Cytokine Storm Manifesting As Myocarditis as A Sequela of COVID-19

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Received Date: July 21, 2021; Accepted Date: August 23, 2021; Published Date: September 07, 2021

Citation: Desai U. (2021) Cytokine Storm Manifesting As Myocarditis As A Sequela Of COVID-19. International J. of Biomed Research. 1(6); DOI: 10.31579/IJBR-2021/027

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Abstract
Myocarditis is known complication in human coronavirus infections and number of myocarditis cases are reported in COVID-19 patients including few cases of fulminant myocarditis. Myocarditis in COVID-19 is thought to be due to combination of direct viral injury and lymphocyte mediated cytotoxicity. Cytokine storm develops as a result of positive feedback activation of T lymphocytes and characterised by raised blood levels of inflammatory markers particularly IL-6. Early recognition and timely management of cytokine storm and myocarditis may help to prevent development of some complications. As many COVID-19 patients have cardiovascular comorbidities, possibility of acute coronary syndrome must be considered. Here we present a case of myocarditis developing in COVID-19 as a part of cytokine storm which was treated with tocilizumab showing good response.

Keywords: covid myocarditis; cytokine storm; tocilizumab; response;

Introduction
COVID-19 which stands for Coronavirus disease 2019 was first described in Wuhan, China in December 2019 [1]. The mortality in COVID-19 is described mainly due to ARDS(Acute respiratory Distress Syndrome), cytokine storm and multi-organ dysfunction. It can cause many secondary conditions directly resulting from infection. One such condition is myocarditis which can be fatal if not diagnosed and treated appropriately. According to AHA(American Heart Association), myocarditis is defined as inflammation of heart muscle and is commonly caused by viral infections. First case of fulminant myocarditis complicating COVID-19 was described in April 2020 [2] and since then myocarditis has been recognised as cause of death in some COVID-19 patients. Usually, pathology is focal, but can progress to cardiogenic shock, arrhythmia, etc. Here we present a case report of myocarditis developing as a part of cytokine storm in COVID-19 patient.

Case report
A 28years old female, non-addict was admitted to our unit in isolation ward with laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection confirming a diagnosis of coronavirus disease 19 (COVID-19) by reverse transcripase polymerase chain reaction (RT- PCR) of swabs taken from her upper respiratory tract. She had sought evaluation in view of loose stools and vomiting for 3 days. On day 7 of illness patient was transferred to intensive care unit (ICU) as she started developing multiple episodes of highgrade fever, respiratory distress and hypoxia. There was no significant past history or family history. On physical examination her pulse rate, respiratory rate, blood pressure and transcutaneous oxygen saturation were 100 per minute, 28 per minute, 110/70mmHg and 92% in room air respectively. The respiratory examination revealed soft inspiratory basal crackles. Results of complete blood counts were as follows: haemoglobin (11.5 g/dl), haematocrit (33.5%), white blood cell count 13000/mm3, 78% segmented neutrophils, 3% monocytes, 23% lymphocytes and 2% eosinophils. Biochemistry analysis such as liver and renal function tests were normal. Initially inflammatory markers such as Erythrocyte sedimentation rate (ESR), C- reactive protein (CRP), Serum ferritin, Lactate dehydrogenase (LDH) were normal except for D-Dimer (1261 ng/ml) and Interleukin 6 (IL-6) (11.33 pg/ml) which was slightly raised. Later in view of Electrocardiogram (ECG) changes such as sinus tachycardia and T wave inversion in anterior leads biomarkers of myocardial injury were done. High-sensitivity cardiac troponin I (Trop I) (19.6pg/ml) and n-terminal brain natriuretic peptide (NT proBNP) (1240 pg/mL) were raised. Inflammatory markers were repeated which revealed elevated Erythrocyte sedimentation rate (ESR)(35mm at the end of 1 hour), C- reactive protein (CRP)(48 mg/L), Serum ferritin(522 ng/ml), Lactate dehydrogenase (LDH)(409 IU/L), D-Dimer (>15000 ng/ml) and Interleukin 6 (IL-6) (3107 pg/ml) suggestive of cytokine storm. Leucocytes were in increasing trend but procalcitonin (PCT) was always normal. High resolution
computer tomography (HRCT) suggestive of bilateral ground glass opacities (GGO) intermixed with dense and patchy confluent areas of consolidations in bilateral dependant areas of lower lobes with Mild bilateral pleural effusion (Figure 1). However, 2-dimension echocardiography (2D-ECHO) was normal. Patient also developed signs of autonomic dysfunction in the form of headache, dizziness, giddiness, nausea, loss of appetite, diaphoresis and fluctuating blood pressures.

Hence Computer Tomography of brain was done to rule out organic cause and it turned out to be normal. Arterial blood gas estimation showed pH- 7.48, pCO2-30mm Hg, paO2-120mmHg, HCO3-23mmol/L and arterial oxygen saturation 96% on High flow nasal canula (HFNC) at flow rate of 60L/min and Fraction of inspired oxygen (FiO2) of 50% with partial pressure of oxygen in arterial blood/ fraction of inspired oxygen (PaO2/ FiO2) of 240. Patient was managed with supplemental oxygen therapy without mechanical ventilation, intravenous corticosteroids, subcutaneous anticoagulants, oral antiviral (Favipiravir) and antibiotics along with convalescent plasma therapy initially. Later, in view of cytokine storm, persistent hypoxia, respiratory distress and raised IL6 patient also received Tocilizumab, a recombinant humanised monoclonal antibody. After this the patient improved clinically, oxygen requirement decreased repeat HRCT showed significant resolution in GGO (Figure 2).

Biomarkers decreased to Trop I (7.2pg/ml), NT pro BNP (89.13pg/ml) IL-6 (164pg/ml) D-Dimer (318ng/ml). Patient was discharged in stable condition. Hence a diagnosis of COVID 19 with Mild respiratory distress syndrome (ARDS) with cytokine storm manifesting as myocarditis was made. Thus Cytokine storm can manifest as fulminant myocarditis but mild ARDS. We achieved our diagnosis by clinical correlation with ECG and cardiac enzymes in conjunction with biomarker elevation.

**Discussion**

Myocarditis is an inflammatory disease of heart muscle cells in which inflammatory infiltrates and myocardial injury are seen without ischaemic cause [3]. Myocarditis can be caused by various infectious agents and noninfectious triggers. Infectious agents can be viruses, bacteria, Chlamydia, rickettsia, fungi, and protozoa while noninfectious triggers can be toxins and hypersensitivity reactions [4]. Viruses identified are enterovirus, parvovirus B19 (PVB19), adenovirus, influenza A virus, human herpes virus (HHV), Epstein–Barr virus, cytomegalovirus, hepatitis C virus, HIV and SARS-CoV2. Many authors have proposed that viral myocarditis is due to combined effect of virus induced direct cell injury and T cell mediated cytotoxicity which is further enhanced by cytokine storm syndrome as seen in COVID-19. Central mediator of cytokine storm is interleukin-6 (IL-6) [5]. In our case also, IL-6 was raised and following administration of Tocilizumab, a recombinant humanised monoclonal antibody against IL-6 receptors, patient improved clinically with improvement in blood levels of inflammatory markers. Largest study of use of Tocilizumab in critically ill COVID-19 patients showed survival benefit [6]. Cytokines cause activation of T lymphocytes which further cause release of cytokines and hence causing positive feedback of immune activation and myocardial damage. T lymphocytes have cardio tropism which is proposed to be due to e-MET. C-MET is HGF (hepatocyte growth factor) receptor on T lymphocytes and heart [7]. SARS-CoV2 enters human cells through ACE-2 (Angiotsensin Converting Enzyme) receptors on human cells with its spike protein [8]. Attachment of spike protein to ACE-2 receptor is enhanced by TMPRSS2, a serine protein [8]. In humans, ACE2 receptors can be found in respiratory tract, cardiomyocytes and GIT [9, 10]. ACE2 is overexpressed in case of heart failure which increases chances of infection with SARS-CoV2 [11]. Symptoms of COVID related myocarditis differ and range from fatigue, dyspnea, chest pain, chest tightness, palpitations, symptoms of heart failure and cardiogenic shock. If heart failure or ventricular dysfunction develops within 2-3 weeks of contracting the virus, then it is known as fulminant myocarditis [3]. Investigations from patients with COVID-19 related myocarditis show raised levels of inflammatory markers like C reactive protein and Erythrocyte sedimentation rate. Cardiac enzymes like troponins and N-terminal pro- B type Natriuretic Peptide are also elevated. Serial negative results of high sensitivity troponins most likely exclude myocarditis as elevated NT-proBNP levels can be seen in cases
of severe respiratory illness causing myocardial stress [12]. ECG may be normal or may show changes like arrhythmia. Echocardiogram may show chamber dilatation, increased wall thickness, pericardial effusion or ventricular systolic dysfunction. Other imaging modalities which can be used are cardiovascular magnetic resonance or contrast enhanced cardiac CT with ECG gating. Without these imaging modalities, it is very difficult to distinguish myocarditis from other differential diagnoses such as acute coronary syndromes and stress induced cardiomyopathy. However, definitive diagnosis of myocarditis can only be made with the help of endomyocardial biopsy (EMB), but it has limitations in the form of requirement of expertise, increased chances of spread of virus and false negativity [13]. Management of myocarditis depends on symptoms, presence or absence of arrhythmias and cardiogenic shock. Fulminant myocarditis is managed with the help of use of vaspressors/inotropes, mechanical ventilation, ECMO (extra corporeal membrane oxygenation) or ventricular assist device. In case reports of coronavirus related myocarditis, where patients were hemodynamically stable, medical treatment was sufficient [14]. In the setting of cytokine storm, IL-6 levels are usually raised and hence, tocilizumab may be beneficial as seen in our case. Role of steroids and immunoglobulins is controversial in managing COVID-19 related myocarditis. NSAIDS (non-steroidal anti-inflammatory drugs) and macrolides should be used with caution in such cases as they may exacerbate cardiac symptoms.

Conclusion

COVID-19 may lead to development of cytokine storm and as a result of which patient can develop myocarditis. Simple bedside tests such ECG monitoring and raised levels of cardiac biomarkers suggest cardiac involvement. Trend in cardiac biomarkers should be observed instead of single value. Diagnosis can be supported by other imaging modalities like echocardiography or cardiovascular magnetic resonance. Treatment can be supportive or in cases of cytokine storm, tocilizumab can be tried. Role of steroids is controversial. Arrhythmia and cardiogenic shock ae few complications of myocarditis.

References

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