ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Mini Review

Post-COVID-19 Pulmonary Fibrosis: Increasingly Recognized Complication of the Pandemic

Syed Muhammad Zubair[1], Ali Bin Sarwar Zubairi[2] and Muhammad Irfan[2]*

[1]*Section of Pulmonary and Critical Care Medicine, Aga Khan University, Karachi, Pakistan*

[2]*Professor, Section of Pulmonary and Critical Care Medicine, Aga Khan University, Karachi, Pakistan*

***Corresponding Author:** Muhammad Irfan, Professor, Section of Pulmonary and Critical Care Medicine, Aga Khan University, Karachi, Pakistan.

Received: August 31, 2020; **Published:** September 19, 2020

Abstract

COVID-19 is a pandemic that has crippled the lives of people globally. Initially started in Wuhan, China and rapidly taking the whole world in its grip. Although the major portion of the world has fought successfully but as patients recover, we are bound to see post-COVID sequelae of one kind or another. One of such sequelae is post-COVID pulmonary fibrosis, a recently recognized non-infectious complication with definite upcoming literature. This review focuses on the upcoming literature, the possible pathogenesis, the risk factors causing it and the future strategies on post-COVID pulmonary fibrosis.

Keywords: *COVID-19; SARS-CoV-2; Complication; Pulmonary Fibrosis*

Introduction

COVID-19 pandemic has affected people in all aspect of lives. This pandemic has been rated as one of the worst in centuries. As the cases of COVID-19 are declining in the major parts of the world, we are now stepping into an era where physicians will have to counter post-COVID-19 sequelae. Broadly classifying, the sequelae can be infectious which includes bacterial and fungal infections and non-infectious which includes pulmonary fibrosis and neuropsychiatric complications.

Post-COVID lung fibrosis is one of the irreversible insult to the lungs seen with previous Corona virus infections. Follow up chest radiographic findings in Middle East respiratory syndrome coronavirus (MERS-CoV) showed 33% of the patients developing pulmonary fibrosis and cases of pulmonary fibrosis were also seen in patients recovering from SARS-CoV [1,2].

The findings of diffuse alveolar damage and thrombosis have already been reported in post-mortem series of patients with COVID-19 [3,4]. Cryobiopsies done in a series of patients who expired in intensive care unit of COVID-19 showed obliteration of airspace, proliferation of fibroblasts and micro-honeycombing [5]. Hence it is being rightly anticipated that fibrotic lung disease will be seen post-COVID 19.

Pathogenesis

Pulmonary fibrosis is a multifactorial insult, various causes of which have been defined. They include activation of polypeptides which causes inflammation that causes proliferation of fibroblasts, certain genetic factors, aging and viral infections [6]. Deposition of collagen in excessive amount has also been linked to the development of fibrosis in some texts [7,8]. Mechanisms described in patients who devel-

oped pulmonary fibrosis after being managed for SARS Corona virus are TGF-β activation and Angiotensin-converting enzyme. Angiotensin-converting enzyme 2 (ACE2) has been described to play a protective role in the development of pulmonary fibrosis hence deficiency of ACE2 can further exacerbate pulmonary fibrosis [9]. SARS-CoV2 is a single stranded RNA virus of Coronaviridae family belonging to β genera along with two other viruses which were previously responsible for epidemics namely SARS-CoV and MERS-CoV. SARS-CoV-2 also shares sequence identity with SARS-CoV and MERS-CoV [10,11]. Some viral infections have already been linked with the development of idiopathic pulmonary fibrosis of which Hepatitis C Virus, Adenovirus, Human Cytomegalovirus, Epstin-Barr Virus (EBV) are the few known ones [12]. Among the viruses, EBV has been the most notorious one as far as pulmonary fibrosis is concerned. It was found in the bronchoalveolar lavage fluid and in DNA of lung tissue of patients with IPF [13,14]. Moreover, EBV and SARS CoV-2 also have similarities in their structure. Both being enveloped with outer spikes [15,16]. Follow up imaging of MERS-CoV and SARS- CoV have shown fibrosis and with similarities in structure of SARS-CoV-2 with SARS-CoV, MERS-CoV and EBV, it is highly likely that post-COVID-19 pulmonary fibrosis will be seen as more patients continue to recover.

Literature on post-COVID-19 pulmonary fibrosis

There is not much data on the long-term sequelae of COVID-19 but there are a few case series in literature review on post-COVID pulmonary fibrosis. Pan., *et al*. and Zhou., *et al*. studied the imaging features of patients with COVID-19 and found that 17.5% and 33.9% of patients developed fibrotic changes respectively [17,18]. H. F. Schwensen., *et al*. reported a case of an elderly female who was managed in intensive care COVID-19 unit and later expired. Autopsy showed fibrotic changes along with honey-combing [19]. Federica Grillo *et al* also described a series of eight patients who showed fibrotic lung parenchymal remodeling on cryobiopsy [5]. C Jing-Yu., *et al*. reported 3 cases of lung transplantation of post ARDS fibrosis after COVID-19 [20]. Mogot Combet., *et al*. described a case of a 38 years old gentleman who rapidly developed pulmonary fibrosis with in a duration of 10 days [21]. Hence looking at this limited available literature and past experience from SARS and MERS, it can be presumed that this sequelae of COVID-19 will be increasingly seen.

Important risk factors for post-COVID-19 pulmonary fibrosis

Although limited evidence is available in the literature, some important factors which presumably have a very critical role in the development of post COVID fibrosis has been recognised. Firstly, aging is an important factor. Other fibrotic lung diseases like IPF has also shown its occurrence in individuals who are above 65 and rarely occurs below the age of 50 [22]. Studies have also shown that patients who developed pulmonary fibrosis after SARS and MERS also had advancing age [1,23].

Secondly, disease severity is also an important cause. Patients with severe COVID pneumonia are more prone to developing fibrosis. Factors like increased C-reactive protein and lactate dehydrogenase (LDH), lymphopenia and lymphocytosis have an important correlation with disease severity [24]. Elevated LDH levels have previously shown a correlation with development of pulmonary fibrosis in patients treated for SARS-CoV and MERS-CoV [1,23].

Thirdly, duration of treatment is also an important factor. Patient whose treatment duration is more with prolonged ICU stay requiring mechanical ventilation are more susceptible of developing fibrosis. Patients with ICU stay have more severe disease with ARDS and possibility of ventilator induced lung injury, all of which contribute in the development of fibrosis [25,26].

Unanswered questions and the way forward

Many questions are still unanswered and needs long term follow-up studies; For example, how much will this fibrosis affect the quality of lives of survivors? Will risk factors, like longer duration of treatment and severity have an effect on the development and progression of fibrosis? With what pace will this fibrosis progress? Will it be as progressive as IPF? and finally what will be the role of anti-fibrotic agents in the management of post-COVID fibrosis? [27].

Conclusion

Post COVID pulmonary fibrosis is increasingly recognized as a non infectious sequelae of COVID pneumonia. As the time passes, more literature is coming that highlights the various pattern, pathogenesis and treatment options for this complication. As a physician one should take into account possibilities of this long term sequelae of COVID-19 and once diagnosed proper follow up should be taken into account so that early management can be initiated.

Disclosure Statement

The authors report no conflict of interest.

Funding Source

None.

Bibliography

1. Das KM., *et al.* "Follow-up chest radiographic findings in patients with MERS-CoV after recovery". *Indian Journal of Radiology and Imaging* 27.3 (2017): 342-349.
2. Venkataraman T and Frieman MB. "The role of epidermal growth factor receptor (EGFR) signaling in SARS coronavirus-induced pulmonary fibrosis". *Antiviral Research* 143 (2017): 142-150.
3. Carsana L., *et al.* "Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study". *The Lancet Infectious Diseases* (2020).
4. Fox SE., *et al.* "Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans". *The Lancet Respiratory Medicine* 8.7 (2020): 681-686.
5. Grillo F., *et al.* "Lung fibrosis: an undervalued finding in COVID-19 pathological series". *The Lancet Infectious Diseases* (2020).
6. Marshall RP., *et al.* "The pathogenesis of pulmonary fibrosis: is there a fibrosis gene?" *The International Journal of Biochemistry and Cell Biology* 29.1 (1997): 107-120.
7. McDonald JA., *et al.* "A monoclonal antibody to the carboxyterminal domain of procollagen type I visualizes collagen-synthesizing fibroblasts. Detection of an altered fibroblast phenotype in lungs of patients with pulmonary fibrosis". *The Journal of Clinical Investigation* 78.5 (1986): 1237-1244.
8. Raghu G., *et al.* "Extracellular matrix in normal and fibrotic human lungs". *American Review of Respiratory Disease* 131.2 (1985): 281-289.
9. Zuo W., *et al.* "SARS coronavirus and lung fibrosis". In Molecular Biology of the SARS-Coronavirus (2010): 247-258.
10. Zhu N., *et al.* "A novel coronavirus from patients with pneumonia in China, 2019". *New England Journal of Medicine* (2020).
11. Lu R., *et al.* "Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding". *The Lancet* 395.10224 (2020): 565-574.
12. Naik PK and Moore BB. "Viral infection and aging as cofactors for the development of pulmonary fibrosis". *Expert Review of Respiratory Medicine* 4.6 (2010): 759-771.

13. Manika K., *et al.* "Epstein-Barr virus DNA in bronchoalveolar lavage fluid from patients with idiopathic pulmonary fibrosis". *Sarcoidosis, Vasculitis, and Diffuse Lung Diseases: Official Journal of WASOG* 24.2 (2007): 134.

14. Stewart JP., *et al.* "The detection of Epstein-Barr virus DNA in lung tissue from patients with idiopathic pulmonary fibrosis". *American Journal of Respiratory and Critical Care Medicine* 159.4 (1999): 1336-1341.

15. Epstein-Barr Virus. "IARC Working Group on the Evaluation of Carcinogenic Risks to Humans Biological Agents Lyon (FR): International Agency for Research on Cancer; 2012 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No 100B) EPSTEIN-BARR VIRUS" (2012).

16. Gorbalenya AE., *et al.* "Severe acute respiratory syndrome-related coronavirus: The species and its viruses–a statement of the Coronavirus Study Group".

17. Pan Y., *et al.* "Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China". *European Radiology* 13 (2020): 1-4.

18. Zhou S., *et al.* "CT Features of Coronavirus Disease 2019 (COVID-19) Pneumonia in 62 Patients in Wuhan, China". *American Journal of Roentgenology* 214.6 (2020): 1287-1294.

19. Schwensen HF., *et al.* "Fatal pulmonary fibrosis: a post-COVID-19 autopsy case". *Journal of Clinical Pathology* (2020).

20. Chen JY., *et al.* "Lung transplantation as therapeutic option in acute respiratory distress syndrome for coronavirus disease 2019-related pulmonary fibrosis". *Chinese Medical Journal* 133.12 (2020): 1390-1396.

21. Combet M., *et al.* "Rapid onset honeycombing fibrosis in spontaneously breathing patient with Covid-19". *European Respiratory Journal* (2020).

22. Richeldi L., *et al.* "Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis". *New England Journal of Medicine* 370.22 (2014): 2071-2082.

23. Wong KT., *et al.* "Severe acute respiratory syndrome: thin-section computed tomography features, temporal changes, and clinicoradiologic correlation during the convalescent period". *Journal of Computer Assisted Tomography* 28.6 (2004): 790-795.

24. Liu X., *et al.* "Risk factors associated with disease severity and length of hospital stay in COVID-19 patients". *Journal of Infection* 81.1 (2020): e95-e97.

25. Desai SR., *et al.* "Acute respiratory distress syndrome: CT abnormalities at long-term follow-up". *Radiology* 210.1 (1999): 29-35.

26. Oeckler RA and Hubmayr RD. "Ventilator-associated lung injury: a search for better therapeutic targets". *European Respiratory Journal* 30.6 (2007): 1216-1226.

27. George PM., *et al.* "Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy". *The Lancet Respiratory Medicine* 8.8 (2020): 807-815.

Volume 9 Issue 10 October 2020