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Case Report

Persistent Residual Lung Abnormalities (PRLAs) as Post COVID Lung Sequel in Recovered Severe Pneumonia Case with Lung Function Abnormality at Two Year Follow Up

Abhishek Vairagade[1], Omprakash Bhangdiya[2], Shital Patil[3*]

[1]Junior Resident, Radiodiagnosis, MIMSR Medical College, Latur, India
[2]Professor, Radiodiagnosis, MIMSR Medical College, Latur, India
[3]Professor, Pulmonary Medicine, Venkatesh Chest Hospital, Latur, India

***Corresponding Author:** Shital Patil
Professor, Pulmonary Medicine, Venkatesh Chest Hospital, Latur, India

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Abstract: Coronavirus related (SARS-CoV-2) global pandemic has caused significant mortality and morbidity globally in the last three years. Although, pandemic has waned since last year, we are not in great peace of relief due to lingering effects of COVID-19 persisted even after two years of illness. Radiological phenotypes are radiological patterns or observable characteristics of COVID-19 pneumonia. Radiological outcomes are initially interpreted as post covid lung fibrosis in short term follow-up of recovered COVID-19 cases in post covid care settings and during long term evaluation these abnormalities are defined as post covid sequalae's. In present case report, 38-year male, presented in outdoor unit for shortness of breath on exertion with history of severe COVID-19 Pneumonia resulted into acute respiratory distress syndrome with hospitalization in intensive care unit one year back and required high flow nasal cannula (HFNC) with Non-invasive ventilatory support (NIV) for two weeks. He was offered oxygen supplementation at home with antibiotics for three months and no requirement of oxygen and some respiratory symptoms even after one year. His HRCT thorax documented at one year of discharge from hospital revealed typical interstitial opacities labelled as Persistent Residual lung abnormalities (RLAs) which are predominantly reticular and linear opacities in peripheral parts of lungs without honeycombing within typical pleural based areas with parenchymal bands and minimally altered lung architecture and preserved lung volume.

Keywords: COVID-19 Pneumonia, HRCT Thorax, Residual Lung Abnormalities, Radiological Phenotype, HFNC, NIV, Inflammatory Markers.

INTRODUCTION

COVID-19 pandemic has evolved over a period of three years with significant mortality and morbidity reported worldwide. Initially, during post covid phase hurdles for clinical and radiological recovery were delayed resolution of lung parenchymal abnormalities occurred during natural COVID-19 illness. Post covid lung fibrosis was the initial term used by researchers and medical experts globally to describe radiological abnormalities after COVID-19 illness & correlating radiological patterns in lung fibrosis were more of interstitial type than alveolar type. Published data reported post covid lung fibrosis in one third of recovered COVID-19 cases in early follow up done during six months of discharge from hospital [1-4]. Lung fibrosis is term with dismal prognosis as per the available evidence for fibrotic lung disease and documented in early short-term follow-up studies which is an indicator of poor outcome.

Post covid lung fibrosis is predicted during course during hospitalization by analyzing oxygenation status, duration of illness, radiological CT severity, laboratory inflammatory markers titers such as CRP [5-8], LDH [9-12], IL-6 [13-18], D-dimer [19-22], and ferritin [23-27], and interventions required during indoor period for the management.

Actually, these clinical, laboratory and radiological markers were considered as 'composite index' which has shown major clinical and radiological outcome defining role observed during treatment and follow up evaluation in post covid care settings [28-29].

Radiological phenotyping will guide during severity assessment at entry point, training and treatment planning of cases during hospitalizations and help in predicate final clinical and radiological outcomes. Authors have studied various types of radiological phenotyping and observed their role in COVID-19 cases as mentioned earlier [30, 31]. Published literature of two radiological phenotypic methods such as 'easy to treat and difficult to treat' & 'evolving and evolved phenotypes' showed significant impact on predicting final radiological outcomes including post covid lung fibrosis [32-34]. Other phenotyping methods were published in abstract short-term analysis such as anatomical, topographical, clinical pathology radiological and pathological classifications [30, 31].

In long term Follow-up of recovered COVID-19 cases showed remarkable improvement in post covid lung abnormalities such as interstitial and alveolar opacities which were initially labelled as post covid lung fibrosis [35-38]. All these opacities were resolved in proportionality large number of affected areas of lung parenchyma and very minimal residual lung abnormalities were reported in majority of cases. still, large number o these cases were having lung function abnormalities documented in lung function tests or spirometry assessment after one year of discharge form indoor settings [39, 40].

Authors [41, 42] have classified Persistent type of RLAs ad and defined as "Lung parenchymal abnormalities in HRCT imaging typically documented as interstitial with parenchymal bands or lines & interlobular septal thickenings or linear opacities. Alveolar opacities with resolving or healed consolidation showing some loss of lung volume. These RLAs are usually bilateral, anatomically demarcated, predominantly peripheral and importantly showing some anatomical distortion but with reticular opacites with or without honeycombing and with or without significant loss of lung volume."

Hence post covid lung fibrosis is not right terminology and most distressing to clinicians and patients of recovered this dreadful COVID-19 illness. Post covid lung sequel may be alternative term to post covid lung fibrosis [43].

CASE SUMMARY

51-year-old, male, shopkeeper by occupation admitted with acute respiratory disease with respiratory failure of recent onset during second wave of COVID-19 pandemic. He was tested COVID-19 RT PCR positive and hospitalized in a respiratory intensive care unit. He was having respiratory symptoms such as dry cough, fever and shortness of breath of one week duration. He was treated at COVID community care center (CCC) for one week and referred to our center after clinical deterioration. His relatives brought a patient to our center with HRCT thorax which has shown CT severity score of 20/25 i.e., severe category of CT Severity scoring. We have documented clinical examination findings as increased respiratory rate to 30 breaths per minute, heart rate 120 per minute, blood pressure 100/60 mm hg and oxygen saturation as 70% at room air and 80% with oxygen support with NRBM (non-rebreathing mask) @18 liters per minute. Her respiratory system examination revealed vesicular breath sounds in bilateral lung fields with adventitious sounds as bilateral crepitations heard over mammary, axillary, interscapular and infrascapular areas. Other systemic examinations were normal.

We have retrospectively analysed laboratory parameters during hospitalization at entry point and noted four-fold raised inflammatory markers such as CRP, IL-6, D-dimer, Ferritin, and LDH. HRCT thorax documented bilateral ground glass opacities and consolidations in upper, middle and lower lobes. [Image 1] HRCT showing consolidations in peripheral pleural based areas extending to central areas, denser in lower lobes with typical crazy paving patterns. Consolidations progressed from peripheral to central portions of lung till hilum [Image 1]. He required oxygen supplementation at 15 liters on admission and gradually decreased to 2 liters per minute to maintain oxygen saturation above 90 %. He was discharged to home after 22 days of hospitalization with advice for continuous oxygen supplementation at 2 liters during rest and increase to 4 liters during ambulation.

Follow-up HRCT done at one year follow-up showed significant reticulations with fibrotic bands, linear opacities and preserved lung volume in Lung windows [Image 2]. Patient was treated with antifibrotics Nintedanib 100 mg three times for six months post discharge from hospital and advised for regular treatment with antiplatelet clopidogrel rosuvastatin 75 plus 10 FDC for 2 years and Nintedanib 100 mg two times till one years with advice for regular follow-up in outdoor unit. His symptoms were improved and we have stopped antifibrotics afterwards and offered pulmonary rehabilitation and breathing exercises with continued antiplatelet medications. We have done rheumatologic workup to rule out underlying CTD by doing ANA profile and results were inconclusive. His spirometry values post-bronchodilator FEV1 is 83%, FVC 71% & FEV1/FVC is 116%. He was maintaining saturation above 90% at rest and during ambulation as well. We have done his 6-minute walk test and documented 495 meters walk distance with minimal breathlessness and normal oxygen saturation at completion of test.

Persistent radiological phenotype according to HRCT thorax findings in our case would be predominantly reticular and linear opacities in peripheral parts of lungs without honeycombing within typical pleural based areas with parenchymal bands and minimally altered lung architecture and preserved lung volume in both lungs [Image 3].

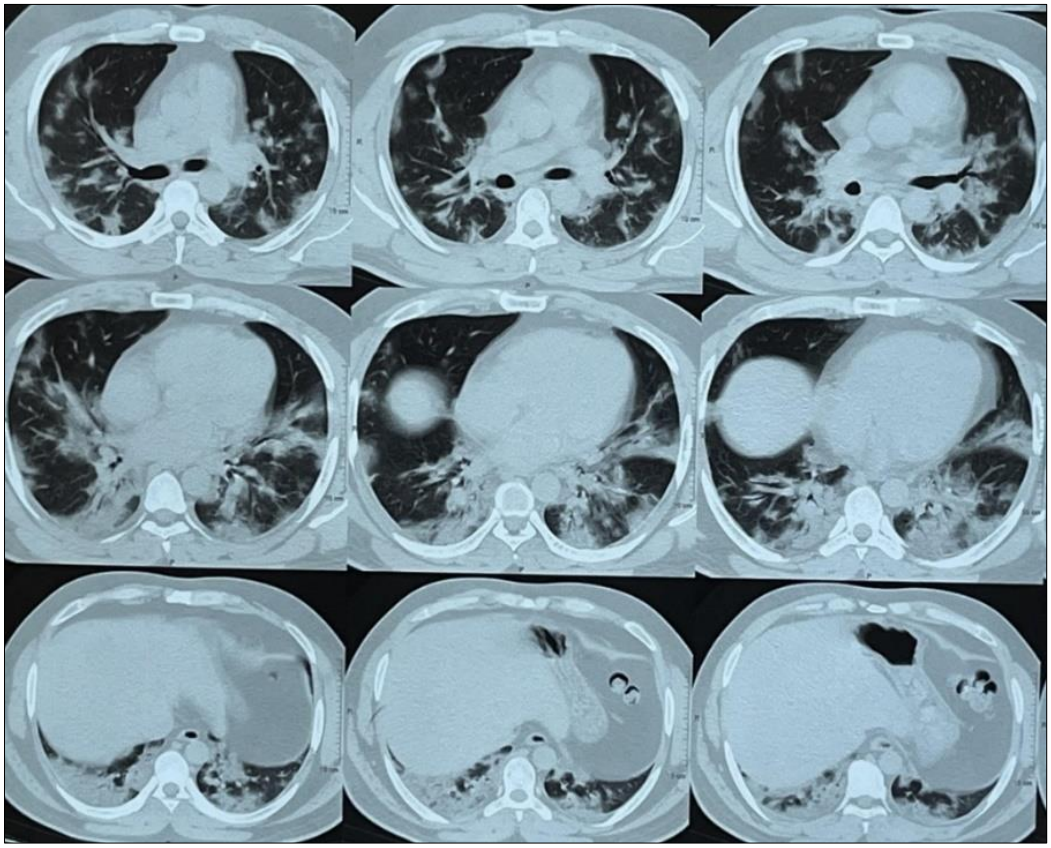

Image 1: HRCT thorax showing bilateral GGOs and consolidations in upper, middle and lower lobes with crazy paving

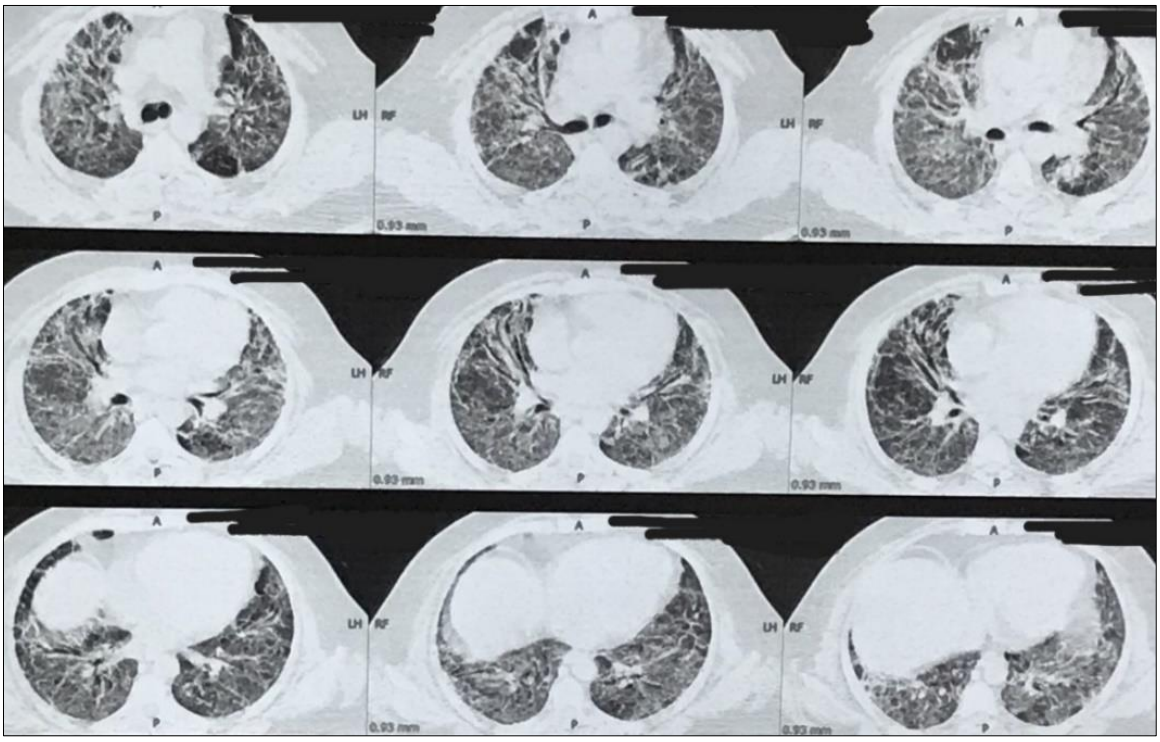

Image 2: HRCT thorax showing Persistent residual radiological lung abnormalities (PRLAs) all lobes with reticulations and fibrotic bands in middle and lower lobes done at one year follow-up

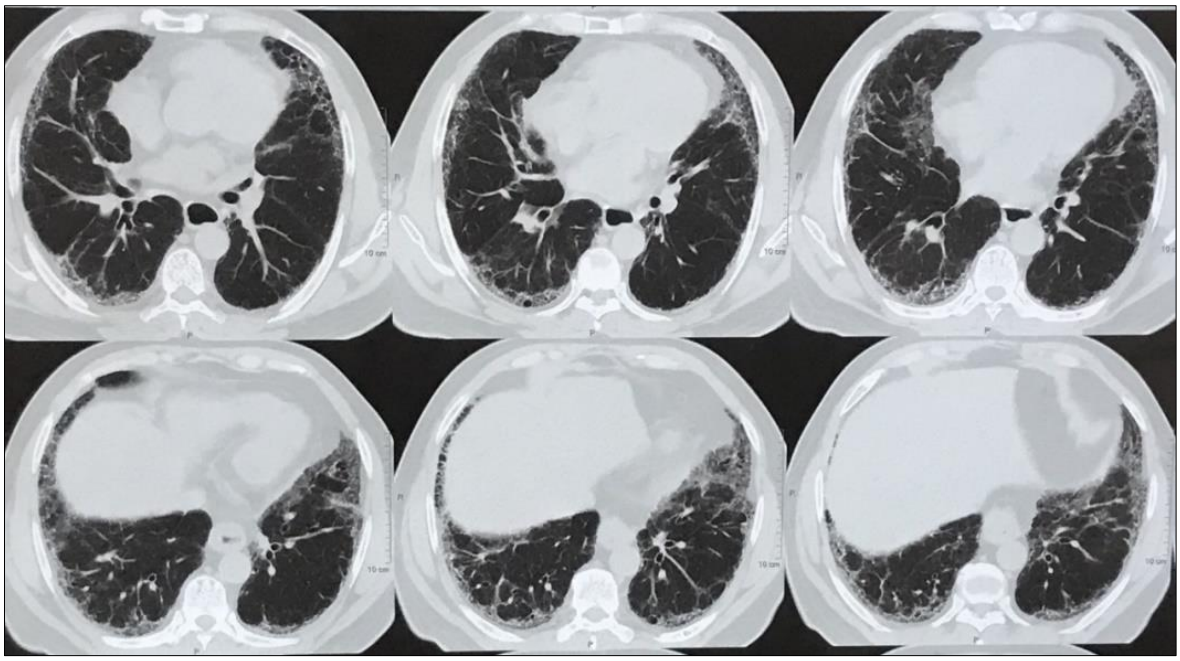

Image 3: HRCT thorax showing Persistent residual radiological lung abnormalities (PRLAs) as final outcome phenotype done at 2 year follow-up with linear, reticular opacites, resolved significantly in comparison with previous scan at one year

DISCUSSION

Long covid is more prevalent chronic health care issue in post covid care settings. We are in great piece of relief due to nearly end of this deadly pandemic which has caused significant change in routine of entire globe. Long covid is an unpredicted sequel of COVID-19 disease documented nearly in half cases globally. Long covid is multisystem syndrome with nonspecific symptoms and organic signs of unidentified pathology occurs after COVID-19 disease. Long covid symptoms has been documented in 'selected' cases irrespective of disease severity or hospitalization and possible link remains unknown. Long covid symptoms has significant impact on quality of life in those cases suffered from disease in recent past and lingering to almost two years since infection. Importantly, not all cases of COVID-19 were shown long covid symptoms. Most common long covid symptoms as joint pain, fatigability, chest discomfort, shortness of breath, hair loss, chest pain, weight gain, anxiety/depression & memory impairment. Pathophysiology resulting into long covid manifestations is still not completely validated. Researchers have reported 'immune dysregulation', 'autoimmunity', 'antigenic mimicry' & 'coagulation abnormalities' are probable pathophysiological mechanism for long covid. Some of the long covid effects shown complete reversibility including post covid lung fibrosis. Reboot system to restore immune dysregulation and recovery in long covid is real concern. Long covid symptoms cases are more health conscious and usually follows pattern of doctor shopping due to underestimation by family physicians either due to lack of suspicion or lack of knowledge regarding treatment protocol. Still, we are not having right answer for exact duration of long covid symptoms and when it will show complete reversibility. Further, it needs 'birds eye vision' to pick up and manage cases with long covid manifestations during routine care in rehabilitation unit [44-51].

Lung is the primary target organ in COVID-19 disease with diverse clinical and radiological presentations and outcome. It has caused minimal to moderate lung disease in some patients and in some cases caused deadly acute respiratory distress syndrome (ARDS). COVID-19 disease caused lung damage by direct virus induced alveolar damage, cytokine induced alveolar and vascular damage and microvascular thrombosis resulting into acute hypoxic respiratory failure. COVID-19 pneumonia evolved over period of three weeks in cases with ARDS as natural course of illness. Usually, ARDS resolves by fibrosis or resolution as final outcome. Similarly, in COVID-19 recovered cases of advanced disease or those suffering from ARDS are having post COVID lung disease. 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. 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 [52-59].

Post COVID Lung Predictors and Pathophysiology

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). 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). Potential contributing etiologies for PCPF include viral pneumonia and pneumonitis; ARDS from COVID-19 pneumonia and COVID-19 related sepsis; trauma due to prolonged mechanical ventilation (MV); thromboembolism; hyperoxia; and dysregulations in the immune response. 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. Post COVID lung fibrosis (PCLF) or Post COVID pulmonary fibrosis (PCPF) pathway is shown in figure 1. There has been some discussion on P-SILI (patient-self-induced lung injury), a form of lung injury that is thought to occur early in ARDS, in which strong spontaneous breathing effort may contribute to lung damage, and there has been debate on if this should affect timing of intubation [60-63].

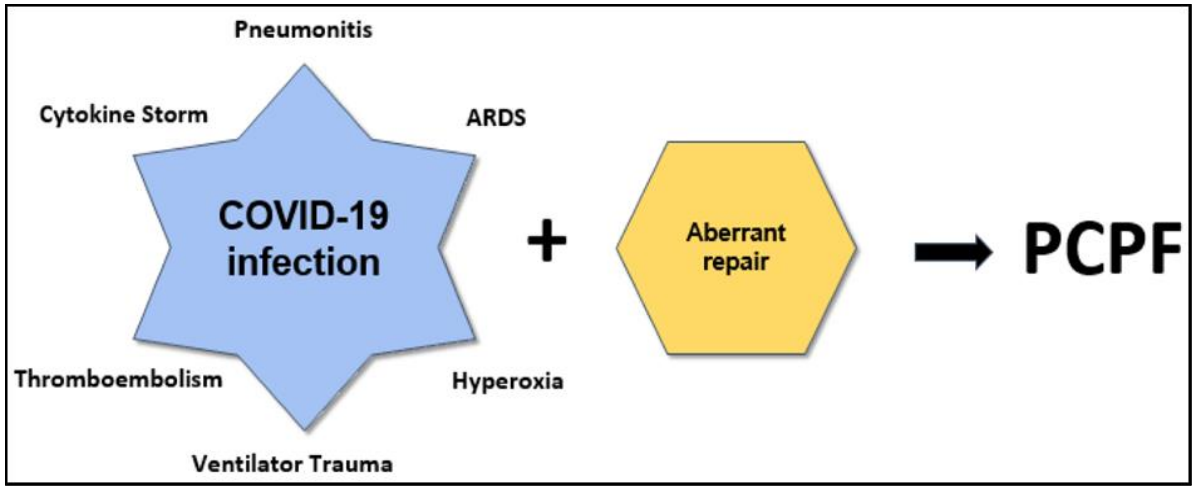

Figure 1: Injury →Inflammatory response → Repair → Fibrosis

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 [64]. These patients tended to have low diffusing capacity for carbon monoxide (DLCO) supporting direct pulmonary injury impacting gas exchange [65]. 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. In response to viral mediated lung damage, dysregulation of epidermal growth factor receptor (EGFR) signaling may lead to a prolonged and exaggerated wound healing response, leading to fibrosis [66].

Direct Trauma from Mechanical Ventilation and Post COVID Lung Fibrosis

A postulated role of prolonged mechanical ventilation-induced lung injury (VILI) in PF has been outlined by several authors [67]. 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. 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. ARDS causing respiratory failure is a frequent cause of morbidity and mortality in COVID-19 patients and often is the reason they need MV [68]. The initial inflammatory injury of ARDS to the lung may be augmented by mechanical forces of MV. VILI presents similarly to and is clinically indistinguishable from ALI/ARDS; 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 [69].

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. 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 [70]. 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 [23-27]. 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 [71]. A possible mechanism would be pulmonary emboli leading to lung injury and damage, triggering or contributing to fibrosis [71]. 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) [72]. 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.

Pro-Inflammatory State and Post COVID Lung Fibrosis

Another mechanism more recently hypothesized as a potential contributor to the immune dysregulation and hypercoagulable state found in COVID-19 patients are neutrophil extracellular traps (NETs). Activated neutrophils have the unique ability to form NETs, which are weblike structures rich in host DNA, modified histone proteins, and granule proteins such as neutrophil elastase (NE) and myeloperoxidase (MPO). Initially discovered for their role in bactericidal activities, NETs are now hypothesized to be involved in a variety of infectious and non-infectious processes that lead to lung damage, thrombosis, and fibrosis. Interestingly, NETs have been found in the airways and pulmonary microcirculation of COVID-19 patients, but were not detected in the lungs of patients who died of other causes. Further investigation is required to more specifically elucidate whether NETs are directly involved in the formation of pulmonary micro-thrombi, but it is possible that under hyper-inflammatory conditions such as those induced by severe COVID-19 infection, NETs could represent a mechanism by which neutrophils contribute to thrombus formation, host-system repair dysregulation, and subsequent pulmonary fibrosis formation. A possible mechanism by which NETs may contribute to PCPF is that in advanced stages, NETs could be replaced by collagen networks [73, 74].

Immunological dysregulation, also known as the “cytokine storm”, may be a significant contributor to multiorgan dysfunction. 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. The immune induced mechanism of PF is important to address. Immune-related damage contributes to COVID related ARDS. Also, transforming growth factor beta (TGF-β) is a cytokine thought to be a crucial mediator of initiation and progression of fibrosis and remodeling. Its expression is increased in animal models of PF and in human lungs with IPF. IL- 6 and IL-16 are other cytokines that may also be implicated in lung or other organs’ fibrosis [13-76].

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. 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 [6-27]. 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 [44-46]. 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 [6-27]. 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 [41, 42].

Does Decreased Oxygenation Status or Hypoxia during Hospitalization Triggers Post COVID Lung Fibrosis or These are two Sides of Same Coin?

Prolonged hypoxia's effect on the development of interstitial pulmonary fibrosis is not specific to COVID-19 but well-documented in the literature [60-62]. Some studies have suggested a link between hypoxia and the development of pulmonary fibrosis, citing the aberrant interplay between hypoxia, fibroblast formation, and extracellular matrix (ECM) deposition. This been supported by studies showing that hypoxia-inducible factor 1-alpha, (HIF-1-alpha), is implicated in initiation and progression of multiple types of tissue fibroses [77].

Hypoxia has documented important trigger for post COVID lung fibrosis. Hypoxia resulting from more advanced lung parenchymal disease as per CT severity which is very well correlated with advanced interventions requirement in intensive care units such as high flow nasal canula (HFNC), non-invasive ventilation (NIV) and invasive mechanical ventilation (MV) [21-27]. Oxygenation status was proportional to disease severity and inflammatory burden. Thus, COVID-19 cases with hypoxia are indirect marker for future post COVID lung fibrosis irrespective of interventions. Authors have documented interventions in intensive care unit has significant association with reversal of hypoxia and inflammatory burden. But this will have minimal effect on final radiological outcome as post COVID lung fibrosis [78].

By the same token, hyperoxia or prolonged exposure to excessively high amounts of supplemental oxygen has also been documented to lead to PF (DAD histopathology) [21-27]. This is difficult to mitigate in COVID patients with profound hypoxemia who are susceptible to the more acute effects of tissue hypoxia, but this mechanism is worth considering, especially with regards to growing understanding of what constitutes acceptable oxygen levels in this illness [79].

Does Inflammatory Makers Analysis During and During Follow Up Predicts Post COVID Lung Fibrosis?

Authors have documented that the follow-up inflammatory markers titer during hospitalization as compared to entry point normal inflammatory markers such as CRP, Ferritin, D-dimer, IL-6 and LDH has significant association in post-COVID lung fibrosis during follow up assessment at three months. They have specifically mentioned that a small fraction of nonsevere patients developed into severe cases in the first 2 weeks after symptom onset. Therefore, health care institutions should also pay close attention to the mild patients, identify progressors early, and provide appropriate treatment to reduce mortality [2-27].

Authors have documented that the Follow-up inflammatory markers titer during hospitalization during hospitalization as compared to entry point abnormal inflammatory markers such as CRP, Ferritin, D-dimer, IL-6 and LDH has significant association in post-COVID lung fibrosis during follow up assessment at three months [16-27]. Authors have documented that serial inflammatory markers measurement of during hospitalization irrespective of entry point level has very well correlation with outcome and requirement of interventions in intensive care setting, which will indirectly help in predicting future risk of development of post COVID lung fibrosis in majority of cases required aggressive interventions like high flow nasal canula, BIPAP/NIV, ECMO, Invasive mechanical ventilation irrespective of inflammatory markers level reaching to cytokine storm. Serial measurements also predict chances of lung fibrosis in these patients as cytokine induced lung damage resulted in lung necrosis and resultant lung fibrosis [20-27]. Few studies have documented inflammatory markers analysis after few months of follow-up is not very good predictor of post COVID lung fibrosis especially after one year duration [20-27]. Authors have mentioned that retrospective analysis of cases required ventilatory support, poor oxygenation status and four fold raised inflammatory markers were key pointers for post COVID lung fibrosis [2-27].

Why Post COVID Lung Fibrosis Outcomes Were Different During Different COVID-19 Waves?

Genetic makeup of corona virus was determining factor for overall outcome different waves COVID-19 as in first was classical 'Wuhan variant virus' and second one was mutant 'Delta variant' corona virus; and third wave 'omicron variant'. Delta variant was deadly mutant documented in second wave which was associated with increased morbidity and mortality. In all the waves, COVID pathophysiology were same i.e., immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues. Rapidly evolving pneumonia or 'accelerated acute respiratory distress syndrome' (a-ARDS) was more commonly documented in second wave and more number of patients were presenting with similar syndrome in second wave with time interval of less than a week, with rapidly deteriorating radiological and clinical-laboratory parameters like increased CT severity score, worsened oxygenation, increased inflammatory markers like CRP, IL-6, Ferritin, LDH, D-dimer, decreased leucocyte and platelet counts. Post-COVID lung fibrosis and mucormycosis were two deadlier complications documented during the evolution of COVID-19 pneumonia, predominantly in the second wave as compared to the first wave across the country. Rational for the occurrence of both the complications was not clear, post-COVID fibrosis was documented more commonly in the second wave and related to more virulent nature of mutant Delta variant virus as compared to Wuhan variant of the first wave [80-85].

Although mortality documented in COVID-19 is less as compared to SARS and MERS, various variants evolved during COVID-19 disease have different trends of mortality. Importantly why the second wave "delta" variant of COVID-19 has highest mortality as compared to first wave variant, and negligible in third wave omicron variant, is still unknown. Maybe, genetic makeup of coronavirus was the determining factor for overall outcome in the first and second wave different variants of coronavirus with genetic mutations; which was associated with increased morbidity and mortality in comparison to currently ongoing omicron variant with negligible mortality. Pulmonary involvement was predominant over extrapulmonary in second wave with delta variant, pulmonary and extrapulmonary proportionately similar in first wave Wuhan variant and predominant extrapulmonary with minimal pulmonary involvement was commonly documented in third wave omicron variant [86-95]. This diverse presentation is documented all over the world but rational for heterogeneous scenario needs further research.

Various myths regarding Post COVID lung fibrosis have been documented during routine care of these cases in post COVID care settings [86-95]. Survivors of critically ill COVID-19 disease cases were seeking attention regarding doubtful role of remdesivir and steroids in their illness during hospitalization and these rational treatment options for COVID are the link towards post COVID lung fibrosis. This was real myth, and steroids and remdesivir are the only scientifically proven treatment options along with anticoagulants during this pandemic and we have saved millions of lives with these lifesaving medications [86-95]. Social media has played a crucial role in spreading wrong message regarding doubtful role of Remdesivir in COVID-19 and these non-scientific comments and statements spread without available research has created misunderstanding in majority of recovered cases, especially in those facing "long COVID" manifestations.

Evaluation of Post COVID Lung Fibrosis during Follow-Up

Post-COVID-19 pulmonary fibrosis is defined as the presence of persistent and different fibrotic tomographic changes identified on follow-up, often combined with impairment in pulmonary function tests. During follow-up in post COVID care settings, clinical, radiological, laboratory and lung function assessment were key steps during evaluation of Post COVID lung fibrosis. Clinical assessment includes symptoms of cough, shortness of breath, chest discomfort & oxygen saturation, vital parameters at rest and during ambulation. Oxygen saturation and stable heart rate after ambulation is considered as best marker of improvement in these cases. Laboratory assessment of anemia is important in these cases with tachycardia with borderline oxygen saturation during routine walk. Pulmonary functions test & 6-Minute walk test is performed during routine follow-up for more precise assessment of pulmonary and cardiopulmonary status respectively [39-40]. Pulmonary functions abnormality in post-COVID-19 pneumonia cases has been documented and should be assessed cautiously to have successful treatment outcome. Restrictive lung disease is the predominant lung function impairment in post-COVID 19 recovered lung pneumonia cases. Age above 50 years, male gender, diabetes, High CT severity, longer duration of illness, proper timing of initiation of BIPAP/NIV therapy, has documented significant impact on post-COVID lung functions at 12 weeks assessment [39, 40].

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 was 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. 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 [96]. According to the literature, pulmonary fibrosis can develop right after discharge or several weeks later [40-96].

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 [31-43].

Lastly, we recommend to assess inflammatory markers assessment in all cases suspected with any respiratory symptoms during follow up in post covid care setting especially those having any systemic long covid manifestations involving respiratory system [31-43]. 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 respiratory symptoms and post covid sequel in selected symptomatic cases of recovered COVID-19 cases [31-43].

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 [41-43].

Role for Antifibrotic Therapy with Nintedanib or Pirfenidone and Immunomodulators:

Pulmonary fibrosis is one of the fatal complications in severe or critical COVID-19 patients. 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 [2, 3].

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 [97].

Another clinical trial of pirfenidone in patients with fibrotic changes after COVID was launched in August 2020 [98]. 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 [99-100]. 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 [39-40].

L-Arginine is an amino acid with multiple beneficial effects such as immunomodulatory effects which regulates immunological responses that inhibit dysregulated immune system in addition to its universally known antioxidant, vasodilatory and regenerative and cellular proliferation effects on immune cells. Hydroxychloroquine (HCQ) remains a drug with an ever-expanding number of underlying mechanisms. HCQ was tried initially for prophylaxis treatment of COVID-19 due to its anti-inflammatory properties but has not shown any dramatic results. HCQ is a drug with multiple beneficial pleiotropic effects such as immunomodulatory effects which regulates immunological responses that inhibit dysregulated immune system. These Immunomodulatory and or diseases modifying effects of HCQ makes it the future candidate with 'game changer' role for management of Long covid resulting from immune dysregulation as a core pathophysiologic pathway of this Dragon Pandemic [101-102].

CONCLUSION

In our case report, we have documented partially reversible and persistent nature of post covid fibrosis or sequel and reported as persistent residual lung abnormality (PRLAs). Radiological abnormalities presented with fibrosis were treated with a short course of steroids and antifibrotics for three months and observed persistent radiological type. Patient was symptomatic at one year with PRLAs with impaired lung functions during spirometry assessment and showed restrictive lung functions. We have offered inhaled bronchodilators and pulmonary rehabilitation with breathing exercises and observed satisfactory improvement in quality of life.

Clinical Implications of Residual Lung Abnormalities (RLAs) & Final Outcome Radiological Phenotypes as Post Lung Sequalae's in Present Study:

Persistent RLAs:

These radiological abnormalities were clearly differentiated from progressive and resolving types in long term follow-up chest imaging. Proportionate number of persistent RLAs will resolve over a period of additional one year and we have documented in two-year follow-up imaging in selected cases. Few cases have still documented persistent abnormalities even after two years. These abnormalities are not associated with significant impact on quality of life. We have documented spontaneous resolution in persistent RLAs without any antifibrotic treatment during follow-up from diagnosis to second year of follow up. We don't recommend treatment for persistent RLAs.

Key Learning Points from this Case Report Are

1. Persistent residual lung abnormalities (PRLAs) as Final post covid radiological outcome phenotypes are predominantly reticular and linear opacities, usually bilateral, symmetrical or asymmetrical in peripheral parts of lungs without honeycombing within typical pleural based areas with parenchymal bands and minimally altered lung architecture with preserved lung volume.
2. Post covid lung fibrosis is a very disappointing term and should be replaced with post covid sequel and 'Residual lung abnormality' will be more appropriate. Post covid final radiological outcomes can be categorized as resolving, persistent and progressive types.
3. Persistent residual lung abnormalities are the second most common final radiological outcome phenotype after resolving type. This phenotype needs further workup and should keep watch on further progression or resolution in subsequent follow up and at present there is no clear-cut recommendation for use of antifibrotics.
4. Persistent residual lung abnormalities (PRLAs) have shown restrictive lung function abnormalities and these cases are having exercise limitations in few cases in published literature as in our case. These cases should be treated with inhaled bronchodilators and should be prescribed and trained for pulmonary rehabilitation.
5. We recommend these radiological outcome phenotypes as persistent radiological abnormalities (PRLAs) at one year should be considered as sequel from 'pulmonologist perspective' and not fibrosis as per 'radiologist perspective' because former one is best suitable as a predictor of good outcome.

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