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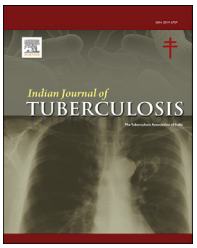

Case report

A silent march-Post covid fibrosis in asymptomatics – A cause for concern?

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ARTICLE INFO

Article history:
Received 6 May 2022
Received in revised form
10 May 2022
Accepted 17 May 2022
Available online xxx

Keywords:
COVID-19
UIP
Post COVID fibrosis

ABSTRACT

We report a case series of patients presenting with undiagnosed pulmonary fibrosis as a primary manifestation. On evaluation, after excluding other causes, the fibrosis was attributed to asymptomatic or mild COVID illness in the past. This case series serves to highlight the difficulties posed to clinicians while evaluating pulmonary fibrosis in the post-COVID era, more so in mild to asymptomatic COVID-19. The intriguing possibility of fibrosis setting even in mild to asymptomatic COVID is discussed.

1. Introduction

COVID-19 pandemic caused by SARS-CoV-2 had a devastating effect on health, economic and social sectors globally. The presentation of COVID-19 infection varies from asymptomatic to hypoxemic respiratory failure and respiratory distress syndrome. Long-standing sequelae involving the lungs such as fibrosis are seen in patients who have recovered from COVID-19 infection.[1] Other pulmonary complications like cavitary lung disease, bronchiectasis are also seen in addition to persistent symptoms such as dyspnea and fatigue.[2,3] The pulmonary sequelae are mostly seen in hospitalized patients with severe COVID-19 infection.[4] Asymptomatic COVID-19 patients developing lung fibrosis is an unheard-of entity. It is alarming that, unlike in idiopathic pulmonary fibrosis where fibrosis usually occurs in the elderly, post-COVID fibrosis is seen irrespective of age and other co-morbidities. Here we report a series of four cases presenting with pulmonary fibrosis as initial manifestation and lacking a definitive association with microbiologically proven COVID. Pulmonary fibrosis in these patients was largely attributable to post COVID complications amongst asymptomatic COVIDs. Pulmonary fibrosis is generally seen in patients with moderate to severe disease and is very rarely described in asymptomatic and mild cases of COVID-19. The radiological similarity between usual interstitial pneumonia (UIP) and post COVID

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https://doi.org/10.1016/j.ijtb.2022.05.004
0019-5707/

Please cite this article as: Antony T et al., A silent march-Post covid fibrosis in asymptomatics – A cause for concern?, Indian Journal of Tuberculosis, https://doi.org/10.1016/j.ijtb.2022.05.004

fibrosis, symptomatology overlap, and difficulties posed by clinicians in differentiating these two entities in the post-pandemic era has been discussed in this case series.

2. Case 1

A 43-year-old female, homemaker, known diabetic, who was not vaccinated against COVID-19 infection, presented with a 1-month history of progressive exertional breathlessness. She reported no history of any joint pain or any other extra-pulmonary symptom. Her baseline vital parameters were within normal limits. She gave no prior history of respiratory infection, fever, or any hospital admission in the recent past. Chest X-ray showed bilateral reticular opacities. HRCT of the thorax showed fibrosis with traction bronchiectasis, primarily involving the lower lobes with predominant sub-pleural involvement (Fig. 1A). COVID testing using cartridge-based RT-PCR did not detect SARS-COV2 RNA. Connective tissue work-up was done and showed a negative rheumatoid factor, anti-cyclic citrullinated peptide (CCP), antineutrophilic cytoplasmic antibody (ANCA), and antinuclear antibody (ANA). Echocardiography did not show any abnormality. However anti-SARS-COV2 IgG quantitative test antibodies for COVID-19 came positive (>200 BAU/ml). Pulmonary function test showed restrictive pattern (FEV1: 0.80 L, 31% predicted; FVC: 0.92, 30% predicted), reduced DLCO (8.7 ml/min/mmHg, 34% predicted). She was unable to perform a six-minute walk test. She was started on anti-fibrotic therapy, injectable steroids, and pulmonary rehabilitation and is currently on follow-up.

3. Case 2

A 51-year-old male patient, ex-smoker, farmer, with no co-morbid illness, recently vaccinated with the first dose against COVID-19, presented to the respiratory medicine clinic with two weeks history of progressive exertional breathlessness and dry cough. He had a history of fever lasting for 2 days that preceded symptoms of dry cough. He had not undergone testing for COVID then. There was no history of any joint pain or fever. General examination was unremarkable, except for low peripheral oxygen saturation on presentation (92% on room air). Systemic examination showed bilateral basal crepitations on auscultation. Chest X-ray showed bilateral reticular opacities. Sputum aerobic culture and CBNAAT for tuberculosis did not reveal any organisms. COVID testing using cartridge-based RT-PCR did not detect SARS-COV2 RNA. HRCT thorax showed diffuse, predominantly subpleural areas of fibrosis and bronchiectasis (Fig. 1B). Echocardiography showed normal biventricular function and no evidence of pulmonary artery hypertension. Spirometry showed restrictive pattern (FEV1: 0.82 L, 28% predicted; FVC: 1.01, 28% predicted), reduced DLCO (6.6 ml/min/mmHg, 24% predicted). His six-minute walk test showed a reduction in total distance covered (120 meters at six-minute) and the lowest recorded

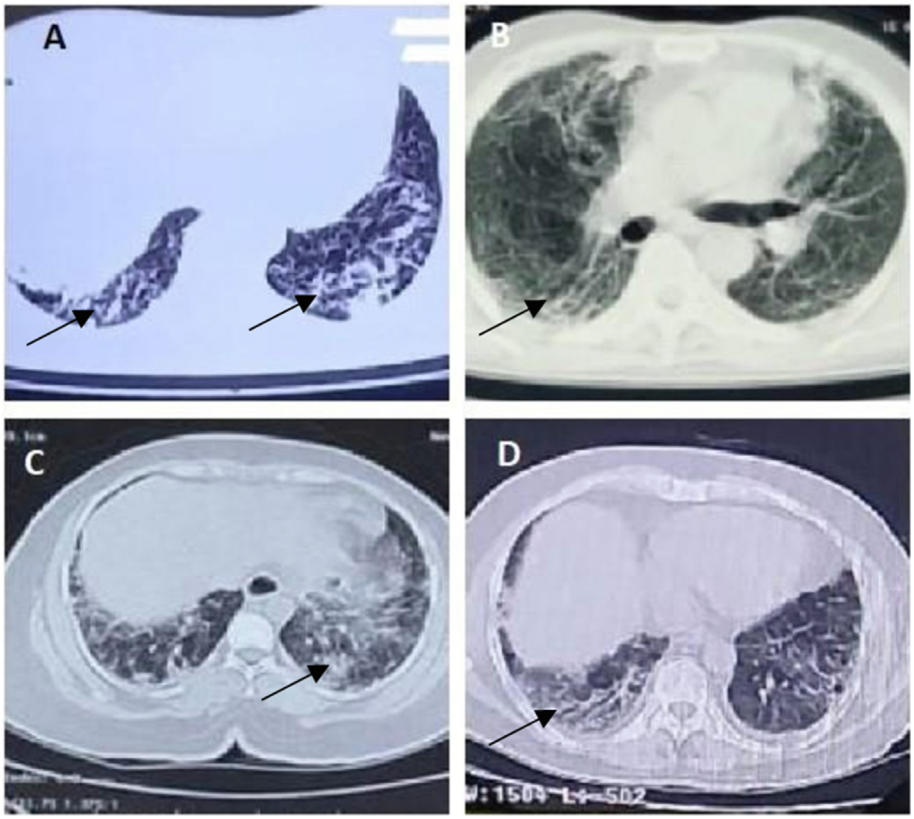

Fig. 1 – A: Case 1, B: Case 2, C: Case 3, D: Case 4. (A–D) Images of HRCT thorax showing areas of fibrosis, involving the lower lobes with dominant subpleural pattern of distribution (marked with black arrow).

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oxygen saturation of 88% on room air. The patient was started on anti-fibrotic agent, injectable steroids. The patient partly responded to treatment and is currently on follow-up.

4. Case 3

A 28-year-old female patient, homemaker, with no comorbid illness, not vaccinated against COVID-19, presented with 20 days history of exertional breathlessness and dry cough. General examination was unremarkable and peripheral oxygen saturation on presentation was 95% on room air. Bilateral basal crepitations were present on auscultation. Chest X-ray showed reticular opacities bilaterally. HRCT thorax showed diffuse, predominantly sub-pleural areas of fibrosis involving lower lobes (Fig. 1C). COVID testing using cartridge-based RT-PCR did not detect SARS-COV2 RNA. The patient was tested for COVID-19 antibody using anti-SARS-COV2 IgG quantitative test and was found to be significantly elevated (>200 BAU/ml). Echocardiography did not reveal any significant abnormality. Pulmonary function assessment showed restrictive pattern (FEV1: 0.96 L, 38% predicted; FVC: 1.10, 38% predicted), reduced DLCO (7.8 ml/min/mmHg, 27% predicted). She covered a total distance covered (360 meters at six-minute) during a six-minute walk test with the lowest recorded oxygen saturation of 88% on room air. The patient was managed with supportive care, anti-fibrotic agent, and injectable steroids. The patient is currently on follow-up.

5. Case 4

A 75 -year-old male, ex-smoker, with diabetes mellitus, fully vaccinated against COVID-19, tested positive for COVID testing using cartridge-based RT-PCR. He was largely asymptomatic then and opted for home quarantine. He developed progressive breathlessness after a month of testing positive. The patient was tachycardic and with a respiratory rate of 28 breaths per minute. His peripheral oxygen saturation was 89% on room air at presentation. Chest X-ray showed bilateral reticular opacities. HRCT of the thorax showed bilateral basal predominant areas of fibrosis (Fig. 1D). Echocardiography did not show any significant abnormality. His spirometry showed restriction abnormality and DLCO was reduced. The patient was managed with supportive care, started on anti-fibrotic agent, injectable steroids. The patient was stable on discharge is on follow-up.

6. Discussion

There has been an unprecedented spurt in the cases of pulmonary fibrosis following the COVID-19 pandemic. Although it is a known complication in severe COVID-19 pneumonia, the possibility of lung fibrosis secondary to an asymptomatic or mild COVID-19 infection is also probable as reported in this case series.

Two of the patients had no history of COVID-19 infections, were unvaccinated, and had an elevated anti IgG titer for COVID-19 confirming an asymptomatic COVID-19 infection in the recent past. The third patient was partially vaccinated with a history suggestive of a recent mild COVID-19 infection. The fourth patient was fully vaccinated with a confirmed mild COVID-19 infection. All four cases were diagnosed with pulmonary fibrosis, which was unlike typical of post COVID fibrosis making the etiology of fibrosis a diagnostic dilemma. In all our cases, a comprehensive workup for baseline connective tissue disorders and detailed occupational history was inconclusive ruling out other possible etiologies for pulmonary fibrosis. Thus, it should be kept in mind that fibrosis could be sequelae in spite of the vaccination status of the patients. Raised IgG antibodies against COVID-19, who is not vaccinated and in those with no prior history of any past or current COVID-19 infection gives indirect evidence of asymptomatic COVID infection in the recent past.[5]

Although fibrosis of lungs in asymptomatic COVID patients is not yet studied, it could be assumed that the pathogenesis could simulate that in severe infection. The correlation between the antibody levels and the extent of lung fibrosis needs to be studied further. Possible mechanisms of injury could be direct injury related to viral infection or due to immune-mediated injury following the release of pro-inflammatory and pro-fibrotic cytokines/factors such as TGF-β, TNF-α, MMPs, TIMPs, IL-1, IL-4, IL-5, IL-6, IL-13, and IL-17.[6] Other possible causes such as cardiac function and an active infection should be ruled out in such patients.

A significant proportion of patients with asymptomatic to mild COVID-19 cases have demonstrated ground-glass opacities and pneumonia on HRCT.[7] However, the impact on lung function over medium to long term and silent progression to fibrosis remains unclear and has not been studied in great detail. Some studies have amply demonstrated pulmonary function impairment after 4 months of acute COVID-19 even in asymptomatic COVID-19 cases as characterized by diffusion impairment, reduced total lung capacity, and forced vital capacity. Surprisingly 20% of patients with the mild disease showed a decrease in paO2 on exercise indicating a subtle gas exchange abnormality.[8] Reduction in diffusion capacity persisting after 4 months suggests ongoing interstitial process even amongst those with mild disease.

There is also evidence that viral infections including COVID-19 may predispose, trigger or exacerbate respiratory pathologies like pulmonary fibrosis.[9,10] This has been explained by the "two-hit" hypothesis wherein an initiating insult causes changes in the lung microenvironment increasing its susceptibility to a fibrotic process following a secondary insult. Viral infections can upregulate expression, signaling pathway, and production of growth and pro-fibrotic factors triggering progressive fibrotic process.

In the post-COVID era, early and accurate diagnosis of post-COVID fibrosis from usual interstitial pneumonia (UIP) becomes a nightmare as both these entities have a near similar HRCT presentation with bilateral sub-pleural honeycombing with reticulation and traction bronchiectasis. In such clinical contexts, confirmation of past active COVID illness with RT-PCR or elevated anti-COVID antibody titers in the unvaccinated (as evidenced in two of our cases) becomes critical in clinching the diagnosis. Diagnosing post-COVID fibrosis in the asymptomatic untested but vaccinated, is often a probable diagnosis and hinges primarily on history

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suggestive of COVID-like illness as related in the third patient from our series. It is probable that many elderly asymptomatic populations might have moderate–severe pneumonia but the symptoms might not be overt in their manifestation considering the age, immunity, and activity levels. Often this section of the population might present with pulmonary fibrosis as the initial and sole manifestation of COVID-19 sequel.

Established post- COVID pulmonary fibrosis has an unpredictable course and continues to confound clinicians' world over with its myriad presentations, variable response to therapy, and long-term prognosis. In some extensive fibrosis is known to resolve spontaneously over time, while in others anti-fibrotic therapy might slow down the fibrosis while in some the disease marches, all novel interventions notwithstanding. Though there exists a slew of data there is little consensus on factors modifying the onset and progression of fibrosis in individual patients.

Antifibrotics are often used commonly in patients with post-COVID fibrosis and UIP, it is extremely important to differentiate the two processes in terms of long-term prognostication and outcome. Clinicians are often faced with this dilemma as seen in our case series when patients present with pulmonary fibrosis as initial presentation and a history of microbiological confirmation of COVID positivity is lacking. This case series seeks to highlight this vexing clinical issue posed to physicians in the post-COVID era.

There is no definitive treatment for post-COVID fibrosis of the lungs. Studies have shown the potential benefit of anti-fibrotic agents in preventing the worsening of lung function. The use of anti-inflammatory agents like steroids has a possible role in reducing immune-mediated lung injury and fibrosis.[7,8] Other supportive such as pulmonary rehabilitation and regular physical exercise could have some role in management.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Martin Rumende C, Susanto EC, Sitorus TP. The management of pulmonary fibrosis in COVID-19. *Acta Med Indones Indones J Intern Med*. 2021;53.
2. Ahmed OF, kakamad FH, Hama Amin BJ, et al. Post COVID-19 pulmonary complications; a single center experience. *Ann Med Surg*. 2021 Dec 1:72.
3. Esendağli D, Yilmaz A, Akçay Ş, Özlü T. Post-COVID Syndrome: Pulmonary Complications. *Turk J Med Sci*. 2021;51:3359–3371.
4. Crisan-Dabija R, Pavel CA, Popa IV, Tarus A, Burlacu A. "A chain only as strong as its weakest link": an up-to-date literature review on the bidirectional interaction of pulmonary fibrosis and COVID-19. *J Proteome Res*. 2020;19(11):4327–4338.
5. Ali H, Alahmad B, Al-Shammari AA, et al. Previous COVID-19 infection and antibody levels after vaccination. *Front Public Health*. 2021 Dec 1:9.
6. Huang WJ, Tang XX. Virus infection induced pulmonary fibrosis. *J Transl Med*. 2021;19.
7. Ali RMM, Ghonimy MBI. Radiological findings spectrum of asymptomatic coronavirus (COVID-19) patients. *Egypt J Radiol Nucl Med*. 2020 Dec 1;(1):51.
8. Munker D, Veit T, Barton J, et al. Pulmonary function impairment of asymptomatic and persistently symptomatic patients 4 months after COVID-19 according to disease severity. *Infection*. 2022 Feb 1;50(1):157–168.
9. Naik PK, Moore BB. Viral infection and aging as cofactors for the development of pulmonary fibrosis. *Expet Rev Respir Med*. 2010;4:759–771.
10. Qiao J, Zhang M, Bi J, et al. Pulmonary fibrosis induced by H5N1 viral infection in mice. *Respir Res*. 2009 Nov 12:10.

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