

# A COPD Patient Who Developed Pulmonary Fibrosis Following COVID-19: A Case Study

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**Abstract:** The new virus called severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) causing Coronavirus disease 2019 (COVID-19) has spread to several countries and caused the current pandemic. Different types of clinical manifestations are associated with that infection.

Some drugs have been approved such as anti-viral agents but the use of corticosteroids is controversial. Pulmonary fibrosis is a frequent consequence of Covid-19 that may requires a special attention and a specific follow up.

Herein we report a case of a 68-years-old patient affected by SARS-Cov-2 infection complicated by pulmonary fibrosis who healed from Covid-19 infection after a total inpatient stay of 12 days by with remdesivir treatment. The patient presented a chest fibrosis picture at the discharge that went on at 10 days check with a decline of respiratory functional parameters. For this reason a combined treatment with high dose prednisone and N-acetyl-cysteine was started.

The patients benefited from high dose corticosteroids plus N-acetyl-cysteine leading to a clinical and functional improvement. Indeed, the patient underwent a chest CT-scan and spirometry at one month check after the beginning of the treatment.

Notably both the radiological pattern of fibrosis and respiratory function improved after treatment with prednisone 50 mg a day for 15 days followed by 25 mg for additional 15 days and N-acetylcysteine 600 mg twice a day.

**Keywords:** SARS-Cov-2 pneumonia, Covid-19 related pulmonary fibrosis, Respiratory functional analysis, Steroid, Acetyl-cysteine.

## INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) causes the coronavirus disease 2019 (COVID-19) that is a new viral illness that became pandemic with a complex biological structure [1].

The clinical manifestations range from mild illness characterized by fever, dry cough, weakness, sore-throat to severe pneumonia with respiratory failure and its prevalent radiological presentation is an interstitial pneumonia with ground glass infiltrations [3, 4].

Among the possible complications, a pulmonary fibrosis and lung failure may be developed.

Herein we report a case of a COPD patient with a positive oral and naso-pharyngeal swab test for Covid-19 and multiple outbreaks of pneumonia with associated pulmonary embolism at chest CT scan complicated by lung fibrosis.

Our study was approved by the Ethics Committee of Sant'Andrea Hospital- Sapienza University. A consent for publication was provided by the patient.

## Case Presentation

A 68-year-old male presented to the emergency department of our hospital in May 2020 with a ten-day history of fever, dry cough, sore throat, thoracic pain and breathlessness.

He was retired, and he was a bank employee without a professional exposure.

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He is a former smoker with a pack-years of 35 reporting passive smoking exposure.

No interstitial abnormalities were detected at a previous radiological test.

The foremost comorbidity was chronic obstructive pulmonary disease (COPD) documented by a previous spirometry performed in 2019 with a reported rate FEV1/FVC <70%, FEV1 2.1 l (65% of predicted), FVC 3.1 l of the predicted. An additional comorbidity was hypertension.

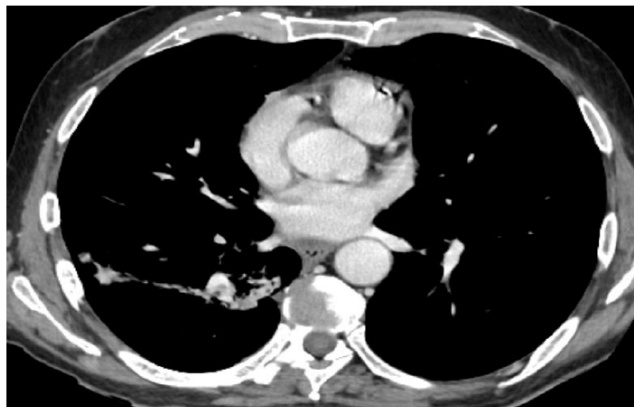
A previous chest X-ray showed only a mild reinforcement of the bronco-vascular pattern.

On examination his respiratory rate was 27 breaths per minute with heart rate of 81 and oxygen saturation of 90% at room temperature. The PaO<sub>2</sub>/FiO<sub>2</sub> was 250. His blood pressure was 110/70 mmHg. There were bilateral basal crepitations on chest auscultation.

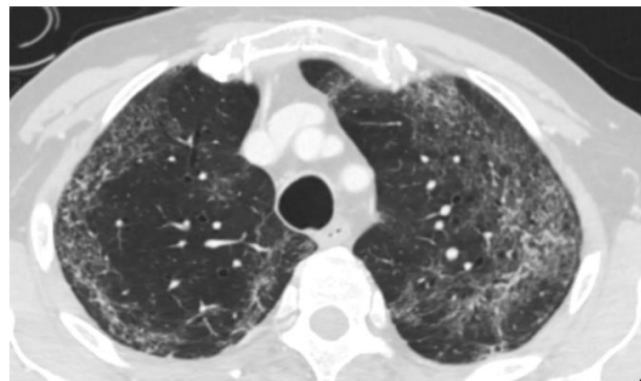
### **Investigations**

A routine blood tests revealed a mild anemia with an elevated D-dimer, a mild lymphopenia of with an increased C reactive protein:

haemoglobin 11.3 g/dl, lymphocytes 650/μl, platelets 150,000/μl, white blood cells 10,000/μl, D-Dimer was 1,000 ng/ml, C reactive protein (CRP) 12.4 mg/dl. At baseline the body mass index was 25, ferritin was 430 ng/ml, D vitamin 27.4 ng/ml, the PaO<sub>2</sub> value was 65 mmHg. A chest CT scan showed a crazy paving pattern with confluent interstitial infiltration mainly located in the upper lobes, compatible with Covid-19 infection. In addition pulmonary embolism was found in the right arterial branches (Figure 1,1A).



**Figure 1:** CT scan of the chest showing thrombo-embolism located in the right lower lobe.



**Figure 1A:** Multi-focal patchy consolidations detected at parenchymal window. Ten days post-discharge check.

Afterwards the patient underwent an oral and nasopharyngeal swab test for rRT-PCR assay with a positive result for Covid-19.

As a consequence the patient was admitted to an internal medicine unit.

### **Treatment During Hospitalization**

The patient required a small amount of oxygen supplement in the first three days of his admission.

He was treated with remdesivir that was started together with a low weight molecular heparin, enoxaparin. Remdesivir was administered at a dosage of 200 mg for a day followed by 100 mg daily for 4 days, enoxaparin was provided at a dosage of 6,000 IU twice a day.

He was also treated with a course of intravenous amoxicillin-clavulanic acid for an adequate anti-bacterial coverage.

On day 10 of admission his breathing work was improved and the SpO<sub>2</sub> was 92% without oxygen supplement.

On day 12 of admission an additional oral and nasopharyngeal swab test was performed with reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay and the result was negative.

Accordingly it was decided to discharge the patient after the receipt of the swab test result. Exertional dyspnea was persisting along with mild cough.

### **Follow Up After the Discharge**

Ten days after discharge the patient performed a spirometry and a diffusion test for carbon monoxide with detection of carbon monoxide transfer coefficient (KCO).

Moreover the patient underwent chemical blood detection. All functional data and chemistry are summarized in Table 1. The flows and dynamic volumes were measured by the pneumotacographic method according to the ATS-ERS guidelines [4]. The post-bronchodilator Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1) were recorded. The bronchodilation was obtained by the administration of salbutamol 400 µg.

The diffusion test was performed with a single breath maneuver recording the transfer of carbon monoxide related to the alveolar volume.

The values were decreased compared with previous lung function test, FEV1 was 1.9 l in absolute value, and 64% of the percentage predicted, FVC value was 2.8 l whereas the carbon monoxide transfer (KCO) was 0.87 mmol/min/KPa/l corresponding to 65% of predicted (Table 1).

A new chest CT scan was performed with a persistence of crazy paving and ground glass pattern located in the upper lobes.

**Table 1: Functional Assessment Before and After Treatment for Fibrosis**

	10 Days After the Discharge	One Month After the Combined Treatment
Pack year	35	
BMI (kg/m <sup>2</sup> )	25	26
CRP mg/dl	12.4	2.6
Vit D ng/ml	27.4	35.2
Ferritin ng/ml	430	320
PaO2 mmHg	65	77
FEV1 l	1.9	2.5
FEV1 %	64%	75%
KCO %	65%	75%
KCO mmol/min/KPa/l	0.87	1.25
FVC l	2.8	3.5
FVC %	75	85
D-dimer ng/ml	1,000	560

CRP(C reactive protein) normal range(0-0.5), Vit D3 (insufficiency 10-30, sufficiency 30-100), ferritin (11-336), PaO2(80-100) DLCO(diffusion lung CO), FVC(forced vital capacity), BMI(body mass index), FEV1.

**Acetylcysteine and Prednisone Combined Treatment**

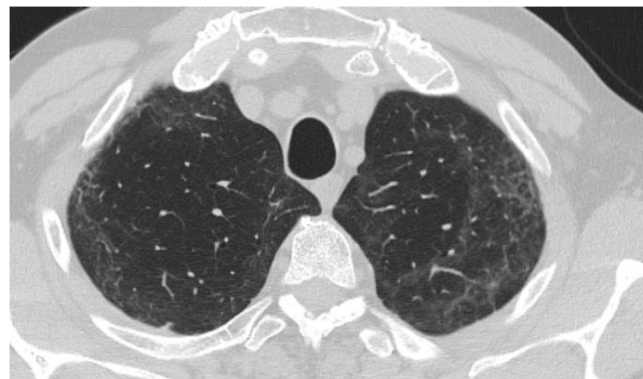
Accordingly a new treatment was started with acetylcysteine 600 mg twice a day and prednisone 50

mg a day for 15 days followed by prednisone alone 25 mg a day for additional 15 days for a total of 30 days.

One month after the beginning of the above treatment a new check was set for chemical parameters and functional evaluation revealing the following results: the arterial SpO2 improved with an increase of PaO2 up to 77 mmHg (Table 1). FEV1 value increased up to 2.5 l, and 75% of predicted value . FVC increased from 2.8 to 3.5 l.

The carbon monoxide transfer, KCO was in turn increased from 0.87 to 1.25. The blood chemistry sample test revealed an improvement of all considered parameters: CRP was reduced up to 2.6, D vitamin was increased up to 35.2, D-Dimer was reduced up to 560 and ferritin value dropped down from 430 to 320.

A new CT scan was also performed 30 days after starting therapy and it showed a significant reduction of the interstitial infiltration as well as a reabsorption of the ground glass opacities compared with the previous CT-scan (Figure 2).



**Figure 2:** CT scan showing the reduction of ground glass lesions. One moth check after the start of the therapy.

**DISCUSSION**

Covid-19 is an aggressive infection whose pathogenetic mechanisms are not yet well understood.

The clinical manifestations range from a sore-throat to a mild or severe pneumonia, and lung failure [1-3].

A frequent clinical evolution of the infection is pulmonary fibrosis which occurs in patients who healed from the disease. In our experience patients admitted to the Hospital with bilateral pneumonia and crazy paving imaging experience an irreversible fibrotic outcome after healing from Covid-19 infection without a specific therapeutic intervention.

The oral and naso-pharyngeal swab test with RT-PCR analysis is the mainstay for SARS Cov-2 diagnosis [6].

Some anti-viral agents were approved off-label for this infection [4] but they can be used in selected patients as well as in the present case.

The present case report points out the possibility of Covid-19 infection to be complicated by pulmonary fibrosis and the need of a new specific treatment. The data highlight the efficacy of prednisone along with N-acetylcysteine (NAC) at high dosage favoring the recovery from fibrosis in a short time.

The rationale of the use of prednisone and NAC is determined by their proved efficacy in pulmonary fibrosis and lung interstitial disorders such as in COPD with exacerbations [7].

In the present study a substantial improvement was observed in terms of respiratory symptoms, chemical parameters and respiratory function. The patient presented COPD as a comorbidity and we know it could affect the survival of Covid-19 [8].

Interestingly the patient had no previous history of interstitial pneumonia.

At the admission the radiological findings of interstitial thickness and ground glass opacities besides pulmonary embolism were found.

The patient presented with mild hypoxia and the clinical course of the disease evolved toward pulmonary fibrosis as a possible consequence of acute and chronic interstitial lung inflammation as we know from the literature [9, 10].

The latter is characterized by unsuccessful reconstruction of the damaged alveolar epithelium, and excessive deposition of collagen leading to the development of acute lung injury.

In the present report the clinical course consisted of a healing from infection but it was not followed by a recovery of normal lung parenchyma.

After one month of treatment by high dose N-acetylcysteine along with high dose prednisone a reduction of interstitial thickening was observed followed by the improvement of alveolus-capillary lung diffusion and all parameters detected by spirometry.

The treatment was safe and well tolerated by the patient without any mention of side effects. There was

no increase in blood pressure and no change in metabolic values.

N-acetylcysteine has some antioxidant properties, inhibiting adhesion molecule expression and cytokine production in lung tissue [10]. In previous studies it was demonstrated that NAC may act reducing inflammatory cells and increasing glutathione levels in the epithelial lining fluids. NAC administration attenuated cellular infiltration in both bronchoalveolar lavage fluid (BALF) and alveolar tissues [11]. The application of high dose NAC therapy along with steroids or anti-fibrotic agents are able to reduce the decline of lung function expressed by parameters such as FVC and DLCO, and slowed the progression in idiopathic pulmonary fibrosis [12, 13].

Pulmonary fibrosis is a possible fatal sequelae of viral infections such as COVID-19.

Although there is currently no clinical data on the frequency and mechanism of post-COVID-19 pulmonary fibrosis, it is deemed to affect around one-third of the patients hospitalized with SARS-COV-2 [14, 15].

Direct evidence for the use of corticosteroids in COVID-19 is very limited, however previous studies showed a controversial application [16].

Steroids were found to be associated with better radiological findings in Covid-19 patients reducing the secretion of inflammatory cytokines such as IL-6 IL-8, IFN- gamma [17, 18].

Indeed, SARS-Cov-2 virus penetrates cells through the binding to two receptors, an angiotensin-converting enzyme (ACE2) and a transmembrane serine protease 2 (TMPRSS2) that are both up-regulated in Covid-19 stimulating a cytokine storm, accordingly steroids are indicated to overcome the downstream inflammatory cascade induction [19, 20].

Regarding vitamin D that was found increased after treatment, we know that a deficit of vitamin D is often associated with the severity of the disease [21]. Since vitamin D Vitamin D can modulate the innate and adaptive immune responses [22] we can deduce that vitamin D increases when the immune and anti-inflammatory response overcomes the infection.

## CONCLUSIONS

Pulmonary fibrosis is a frequent complication of Covid-19 infection which is frequently associated with COPD.

High dosage N-acetylcysteine along with prednisone for one month shows quick efficacy in reducing the interstitial pulmonary fibrosis and leading to a better pulmonary function.

## ETHICS APPROVAL AND PATIENT CONSENT

Our study was approved by the Ethics Committee of Sant' Andrea Hospital- Sapienza University.

A consent for publication was obtained from the patient.

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## DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## AUTHORS' CONTRIBUTION

Conceptualization and writing: Aldo Pezzuto, Massimo Ciccozzi, Data Curation: Giuseppe Tonini, Antonella Tammaro, Massimo Ciccozzi, Alessandro Laviano, Gerardo Salerno.

Nothing to declare

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