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(CASE REPORT)

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Post covid lung fibrosis (PCLF) or post covid lung sequelae (PCLS) in treated case of severe COVID-19 Pneumonia case in Intensive care unit with ventilatory support and home oxygen therapy for twelve weeks

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Abstract

Lung fibrosis is final radiological outcome of COVID-19 pneumonia documented in proportionately majority of cases. Post COVID lung fibrosis is considered as worrisome radiological complication observed during early phase of pandemic. Time trends of final radiological outcome has evolved over months with or without treatment with antifibrotics and steroids. Importantly, Post covid lung fibrosis resolved more than fifty percent cases in six months and nearly in all cases after one year. In this case report we have documented PCLF in 32-year male hospitalized for severe COVID-19 illness with acute hypoxic respiratory failure secondary to ARDS (acute respiratory distress syndrome). He required high flow nasal canula oxygen supplementation with noninvasive ventilatory support for three weeks. He responded to medical treatment such as injection remdesivir, methylprednisolone and low molecular weight heparin injection. He was discharged to home with advice for home oxygen therapy and medicines such as steroids and antifibrotics Nintedanib. He required oxygen for twelve weeks. His chest imaging done at one year shown residual post covid sequel without any cardiopulmonary and exercise performance impact.

Key words: COVID-19; ARDS; Post covid lung fibrosis; Post covid sequelae; Remdesivir; Antifibrotics

1. Introduction

he severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a recently emerged viral pathogen that leads to coronavirus disease-2019 (COVID-19). A large proportion of infected COVID-19 cases have very mild symptoms such as loss of taste or smell, fever, fatigue, and dry cough - or are completely asymptomatic. However, in about 14% of the cases, acute respiratory distress syndrome (ARDS) can develop which is a potentially fatal condition. [1] Pulmonary fibrosis is an interstitial lung disease (ILD) that is characterized by progressive scarring of the lung tissue, impacting lung function, and leading to impaired gas exchange and difficulty breathing.[2] Currently, the incidence of pulmonary fibrosis is increasing significantly.[3] The development of pulmonary fibrosis is associated with many risk factors, such as aging, smoking, genetic predisposition, and exposure to occupational dust and asbestos.[4] The risk of mortality is increased in patients with pulmonary fibrosis owing to a lack of effective therapies to halt disease progression.[5] Pulmonary fibrosis has been linked to viral pneumonia, such as coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); however, it is thought to be uncommon.[6-8] COVID-19 may cause atypical pneumonia that progresses to acute lung injury and acute respiratory distress syndrome (ARDS). The symptoms associated with COVID-19 range from mild upper respiratory tract involvement to severe ARDS requiring long-term oxygen therapy due to pulmonary fibrosis.[9] The risk of mortality in COVID-19 patients with pulmonary fibrosis increases as pulmonary fibrosis is a progressive disease that leads to respiratory failure and is associated with

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a poor prognosis; lung transplantation is the only treatment demonstrated to improve outcomes.[10] Few studies have documented progressive, persistent and resolving type in short time follow up of three to six months. [11]

2. Case summary

32-year-old male, college student, non-smoker, normotensive, non-diabetic, admitted in intensive care unit as a case of COVID-19 pneumonia with acute hypoxic respiratory failure.

He was having-

- Shortness of breath at rest since one day
- Dry cough for 3 days
- Low grade fever for 10 days
- Weakness and decreased appetite for 12 days

His family member was suffered from COVID-19 illness and received treatment in our center 10 days before his symptoms. His symptoms started 12 days before and he also tested positive for COVID-19 RT PCR and confirmed as COVID-19. His oxygen saturation was 98% at room air during rest and 95% during ambulation. He was treated with oral medicines favipiravir, paracetamol and advised for home isolation and guided for strict monitoring of symptoms and oxygen saturation. He said that he was alright 3 days before his current stage to start with dry cough. His relatives narrated about his worsened shortness of breath and increased cough in last three days. He was hospitalized in private hospital for his worsened health and started on medical management with oxygen supplementation. His medical condition and respiratory parameters worsened in last three days to have shortness of breath at rest with increased oxygen requirement and impending respiratory failure. He was referred to our center for ventilatory support for his worsened COVID-19 respiratory illness. He was sent in advanced basic life support ambulance with oxygen and ventilatory support non-invasive ventilator for CT Thorax assessment for proper assessment of COVID-19 severity.

HRCT thorax documented bilateral ground glass opacities with consolidations, fully studded lung parenchyma in upper, middle and lower lobes nearly occupying all segments in both lungs. [figure 1, figure 2]

HRCT thorax reported as-

CORADS-6

CT severity score-24/25 (very severe lung involvement)

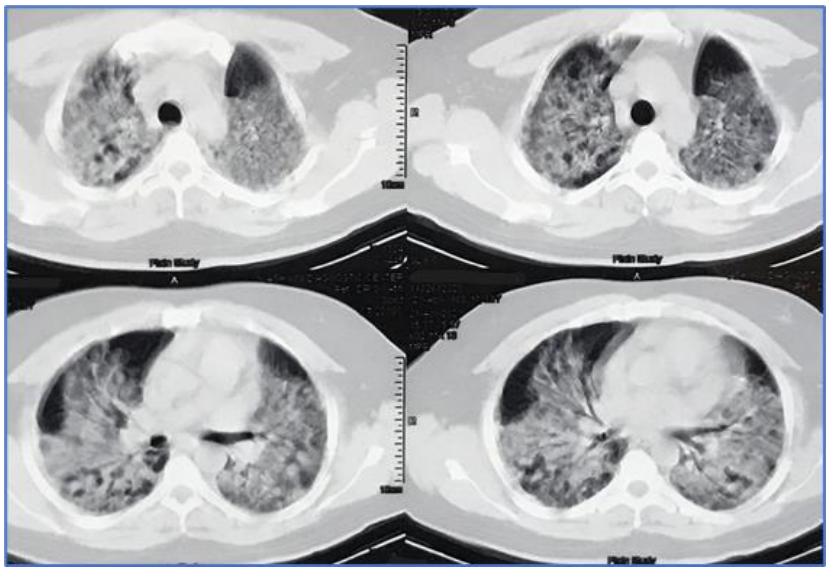

Figure 1 HRCT thorax showing bilateral GGOs and consolidations in upper and middle lobes

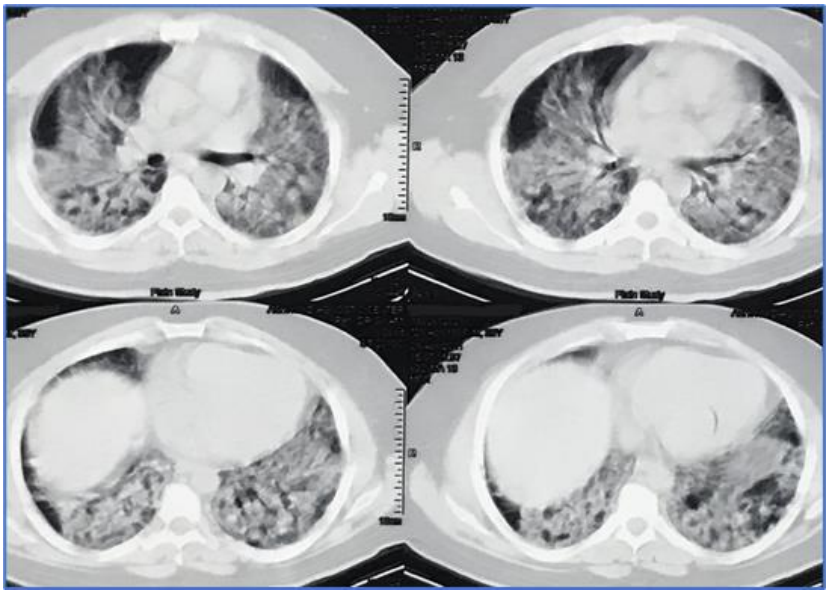

Figure 2 HRCT thorax showing bilateral GGOs and consolidations in middle and lower lobes

2.1. Clinical examination documented-

Moderately built, restless male, cyanosis present

Heart rate-148/min Respiratory rate: 38/bpm, BP-110/60 mmhg

PsO2: 45% @ room air resting & 78% @ with oxygen supplementation 60 litres/min by high nasal canula

Respiratory system examination revealed- bilateral breath sounds normal, adventitious sounds as bilateral crepitation's heard bilateral basal area

Other systems examinations were normal.

2.2. Laboratory examination documented as-

- Hemoglobin-11.0 gm% total white blood cells-4100/mm3 Polymorphs-32%, lymphocytes-62% Platelet count-49000/uL
- KFT – Serum Creatinine- 1.7 mg/dl (0.6-1.2 mg/dl), blood urea- 68 mg/dl (10-40 mg/dl)
- Liver function tests- Sr Bilirubin-1.4 mg/dl (06-1.2 mg/dl)
- CRP-281 mg/L (0-6 mg/L), random blood sugar level-380 mg%
- LDH-3200 IU/L (70-470 IU/L), Uric acid-3.4 mg (3.5-7.5 mg/dL)
- Pro-BNP- 110 pg/ml (<125 pg/ml)
- Serum electrolytes: Sodium-138 meq/L (135-145 meq/L) Potassium-5.9 meq/L (3.5-5.5 meq/L) Ionic calcium-1.26 meq/L (1.09-1.36 meq/L)
- D-dimer-7890 ng/ml (<500 ng/ml)
- Ferritin- 998 ng/ml (14-250 ng/ml)
- IL-6- 341 pg/ml (<7 pg/ml)

2.3. During hospitalization

He was admitted in isolation intensive care unit (level III) with HFNC and BIPAP/NIV with oxygen supplementation 60 liters/min. He was treated with Injection remdesivir 200 mg bolus on day one and 100 mg one time daily for 5 days, Injection Methylprednisolone 40 mg three times, Injection Teicoplanin 400 mg one time daily, Injection Meropenem 1 gram three times daily, Injection low molecular weight heparin 60 units one time subcutaneous daily for 14 days. His blood sugars were monitored four hourly and short acting Insulin injections were given to maintain target blood sugar level 140-160 mg/dL. His oxygen supplementation was titrated with oxygen saturation target above 90 percent. He was difficult to tolerate NIV initially due to high oxygen requirement and unstable respiratory parameters with high respiratory rate. With adequate and rational drug administration, his respiratory parameters and oxygenation shown

improvement after one week and his oxygen requirement decreased to 5 liters after two weeks. He was treated with intermittent BIPAP/NIV and then shifted to during night time with oxygen supplementation 2 liters/min. He was received 40 mg methylprednisolone one time daily till 26 days of hospitalization with 2 and 4 liters of oxygen supplementation during rest and ambulation respectively. He was discharged on day 31 of hospitalization with advice for home oxygen therapy by oxygen concentrator machine at rest and oxygen cylinder during ambulation as per requirement for patient comfort with target oxygen saturation 90 percent.

2.4. Discharge medicines

Oxygen supplementation at home with oxygen machine or cylinder as per requirement

Tablet Nintedanib 100 mg two times daily

Tablet methylprednisolone 24 mg two times daily for 7 days and decreased 4 mg daily for 10 days and then advised for 4 mg two times for one month. Later on prescribed 4 mg one time daily in second month and 4 mg alternate day in third month.

Tablet Rivaroxaban 2,5 mg one time daily for three months till final assessment.

Tablet Glimepiride plus metformin for blood sugar control

Tablet vitamin B12, folic acid, zinc supplementation

2.5. Monthly monitoring for first three months

Clinical parameters such as respiratory rate, heart rate, oxygen saturation at rest and ambulation with oxygen supplementation

Laboratory assessment with haemoglobin, white blood cell counts, platelets, liver and kidney functions, blood sugar level

Inflammatory markers IL-6, CRP, LDH, D-Dimer, Ferritin

2.6. Assessment at three months

As his oxygenation requirement decreased and able to maintain oxygen saturation at rest and during ambulation above 90 percent, we have performed 6-minute walk test and spirometry.

Spirometry analysis documented-

- FVC- 50.9% (1.66 litres)
- FEV1-48.1% (1.36 litres)
- FEV/FVC- 105.82%
- 6-MW Test- (6-minute walk test) documented
- Walk distance- 450 meters without oxygen support
- Oxygen saturation- 97% before and 93% after walk distance.
- Heart rate- 96/minute pre procedure and 118/minute post procedure
- Reparatory rate- 20/breath per minute pre procedure and 36/breath post procedure
- Recovery time to reach basal vital parameters were 2 minutes.

2.7. Echocardiography

Normal all heart chambers, no regional wall motion abnormality, no pulmonary hypertension, no evidence of clot/vegetation or embolus and left ventricular ejection fraction was 60%.

Treatment continued after 3 months till one year:

- Tablet Nintedanib 100 mg two times daily
- Tablet Rivaroxaban 2,5 mg one time daily for three months till final assessment.
- Tablet Glimepiride plus metformin for blood sugar control

We have repeated HRCT thorax after one year of discharge from hospital. HRCT thorax documented bilateral interstitial opacities with linear fibrotic bands in all lobes. Linear opacites are intermixed with reticular opacities at some point in upper and lower lobes sparing middle lobes without loos of lung volume. [Figure 3 and Figure 4]

We have documented significant role of antifibrotics and steroids in early post discharge phase till 12 weeks in controlling post covid lung disease.

Absence of honeycombing, tractional bronchiectasis and absence of predominant subpleural reticulations was really good sign of radiological outcome.

We have stopped all three medicines as Nintedanib, Rivaroxaban as HRCT thorax was satisfactory with no risk of progression of post covid lung fibrosis.

His blood sugar were controlled and we have stopped oral anti-diabetes medications and advised for strict diet and life style modifications.

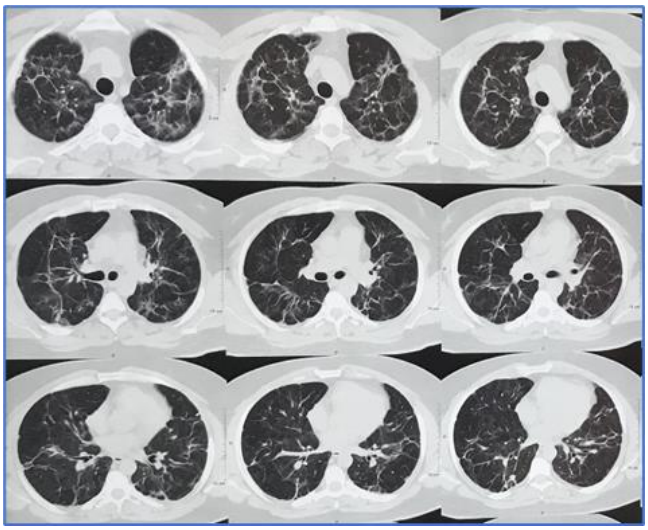

Figure 3 HRCT thorax showing interstitial opacities classically described as linear and parenchymal bands without loss of lung volume in bilateral upper lobes

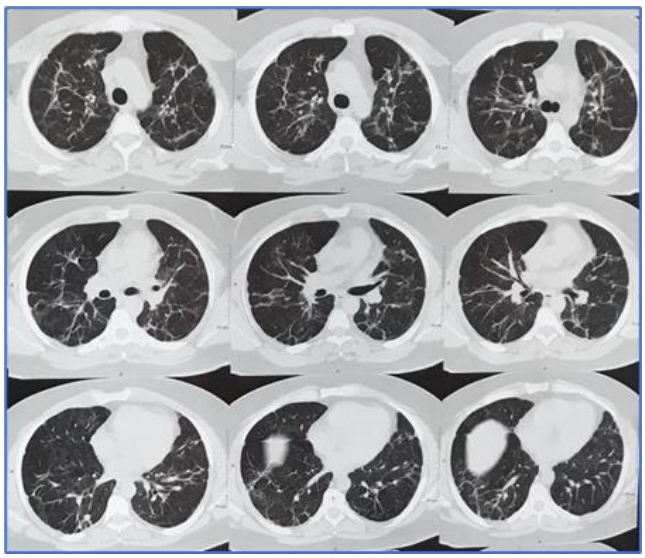

Figure 4 HRCT thorax showing minimal liners opacities and parenchymal bands in lower lobes on both sides

3. Discussion

The first reports of a novel coronavirus SARS-CoV-2 came from Wuhan, China, in December 2019. As this highly transmissible virus spread rapidly across the globe, it quickly overwhelmed medical and critical care resources, becoming a leading cause of morbidity and mortality worldwide. Due to the high prevalence of respiratory failure and the need for mechanical ventilation in patients with severe manifestations of the disease, there has been increasing concern about the pulmonary sequelae, most notably pulmonary fibrosis (PF) [2]. Given that survivors of COVID-19 who develop persistent pulmonary disease will require long term specialty care, all clinicians have a vested interest in understanding and mitigating the various risk factors associated with post-COVID-19 pulmonary fibrosis (PCPF).

3.1. Post covid lung predictors and pathophysiology

Potential contributing etiologies for PCPF include viral pneumonia and pneumonitis [12-18]; ARDS from COVID-19 pneumonia and COVID-19 related sepsis [16-21]; trauma due to prolonged mechanical ventilation (MV) [21-24]; thromboembolism [17,19,25,26]; hyperoxia [18,19,27,28]; and dysregulations in the immune response [29-34]. Pathophysiology of post covid lung fibrosis is well established and follows same pathway of ARDS due to any cause such as injury, inflammation, exaggerated inflammation, repair and fibrosis.

3.2. Post-ARDS Pulmonary Fibrosis

By contrast, in ARDS survivors there is extensive literature documenting the correlation of physiologic and radiologic data with health-related quality of life (HR-QOL), as well as pulmonary-specific measures. Survivors may have various pulmonary abnormalities including restriction, which may be due to neuro-muscular weakness (NMW) and deconditioning more so than parenchymal injury. Burnham et al. showed the radiographic changes and physiologic measures correlated well with patient's symptoms and reduced pulmonary function months after diagnosis in a number of acute lung injury (ALI)/ARDS survivors [35]. These patients tended to have low diffusing capacity for carbon monoxide (DLCO) supporting direct pulmonary injury impacting gas exchange [36]. Common variables for fibrotic lung disease following viral respiratory failure are advanced age, prolonged duration of mechanical ventilation, and worsened initial radiographic changes, all of which are consistent with a baseline more severely ill population. The underlying pathophysiology is likely multifactorial, with the largest contributions coming from mechanical ventilation induced trauma to the lungs, as well as aberrant reparative processes.

3.3. Direct Trauma from Mechanical Ventilation and post covid lung fibrosis

A postulated role of prolonged mechanical ventilation-induced lung injury (VILI) in Pulmonary Fibrosis has been outlined by several authors [24]. Although mechanical ventilation (MV) is the most important supportive therapy for ARDS, it can cause or worsen lung injury which is referred to as VILI [24]. A significant proportion of patients with COVID-19 require MV as a supportive treatment and in one study of 5700 hospitalized COVID-19 patients, 20% required MV [37]. ARDS causing respiratory failure is a frequent cause of morbidity and mortality in COVID-19 patients and often is the reason they need MV [38,39]. The initial inflammatory injury of ARDS to the lung may be augmented by mechanical forces of MV [40]. VILI presents similarly to and is clinically indistinguishable from ALI/ARDS [41]; thus, it is difficult to determine cause and effect and whether the virus, the disease process (ARDS), or the treatment (MV) is the culprit for any ensuing and persistent lung injury [41,42].

3.4. Thromboembolism and post covid lung fibrosis

In addition to causing a clinical array of respiratory-related disorders, COVID-19 has also been shown to result in a profoundly prothrombotic state leading to both micro- and macro-thrombotic disease [10]. At present, the specific pathophysiology underlying this hypercoagulable state remains unclear; proposed mechanisms include a combination of hyperinflammatory processes triggering thrombo-inflammation; dysregulation of complement, fibrinolytic and plasminogen systems; and viral-mediated endothelial cell injury [47]. However, this is not specific to COVID-related ARDS; ARDS in general is associated with pulmonary thrombosis and it is not clear that COVID-related ARDS has more or less thrombosis than non-COVID related ARDS.

Thromboembolism and hypercoagulability may be implicated in pathogenesis of pulmonary fibrosis. Epidemiologic observations have supported this possibility. [17,25,26] A large cohort study showed that the incidence rates of ILD were higher in patients with a history of venous thromboembolism or pulmonary embolism than in control patients [43]. A possible mechanism would be pulmonary emboli leading to lung injury and damage, triggering or contributing to fibrosis [43]. Grosse et al. evaluated the spectrum of cardiopulmonary histopathology of COVID-19 based on non-minimally invasive autopsies, and their findings revealed different stages of DAD in all fourteen patients assessed, with the presence of thrombotic/thromboembolic vascular occlusions in an overwhelming majority (11/14) [44]. Thus,

pulmonary artery thrombi in COVID-19 may be attributable to dysregulation of the inflammatory and reparatory mechanisms as a result of DAD. Prior autopsy series from patients infected with SARS-CoV-1 seem to support this theory as the authors considered fibrin microthrombi in small pulmonary arteries as a common finding of DAD, however, this is a common finding in autopsies of patients with ARDS from other disease states and may simply be a reflection of illness severity.

3.5. Pro-Inflammatory State and post covid lung fibrosis

Immunological dysregulation, also known as the "cytokine storm", may be a significant contributor to multiorgan dysfunction. [15] Many cytokines have been reported at elevated levels in COVID-19 cases, including IL1-β, IL-6, IL-7, IL-8, and tumor necrosis factor-α (TNF-α). Elevated proinflammatory cytokines correlate with disease severity [45,46]. The immune induced mechanism of PF is important to address. Immune-related damage contributes to COVID related ARDS. [12-17] Also, transforming growth factor beta (TGF-β) is a cytokine thought to be a crucial mediator of initiation and progression of fibrosis and remodeling [47]. Its expression is increased in animal models of PF and in human lungs with IPF [48]. IL- 6 and IL-16 are other cytokines that may also be implicated in lung or other organs' fibrosis [49,50].

3.6. Impact of CT severity on Post COVID Lung Fibrosis

CT severity as the best visual marker of severity of COVID-19 pneumonia which can be correlated with inflammatory markers as IL-6, ferritin, CRP, LDH, D-dimer and lymphopenia, lymphocyte platelet ratio, and it will help in triaging cases in casualty and help in targeting interventions in indoor units accordingly to have successful treatment outcome. [29-34] CT severity classification done according to anatomical involvement of lung parenchyma in both lungs in different lobes and segments. As CT severity increases the lung involvement is also increases. Thus, CT severity score more than 12/25 was associated with lung fibrosis and is correlated well with inflammatory markers. [29-34] A large single center study involving more than 6000 cases with long covid symptoms has documented post covid fibrosis in significant number if cases at three months following discharge form hospital. [51] Authors have mentioned CT severity is good predictor of requirement of interventions in indoor unit during hospitalization and very well correlated with inflammatory markers. Higher the CT severity, there will be more lung parenchymal necrosis and inflammatory burden which exaggerate lung inflammation and more synergistic effect on lung healing with altered repair resulting into fibrosis. [29-34,51] Authors have also documented that reversible nature of post covid lung fibrosis with antifibrotics mediations such as Nintedanib and pirfenidone. In their study, follow up HRCT thorax done at one year before labelling as reversible nature of post covid lung fibrosis. [52]

3.7. Post covid lung: is it fibrosis (PCLF) or sequel (PCLS)?

Initially after first wave of COVID-19 pandemic, many covid survivors in intensive care units those required oxygen supplementation, ventilatory support or high flow nasal canula, longer hospital stay, high CT severity were documented post covid lung fibrosis. The development of pulmonary fibrosis is considered one of the key concerns regarding COVID-19 pulmonary sequelae as it is associated with architectural distortion of the lung parenchyma and overall impairment of lung function resulting in decreased quality of life. [8,51] The pathogenic progression of pulmonary fibrosis post-COVID-19 is yet to be fully illuminated; however, it is thought to be multifactorial. Whatever the cause, fibrosis is considered to be due to the abnormal healing of the injured lung parenchyma. In COVID-19 patients, possible sources of injury include cytokine storm due to improper inflammatory response, bacterial co-infections, and thromboembolic events causing microvascular damage and endothelial dysfunction. [51,52,73] According to the literature, pulmonary fibrosis can develop right after discharge or several weeks later. [8]

Post covid lung fibrosis at any stage ranging from minimal lung parenchymal abnormalities as parenchymal bands to reticular opacities and complete architectural distortion with or without tractional bronchiectasis and honeycombing shown near complete resolution in one to two years. Authors have also mentioned role of anti fibrotics in some cases and some cases were treated with short course of steroids. Authors have mentioned that some cases shown complete recovery without treatment with steroids and antifibrotics. Thus, post covid lung abnormalities or lung fibrosis is completely reversible process. [8,51,52,53]

3.8. Role for antifibrotic therapy with Nintedanib or Pirfenidone

Pulmonary fibrosis is one of the fatal complications in severe or critical COVID-19 patients [54,55]. Based on the resemblance of pulmonary fibrosis' pathophysiological mechanisms between IPF and COVID-19 infection, it is considered that IPF regimens could be beneficial in COVID-19 pneumonia treatment. The clinical rationale of using antifibrotic therapy in COVID-19 patients is to prevent complications of ongoing infection, stimulate the recovering phase, and control the fibroproliferative processes [56].

The first clinical trial of Nintedanib started in April 2020. A single-center, randomized, placebo-controlled trial on the efficacy and safety of Nintedanib for the treatment of lung fibrosis in patients with moderate and severe COVID symptoms was initiated. The cohort included patients 18–70 years old suffering from fibrosis of both lungs after recovery from COVID. The primary efficacy endpoint was the FVC measurement after eight weeks of therapy; the secondary endpoints were DLCO levels, 6MWT parameters, and HRCT eight weeks after therapy [57].

Another clinical trial of pirfenidone in patients with fibrotic changes after COVID was launched in August 2020 [58]. The established inclusion criteria selected (1) adults older than 18, (2) who had verified SARS-CoV-2 infection (3) that led to severe pneumonia and ARDS (4) with convalescence and/or clinical and radiological signs of pulmonary fibrosis on a high-resolution CT (HRCT) scan (with fibrotic changes of no less than 5% after recovery). This trial aimed to study how pirfenidone affected COVID-induced fibrotic changes, the level of forced vital capacity (FVC) of the lung, if it lowered oxygen uptake during exercise, increased exercise tolerance during the 6-min walking test (6MWT), requests for hospitalization (general as well as associated with respiratory disease), requests for emergency or outpatient care due to respiratory diseases, lung transplants, and mortality.

Lastly, we recommend to assess inflammatory markers assessment in all cases suspected with post covid lung fibrosis at discharge with suspected symptoms with oxygen requirement during follow up in post covid care setting especially those having any long covid manifestations [59-63]. These markers have played significant role in assessment of cases form entry point to follow up and sequential change will guide to predict early chances of post covid lung fibrosis in selected cases of recovered COVID-19 cases as analyzed with spirometry in outdoor settings. [63-69].

4. Conclusion

In the present case report, we have documented acute hypoxic respiratory failure with ARDS caused by COVID-19 pneumonia. He required aggressive interventions in intensive care unit with BIPAP/NIV for three weeks and HFNC for two weeks. He was managed with protocolized approach including Remdesivir, low molecular weight heparin, methylprednisolone and antibiotics meropenem and teicoplanin. We have further treated with steroids, antifibrotics, oxygen supplementation at home during rest and ambulation and observed satisfactory clinical, laboratory, lung function improvement at three months and near complete improvement after one year of treatment. Final radiological outcome was excellent without any significant residual lung parenchymal abnormality. His lung function tests as 6-minute walk test and spirometry also shown significant and near normal improvement.

Key learning points from this case report are:

- Post covid lung fibrosis is commonly documented and overestimated during COVID-19 pandemic and distressed patients and pulmonologists globally. Patients with a greater risk for post-COVID-19 pulmonary fibrosis include those who are older, male, and smokers and have comorbidities.
- Other characteristics during the acute phase that enhance the risk of pulmonary sequelae include the presence of dyspnea, duration of hospitalization and intensive care unit stay, use of high-flow oxygen support, need for mechanical ventilation, severity, and development of ARDS. Additionally, higher levels of C-reactive protein, interleukin-6, lactic dehydrogenase, and D-dimer are associated with a greater risk of such pulmonary lesions.
- The pathogenesis of post-COVID-19 pulmonary fibrosis is partially known and likely multifactorial. The mechanisms associated with such pulmonary lesions include the linkage with angiotensin-converting enzyme receptor 2, epithelial and endothelial to mesenchymal transition, and cytokine storm, with activation and migration of several inflammatory cells. Excessive production of reactive oxygen species and non-protective mechanical ventilation are other potential triggers for post-COVID-19 pulmonary fibrosis.
- Tomographic features identified in pulmonary fibrosis secondary to COVID-19 include the presence of architectural distortion, reticular opacities, traction bronchiolectesis, ground-glass opacities, mosaic attenuation, and honeycombing. Strategies to reduce the severity and progression of post-COVID-19 are unclear. Potential therapeutic modalities include anti-fibrotic drugs, prolonged use of corticosteroids, other anti-inflammatory and immunosuppressive drugs, spironolactone, mesenchymal stem cells, and lung transplant.
- Post covid lung fibrosis is considered as ‘health issue of great concern’ initially in post pandemic phase of first wave, and due to its resolving nature over time period; now considered as ‘sigh with relief’ due to its reversible pathophysiology. Post covid sequel is minimal residual effects of COVID-19 lung disease irrespective of disease severity in past. We recommend to use term post covid sequel over post covid lung fibrosis.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

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.

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