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MASSIVE PULMONARY FIBROSIS AFTER SEVERE BILATERAL PNEUMONIA AS POST -COVID-19 COMPLICATION

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Abstract

A large number of hospitalized COVID-19 survivors show that persistent symptoms, radiographic abnormalities and physiological impairments exist months after the initial illness. Persistent chest imaging abnormalities and histopathological findings of lung fibrosis were also found in a majority of survivors of the SARS-CoV-1 suggesting that the SARS viruses may lead to a worse fibroproliferative response than other pneumonias.

Our patient had a severe COVID-19 pneumonia, followed by massive infiltrative changes in both lungs in addition to massive pulmonary fibrosis. After the initial treatment in one of the COVID-19 centers in the Clinical Center in Skopje, the patient with post-COVID-19 (more precisely pulmonary fibrous changes of the lungs) was referred for further treatment to the University Clinic for Pulmonology in a severe clinical condition, where he was treated at an outpatient basis in the period of several months. During that time the condition improved, with a significant withdrawal of the X-ray finding of the lungs, which was registered on CT from 5.5.2021. He is still under observation.

The robust responses of corticosteroid therapy in our case presenting a radiological pattern of organizing pneumonia allowed the patient to return to his baseline clinical condition. But due to the persistence of X-ray residual changes he is under our regular observation.

Keywords: COVID-19, bilateral pneumonia, massive pulmonary fibrosis

Introduction

Pulmonary fibrosis is a feared complication of respiratory infections. Among survivors of severe COVID-19, 20% of non-mechanically ventilated and 72% of mechanically ventilated individuals had fibrotic-like radiographic abnormalities [1].

A diagnosis of post-COVID-19 pulmonary fibrosis should be based on clinical, radiologic, and pathologic information. Lab tests, pulmonary function tests (PFTs), and/or high resolution CT in the setting of a patient with previous or suspected COVID-19 infection may provide evidence to support a diagnosis of post-COVID-19 pulmonary fibrosis.

In the light of current circumstances (shortages of personal protective equipment (PPE), medical providers, and procedural space), it is difficult to justify pursuing high-risk, aerosolizing procedures such as bronchoscopy or surgical lung biopsy for diagnosis, especially since these would not change the management in the acute setting [2,3].

There are no reliable data on the frequency and severity of pulmonary fibrosis associated with COVID-19. Potential contributing etiologies for post-COVID-19 pulmonary fibrosis include viral pneumonia and pneumonitis; ARDS from COVID-19 pneumonia and COVID-19 related sepsis; trauma (prolonged mechanical ventilation; thromboembolism; hyperoxia; and dysregulations) in the immune response. These factors may overlap, and notably, trauma from mechanical ventilation is not necessary for post-COVID-19 pulmonary fibrosis to occur [4].

There has been some discussion on 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 if this should affect timing of intubation [5].

Identifying the predictive factors for the post-COVID-19 lung fibrosis can possibly help in management of such a serious complication through controlling the risk factors and/or administrating the anti-fibrotic drugs in high-risk cases. Specific terminology here can create confusion, and clarification of “post-COVID-19 pulmonary fibrosis” is needed, as it is often used interchangeably to refer to one of the following: post-acute respiratory distress syndrome (ARDS) pulmonary fibrosis [6], post-inflammatory pulmonary fibrosis [7], post-viral pulmonary fibrosis, and post-viral interstitial pulmonary disease (ILD). The etiology, prognosis and progression of post-viral pulmonary fibrosis syndromes may differ from fibrotic ILDs like idiopathic pulmonary fibrosis (IPF) [7].

Wallace *et al.* advocated clarifying nomenclature since fibrosis should refer, by definition, to an irreversible end-state; therefore, he argues "fibrosis" should not apply to the abnormalities seen in cases of post-viral pulmonary fibrosis since these changes could reverse over time [8].

Other authors argue that "fibrosis" can be considered a potentially reversible process, and the term "reversible pulmonary fibrosis" has been used in the current literature [9].

Various CT findings have been reported related to COVID-19 pneumonia with mild to severe lung involvement. Some previous studies also alluded to fibrotic consequences following the infection, which is a considerable issue for the patients' clinical outcomes. For example, a study reported that about one third of the COVID-19 survivors showed fibrotic abnormalities in their CT scans within the 6-month follow-up [10].

Case presentation

Our patient was a 51-year-old male, working as a programmer in a telecommunications company. His main complaints were: fever, lethargy, tightness in the chest, fatigue. Current illness: He was positive for SARS-COV-2 six days before hospitalization due to the deterioration of his clinical condition. The patient was hospitalized in one of the Clinical Covid-19 centars in the Clinical Center in Skopje. Present status: the patient was conscious, oriented in space and time. Osteomuscular structure neat, with normal constitution. Skin and visible mucous membranes normally painted.

Takes an active position in bed, gives the impression of being moderately seriously ill. Chest: normosthenic, symmetrical. Percussion: muffled percussive tone. Auscultation: bilaterally impaired vesicular respiration, diffuse rare bronchial dry rumors, basally and in middle parties bilateral finding of crepitations. Heart: rhythmic action, clear tones, well audible, pathological noises are not heard. Pulse: 80/min, blood pressure: 120/80 mmHg. Other findings by systems: normal.

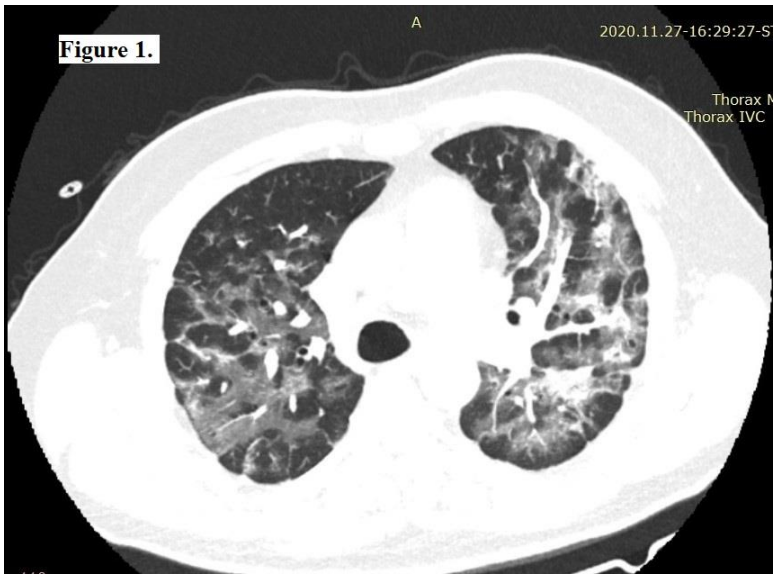

Figure 1.

Decursus morbi and therapy: Following a positive Sars-CoV-2 (nasopharyngeal swab PCR test), the patient was hospitalized because of marked clinical deterioration. From comorbidities there is hypertension. Treatment with dual antibiotic therapy (levofloxacin + ceftriaxone), then with meropenem, low molecular heparin, parenteral glucocorticosteroid: started with dexamethasone (2x4 mg), antihypertensive therapy and oxygen supplementation. After the initial stabilization of the condition, there was deterioration with a decrease in oxygen saturation, and high increase of CRP (up to 154 mg/l), LDH (up to 935 u/l), d-dimers (up to 31735 ng/ml), and extensive X-ray lung changes. Therefore, on 10.11.2020 he was put on pulse therapy with methylprednisolone 240 mg/day, with it gradual reduction. With such intensive therapy, the general condition and laboratory parameters (CRP, LDH, d-dimers) were improved, as well as the findings from the gas analyses. He was discharged from the hospital afebrile (last five days), with recommendation for oxygen support at home (SaO2: 90%). CT of the lungs before the discharge (27.11.2020): bilaterally relatively symmetrical, rough fibroadhesive changes that perform marked distortion of the parenchymal structure but with marked sparing of the subpleural parties bilaterally.

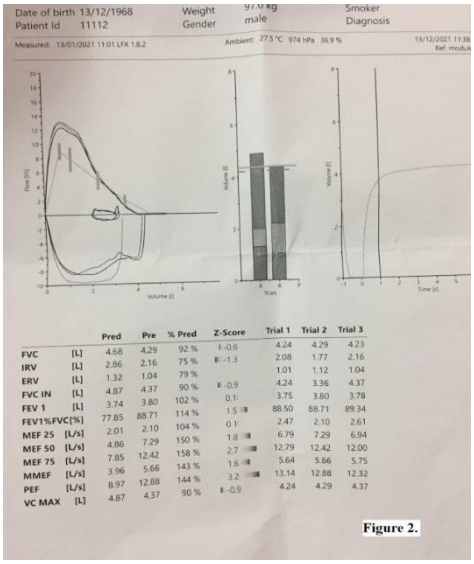

Figure 2.

Changes with slightly lower intensity were followed in middle parties and apically. Blurred demarcated zones of consolidation with attenuation of ground-glass were apically seen. Mediastinal structures - neat. Pleural spaces free. Condition of post-COVID-19 - massive bilateral pneumonia (Figure 1).

The patient was referred to the University Clinic for Pulmonology on 04.12.2020 for further treatment. On examination, the patient was markedly dyspneic, tachypneic, tachycardic, with a finding of attenuated vesicular breathing with prolonged expiration, diffuse finding of sparse shrill bronchial murmurs, and bilateral subcrepitations across both lungs. Gas analyses showed: SaO2: 91.1%, PaO2:7.61, PaCO2:5.2kPa.

The spirometric flow volume curve showed a restrictive pattern of ventilator disorder, although the values of FVC=90%, FEV1=102% were in normal ranges; FEV1/FVC=88.7% was high (Figure 2).

He was prescribed therapy with corticosteroids, vitamins, anticoagulant (d-dimers during hospitalizationn up to 31735, at the end of hospitalization: 1018), hepatoprotective, gastroprotective, inhalation therapy with corticosteroid with LABA and oxygen therapy.

At the next follow-up after two weeks, the patient was in an improved condition, continuing the same therapy (corticosteroid therapy for another month and a half with gradual dose reduction). A CT scan of the lungs was scheduled on the fifth control on 5.4.2021. Diffuse bilateral follow-up residual zones of ground-glass attenuation that give a mosaic aspect to the lung parenchyma. Discrete subpleural strips and reticulations as well as initial bronchiectasis bilaterally basal partie predominantly posterior. Intense zones of alveolar consolidation were not monitored. Pleural spaces free. Comparatively pronounced regression of the primary finding without fibrous reparation with discrete residual zones of opacity of opaque glass is followed. Regular course and regression of inflammatory changes (Figure 3). At the last control on 14.07.2021, the patient felt very good; he returned to work and the values of his gas analyses were normal in relation to his age. The next check-up was scheduled for 2 months

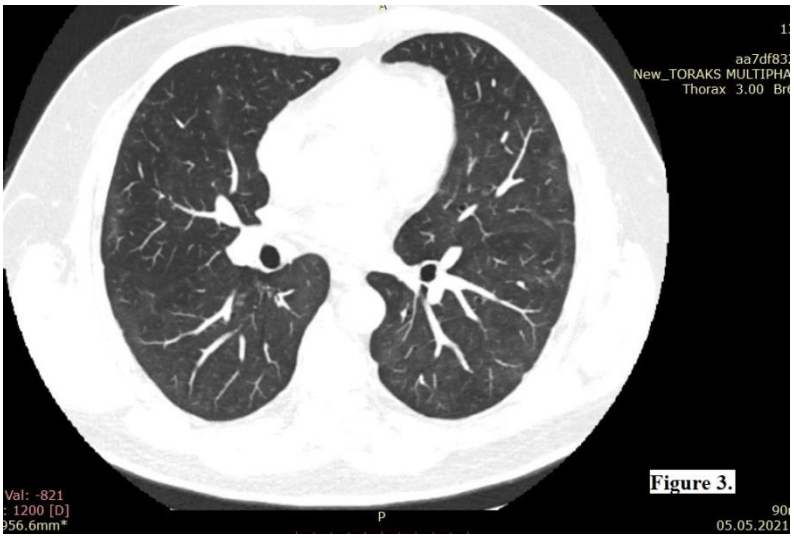

Figure 3.

Discussion

The presence of the radiographic abnormalities correlates with decrements in lung function, cough and frailty. Greater initial severity of illness, longer duration of mechanical ventilation and shorter blood leucocyte telomere length are independent risk factors for the development of fibrotic-like abnormalities [10].

Cohort studies of COVID-19 survivors report that severity of the initial illness is associated with a greater risk of persistent CT abnormalities [10], especially for patients requiring supplemental oxygen or mechanical ventilation, but independent clinical, biomarker and genomic risk factors have not been identified. Also, the extent to which CT findings correlate with symptoms and physical function remains unclear. To address knowledge gaps, we conducted a prospective cohort study of survivors hospitalized with severe COVID-19, half of whom were mechanically ventilated, with 4-month follow-up.

We sought to characterise associations of pulmonary radiographic and physiologic sequela of severe COVID-19, and to identify independent risk factors for the development of post-COVID fibrosis [11].

Reports of hospitalised COVID-19 survivors show that there are persistent symptoms, radiographic abnormalities and physiological impairments months after the initial illness. Persistent chest imaging abnormalities and histopathological findings of lung fibrosis have also been found in a

majority of survivors of the SARS-CoV-1, suggesting that the SARS viruses may lead to a worse fibroproliferative response than other pneumonias [12].

The risk factors for development of fibrotic-like radiographic abnormalities after severe COVID-19 are incompletely described and the extent to which CT findings correlate with symptoms and physical function after hospitalization remains unclear [1].

We have demonstrated that severity of initial illness, duration of mechanical ventilation, lactate dehydrogenase on admission and leukocyte telomere length are independent risk factors for fibrotic-like radiographic abnormalities. These fibrotic-like changes correlate with lung function, cough and measures of frailty, but not with dyspnea [13].

Several recent COVID-19 studies have described patients with residual radiographic abnormalities consistent with pulmonary fibrosis [14] and concomitant findings of fibrotic features on histopathology.

Among 90 hospitalized COVID-19 patients, the majority had residual mild to substantial pulmonary changes on CT at discharge [15].

In the case of our patient, the pulmonary involvement related to SARS-CoV-2 was extensive and severe, complicated by bilateral massive pneumonia, with high d-dimers, high level of LDH and CRP, which required to be managed by the intensive care unit with high-flow oxygen therapy (Fig. 1).

We investigated the development of lung fibrotic-like changes in a patient who recovered from the severe COVID-19 pneumonia within 6-month follow up.

The patient underwent chest CT scan again at 6 months of follow-up. In that period he had a reversal of roendgenological change and a significant improvement of his condition (Fig. 3).

In the study of Han *et al*. [7], fibrotic abnormalities were seen in 35% of patients over the 6 months of follow-up, which was lower than the results we obtained.

Also, another study by Ali *et al.* [12] showed a rate of 32% for pulmonary fibrosis in the COVID-19 patients within 3-month follow-up, which was less than that we found in this study. Mitigation of risk due to the challenges and lack of effective therapies for treating pulmonary fibrosis is an imperative to focus on strategies that aim to reduce the risk of developing post-COVID-19 pulmonary fibrosis.

Such strategies should be directed toward minimizing the factors implicated in perpetuating the cycle leading to persistent lung injury, prolonged inflammatory response, and fibroproliferation [13,14].

At present, the RNA polymerase inhibitors, an antiviral agent are currently approved for clinical use in treatment of SARS-CoV-2. Initial data have shown some promise in terms of symptom-improvement and resolution of disease in select populations, but it is thought to be of greatest benefit to patients early-on in their clinical course and in those with mild-moderate disease [15].

However, since it is not known if early viral clearance is protective, the role of antiviral medications is not certain [16].

Conclusion

The robust responses of corticosteroid therapy in our case presenting a radiological pattern of organizing pneumonia allowed the patient to return to his baseline clinical condition.

Therefore, we believe that the use of corticosteroids is beneficial in survivors of severe COVID-19 pneumonia, who remain symptomatic in the post-infection period, and who present radiological features consistent with organizing pneumonia. Nevertheless, the proof of efficacy of such a treatment requires further validation by rigorously conducted randomized trials, codifying the dosage and duration of treatment**.**

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