are some risk reduction strategies which can be followed such as. 1. Use of Anti Virals and Immunomodulatory medications, 2. Minimize ventilatory induced lung injury with protective lung ventilation, 3. Limit exposure to environmental factors and encourage for smoking cessation.

PATHOPHYSIOLOGY OF POST COVID-19 PULMONARY FIBROSIS

Pulmonary fibrosis is a well-known complication of Acute Respiratory Distress Syndrome (ARDS), the latter occurs in 40% of COVID-19 patients. However, the current understanding suggests that more than 30% of patients develop fibrotic changes in lung.²³

Even though ARDS is a strong predictor of Pulmonary Fibrosis in COVID -19, the type of ARDS seen in COVID -19 is varied from classic ARDS. Hence the mechanism of COVID-19 related Pulmonary Fibrosis is different from classical Idiopathic Pulmonary Fibrosis.

To start with there is invasion of Type 2 Alveolar Epithelial cells via ACE-2 receptor. After the invasion, the virus goes through replication in order to form even more nucleocapsids.

These pneumocytes now release plethora of inflammatory markers and cytokines such as IL-6, IL-1, IL-8, TNF – α , IFN – λ , IFN – β , CXCL-10, etc, This is what is termed as “Cytokine Storm” which acts as attractant for Neutrophils, T Cells, CD4, 8 and helper cells starts getting sequestered into lung tissue.

This leads to persistent damage to Type 1 and Type 2 pneumocytes by inflammatory cells and replication which results in Diffuse Alveolar Damage causing Acute Respiratory Distress Syndrome. (Fig.3)²⁴

Exaggerated inflammatory response in COVID – 19 along with Cytokine Storm, the regulatory pathways come in use to deal with the damaged lung tissue. Prolongation of this response forms a fibrotic response which can be seen as Interstitial Septal Thickening, Ground Glass Opacities, Fibrotic Bands, Crazy Paving Patterns, Tractional Bronchiectasis in CT scans.

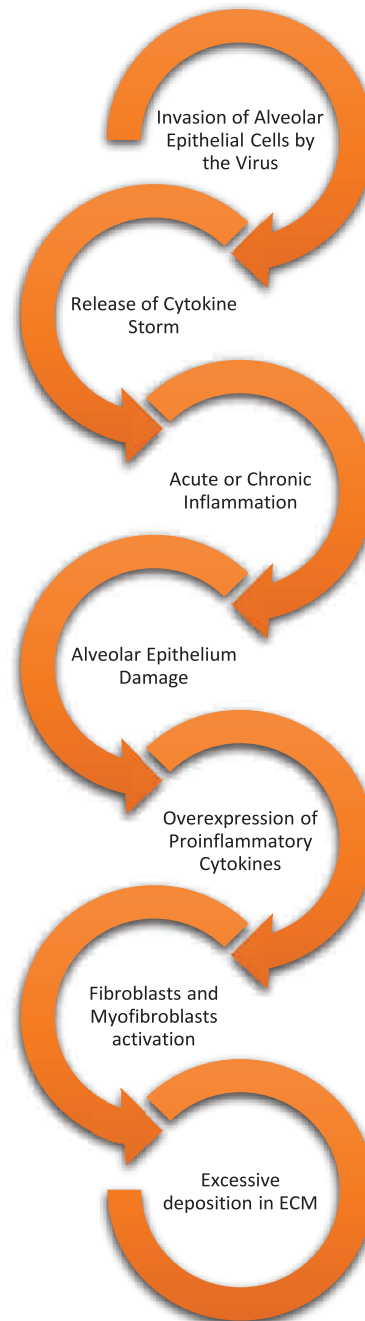


Figure 3: Pathophysiology of Pulmonary Fibrosis in COVID -19

TREATMENT

There has been severe lack of scientifically proven methods to treat Post COVID-19 Pulmonary Fibrosis. Various studies are going for newer treatment options which are at different stages of development.

Corticosteroid (Dexamethasone, Methylprednisolone) have been widely used as one of the treatment options for COVID-19. It has been observed that prolonged use of low dose or pulsed steroid therapy may have some benefit in lung protection.^{25,26}

Besides this there are Anti Fibrotic agents available to use such as Nintedanib and Pirfenidone. These agents not only have anti fibrotic effect, but also have some Anti Inflammatory and anti-oxidative properties; thus, they can be used in the acute phase of the disease. The hepatotoxicity of both these drugs should not be overlooked, and Nintedanib is linked to higher risk of bleeding in patients who are on anticoagulant therapy.

There is literature available which supports the use of Anti Fibrotic agents in the first week of ARDS onset to prevent Pulmonary Fibrosis. This calls for an urgent need of understanding Biomarkers which signifies risk of developing pulmonary fibrosis early in the disease stage.^{27,28}

There is some benefit of Endurance Exercise, Physiotherapy, Rehabilitation especially in early phase of disease have some benefit to improve lung function. However, this data needs to be backed with more scientific evidence to have a conclusion.²⁹

Duncan Richards, Professor of Clinical Therapeutic at University of Oxford, commented that drug-based treatments for this condition are not highly effective and are associated complications. Ideally, treating doctors are the right person to accurately predict which patients have the greatest risk of developing fibrosis, and select drugs designed to tackle this judiciously before serious symptoms develop.³⁰

Lung transplantation is emerging as a final hope in patients with Pulmonary Fibrosis and Respiratory Failure due to COVID-19. There was a study by Jing-Yu Chen et al. in China where three critical patients with COVID -19 underwent lung transplant with full ethical review. Out of those three, two patients survived and started active participation in rehabilitation programme. There is still scarcity of literature available for lung transplant as a potential option and further clinical resource is required.³¹

CONCLUSION

The entire world is in turmoil battling with COVID – 19 pandemic. New information about the disease is coming out regularly and we are getting closer and closer in understanding this Virus completely and thus in turn finding a way out of this storm. Pulmonary Fibrosis as a complication of COVID-19 and ARDS is an emerging threat. It is said to be prevalent in one third of the patients of COVID -19. More scientific data is required to understand the pathogenesis and treatment for this complication. The most important factor in limiting such serious complications still remains timely diagnosis and early treatment with Antivirals and corticosteroids. Lung Transplantation may be a ray of hope in such patients, but extensive studies are required.

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