Original Research Paper

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General Medicine

A CASE OF COVID-19 PNEUMONITIS WITH RAPID ONSET PULMONARY FIBROSIS.

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ABSTRACT SARS-COV-2 which causes COVID19 infection is known to present with a variety of manifestations ranging from an asymptomatic course to mild URTI (Upper respiratory tract infection) to a full blown LRTI (Lower Respiratory Tract Infection) with ARDS (Acute Respiratory Disease Syndrome) like features, ALI (ACUTE LUNG INJURY), Pulmonary or Pan-endotheliitis , an overwhelming Cytokine Storm syndrome, Multi-Organ Dysfunction Syndrome (MODS), Strokes, Encephalitis, Myocarditis and several other complications. One possible complication of pulmonary involvement has been pulmonary fibrosis. Here we report a rare association of SARS-CoV2 infection with rapidly progressing pulmonary fibrosis.

KEYWORDS :

INTRODUCTION:

Pulmonary fibrosis is characterised by impaired healing of damaged alveolar epithelium, persistence of fibroblasts and excessive deposition of collagen and other extracellular components. The aetiology of pulmonary fibrosis includes age, smoking, viral infection, drug exposure and genetic predisposition. Viral infections act as triggers for the initiation of pulmonary fibrosis or as agents exacerbating existing fibrosis. The elderly population is especially prone to viral-induced fibrosis due to immunosenescence and with viral infection acting as a cofactor. Overexpression of pro-inflammatory cytokines (IL-1b, IL-6, TGF-beta, TNF-alpha) amongst older people are responsible for a severe course of the disease in this group of patients. There are no specific mechanisms that lead to this phenomenon in COVID-19, but some information is available from previous Severe Acute Respiratory Syndrome (SARS) or Middle East Respiratory Syndrome (MERS) epidemics. Patients suffering from this phenomenon have chronic breathing difficulties, long-term disability and a poor quality of life due to same. Treatment of COVID-19 should include prophylaxis from infections or therapy of pulmonary fibrosis in order to provide a satisfactory long-term prognosis.

CASE REPORT:

We report a 74 year-old lady with hypertension, ischaemic heart disease and Left Ventricular dysfunction (Ejection fraction-35%) and a history of bilateral total knee replacement surgery 5 years ago, who presented to us at the Fever Clinic with complaints of cough with white scanty sputum expectoration since 5 days associated with fever and chills since 3 days and breathlessness at rest since 2 days. On evaluation, she recorded a body temperature of 99.4^{0}Fahrenheit with a Pulse of 116/min, a Respiratory rate of 32/min, and Blood Oxygen Saturation of 62%, other vital parameters were normal. Respiratory examination revealed bilateral extensive coarse crepitations in the mid to end inspiratory phases on auscultation. Other systemic examination was unremarkable. She was admitted under the Department of General Medicine in a dedicated COVID Intensive Care facility as a case of SARI (Severe Acute Respiratory Illness) ICMR (Indian Council Medical Research) category 4, with a clinical suspicion of COVID induced Pneumonia. After her admission relevant investigations were carried out. She tested positive for SARS-CoV-2 on her Nasopharyngeal and Oropharyngeal Swab by real time Polymerase Chain Reaction. Arterial blood gases revealed hypoxemic Respiratory Failure and initial blood investigations revealed elevated levels of Neutrophil-Lymphocyte Ratio, Ferritin, Erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), D-dimer, Interleukin-6 (IL-6) and a normal coagulation profile.

The patient was promptly transferred to the Intensive Care Unit, where oxygen therapy with non-invasive ventilation (Bi-PAP) was initiated with a fraction of inspired oxygen of 1.0 initially, along with an empirical course of antibiotics (ceftriaxone). In view of raised inflammatory markers and increasing respiratory distress, 480 mg (8mg/kg) iv Inj. Tocilizumab was given on Day-2 and Inj. Methylprednisolone was also given for 7 days. Other medications as per institution protocol Inj. UF Heparin, Oral Vitamin C, Oral Zinc were also given. Over the next few days, He was regularly positioned prone. Although PaO2 levels were around 84 mm Hg on an FiO2 of 70% corresponding to a Horowitz (PaO2/FiO2) ratio of 120, the patient did not exhibit any clinical signs of respiratory distress, no shortness of breath nor tachypnoea. His ROX index [(SpO2/FiO2)/ respiratory rate] remained steadily superior to 5. Considering the above parameters, mechanical ventilation was therefore not initiated. Fever quickly receded, and inflammatory marker levels decreased gradually. Antibiotics were discontinued on day-7 because of lack of evidence of any secondary bacterial infection.

Her oxygen support gradually reduced from day-3 to day-15 (i.e. NIV f/b HFNC f/b simple O2 from 8l/min to 2l/min). She was not able to wean off further from 2l/min O2 support. On day-21 she still required oxygen at 2l/min, further decrease in oxygen support lead to desaturation (Saturation on room air remained to be 82%). In view of this, HRCT Thorax was done on day-21. It showed diffuse interstitial septal thickening, few honey combing cysts, traction bronchiectasis with ground glass opacities, more prominent in the upper lobes (Fig). Search for other causes of interstitial lung disease including auto-immune disease was negative. Treatment included low-dose prednisolone 10mg daily. The patient's condition improved and she was transferred to non-covid ward on day-31 on oxygen therapy at 2l/min.

Lab Ix-

Hb	11.8 g/dl
WBC	10910/mm3
PLT	298000/mm3
NLR	8.6
SGPT	45 U/l
Urea/Cr	49.6 mg/dl / 1.14 mg/dl
S.K+/Na+	4.8 mEq/l / 142 mEq/l
RBS/ HbaIc	114 mg/dl / 6.3

- RT PCR (NP+OP) – POSITIVE
- Arterial Blood Gas
- pH-7.41
- pCO2-27.3 mm Hg
- pO2-109 mm Hg
- HCO3-16.9 mmol/L
- SO2-98.4%

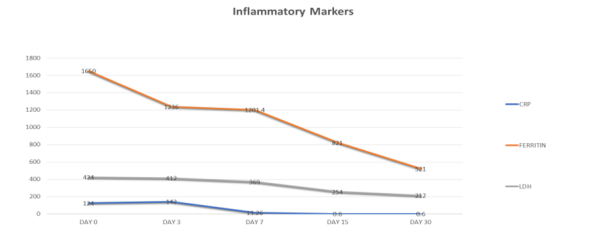
ON NIV 100% FiO2

CRP	124 mg/l
ESR	114 mm/hr
LDH	424 U/l
Ferritin	>1650 ng/ml
D-dimer	>4 micro g/ml
Trop I	0.043 ng/ml
NT-pro BNP	456.8 pg/ml
PCT	0.03 ng/ml
IL-6	90.9 pg/ml
S Ca2+	9.0 mg/dl
S PO4-	4.82 mg/dl
S UA	8.0 mg/dl
Viral Markers	Non-Reactive
Urine RM	NAD

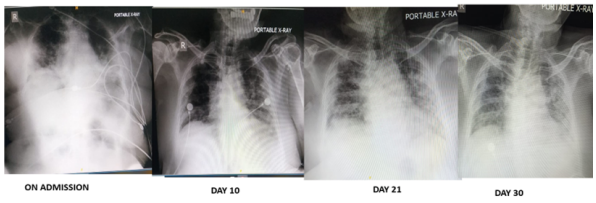
- PaO2:FiO2 Ratio- 109

1. ANA by IF- Positive 1:160 Homogenous (+1)
2. R Factor- < 8 IU/ml NEGATIVE
3. ECG – No Significant ST-T Changes
4. POCUS (Point Of Care Ultra-sound)
   A. BEDSIDE ECHO Screening:-
   LVEF- 35%
   Apex/ Apicoseptal Hypokinesia
   Mild MR/TR
   No Clot/Vegetations/Effusion.
   B. USG Abdomen For Liver And Spleen Architecture- Normal.

INVESTIGATIONS:



Chest X-RAYS During Hospital Stay-



HRCT Thorax On DAY-21

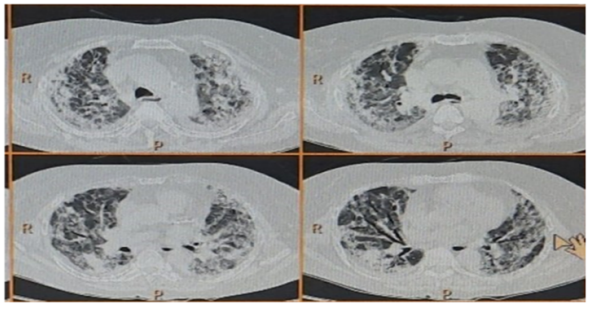


Figure-1 AXIAL View

Fig 1- Diffuse interstitial septal thickening, few honeycombing cysts, traction bronchiectasis and ground glass opacities present with subpleural predominance.

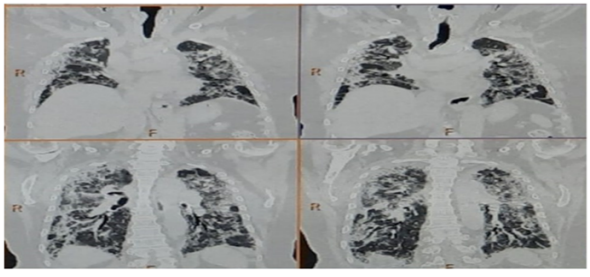


Figure-2 CORONAL View-

Fig 2- Fibrotic changes with coarse reticular patterns and parenchymal bands more prominent in upper and middle lobes of both lungs suggestive of non-specific interstitial pneumonia (NSIP).

DISCUSSION:

Pulmonary fibrosis can be caused by a variety of factors, including viral infections, autoimmune disease, drugs & toxins. Proposed mechanisms for virus induced pulmonary fibrosis includes binding of SARS-CoV2 to ACE2 in the alveolar lumen or on epithelial cells, and CD-98 or RGD-binding integrins which potentially facilitate cellular entry. Within the cell, the virus uses JNK and mTOR pathways for viral replication, which could activate the NLRP3 inflammasome to secrete IL-1 and IL-6 which act as pro-fibrotic molecules. Other possible molecular mechanisms (observed in SARS-CoV (2002) mediated fibrosis) includes upregulation of TGF-beta and downregulation of ACE-2 receptor level, which leads to high ANG-2 level, which further enhances the TGF-beta level. TGF-beta activates Smad proteins via receptor mediated phosphorylation and stimulates Smad-dependent gene transcription which contribute to myofibroblast activation and extracellular matrix accumulation.

A case report published in European Respiratory Journal 2020 by Margot Combet et al. describes a 38-year old male with chief complaints of cough, anosmia, ageusia, asthenia for 6 days. There was no significant past, personal and drug history. On admission the patient was tachycardic, tachypnoeic, and had saturation of 66 %. He was kept on high flow nasal cannula at flow rate of 50 l/min and Fio2-100%. There was no need of mechanical ventilation throughout the hospital stay. He was given corticosteroids with a loading dose 250 mg daily for 3 days followed by 1 mg/kg daily dose. Fever quickly receded, and inflammatory markers levels decreased. On day 10, because the patient still required high levels of oxygen via high-nasal flow cannula, CT Pulmonary Angiography was done, which showed extensive Honeycombing cysts associated with septal thickening, with subpleural predominance with associated traction bronchiectasis but no signs of pulmonary embolism. He was started on nintedanib as antifibrotic therapy along with corticosteroids and other supportive treatment. His condition improved later on and was shifted to ward on day 18. Our patient's clinical and radiological profile was very similar to this.

Another article published in the Lancet Respiratory Medicine May 2020 by Peter M George et al. describes an autopsy study of 159 patients with ARDS due to COVID-19, lung fibrosis was noted in 13 (24%) of 54 patients with a disease duration of between 1 and 3 weeks. Our patient also developed fibrosis within 3 weeks of admission. An article published in the Lancet Respiratory Medicine May 2020 by Paolo Spagnolo et al describes a study of MERS 2012 where chest-X rays takes a median of 43 (32-320) days after hospital discharge to show fibrotic changes. The article also describes a 15 year follow up study of 71 patients of SARS 2002 with 4.6% showing interstitial abnormalities taking about 2 weeks after symptom onset to develop reticular changes. Compared with SARS and MERS, due to wider community spread in COVID-19, the average age of hospitalized patient appears to be older. As advancing age is a risk factor of pulmonary fibrosis (pt. under study- 74year female) and looking at the evidence of fibrosis in previous epidemic SARS and MERS, the burden of pulmonary fibrosis in COVID-19 could be substantial.

Our patient did not have any past history suggestive of autoimmune disease, chronic drug ingestion (having evidence of pulmonary fibrosis), or occupational exposure to silica, asbestos or inorganic dusts. Autoimmune profile (ANA by IF, R factor) was negative for any systemic autoimmune disease. An article published in the Lancet Respiratory Medicine August 2020 by Ganesh Raghu, Kevin Wilson et al describes evidence of fibrotic abnormalities as early as 3 weeks after symptom onset and abnormalities of lung function appears to be more common among patients with severe acute COVID-19 with high level of inflammatory markers.

CONCLUSION:

We report a case of COVID-19 pneumonitis with rapid onset pulmonary fibrosis. A substantial proportion of patients who develop ARDS as a complication of COVID-19, develop progressive pulmonary fibrosis with residual long-term impairment of lung function. The pattern and rapidity of its development is atypical in comparison to the usual fibrotic response following lung injury suggesting a combination of direct effect of virus and an aberrant local immune response. We suggest further follow up compilation of data to identify proportion of such patients and also to look at the risk factors that are likely to cause such fibrosis.

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