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Case Report: Covid-19 Series

# SARS-CoV-2 Viral Sepsis with Meningoencephalitis

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## Abstract

SARS-CoV-2 predominantly involves the lungs producing acute lung injury, but it can also give rise to a variety of complications involving the central nervous system, gastrointestinal system, kidney and also viral sepsis. With this case report, we are discussing unusual series of complication from acute lung injury, followed by viral sepsis then encephalitis, followed by progressive macrophage activation syndrome.

**Keywords:** COVID-19, encephalitis, macrophage activation syndrome, SARS-CoV-2, viral sepsis

## Introduction

Complications of severe SARS-CoV-2 disease are a result of the dysregulated immune system with cytokine storm leading to extensive alveolar and interstitial inflammation with microvascular thrombosis and haemorrhages.[1,2] A macrophage activation syndrome (MAS)-like state that triggers extensive immunothrombosis, especially in the lungs due to uncontrolled inflammation.[3] Clinically, it is characterised by progressive respiratory insufficiency and multiorgan failure. Early laboratory markers of severe pulmonary intravascular coagulopathy are increased D-dimer levels with normal fibrinogen and platelet levels, reflecting pulmonary vascular bed thrombosis with fibrinolysis; some patients may have elevated cardiac enzymes resulting from emergent ventricular stress induced by pulmonary hypertension and/or myocarditis. Patients with progressive increase in D-dimer levels are at increased risk of death.[1] Neurological complications have also been described in SARS-CoV-2 outbreak, including stroke, Guillain–Barre syndrome, critical care illness neuromyopathy and encephalitis[4,5] Li *et al.* observed typical clinical manifestations of shock, including cold peripheries and weak peripheral pulses, in the absence of hypotension in many patients with severe SARS-CoV-2 infection.[6] This is likely to be due to SARS-CoV-2 viral sepsis. In this case report, we describe a patient who has features of viral sepsis with central nervous system (CNS) involvement and progressive MAS-like features in SARS-CoV-2 disease.

## Case Report

A 68-year-old diabetic and hypertensive male was admitted to our hospital on 2 May 2020 with complaints of high-grade fever and exertional dyspnoea for 4 days. On admission, he was febrile (T-101°F), had tachycardia (P-120/min), tachypnoea (RR-24/min) and a normal blood pressure. His SpO2 was 93% while breathing ambient air. His baseline and follow-up investigations are shown in Table 1. Baseline investigations were significant for lymphocytopenia, high neutrophil-to-lymphocyte ratio (NLR), thrombocytopenia and elevated C-reactive protein, ferritin, D-dimer and Creatine phosphokinase (CPK) total (1217 IU/L). The reverse transcription polymerase chain reaction of nasopharyngeal swab for SARS-CoV-2 had been positive on the day of admission. The computed tomography (CT) of the thorax showed bilateral lower lobe, right middle lobe and multifocal ground-glass opacities with emphysematous changes in both apical lung with CT severity score of 12 [Figure 1a coronal section and b: axial section]. Treatment included oxygen inhalation with nasal prongs, azithromycin, hydroxychloroquine, an

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**Received:** 27-06-2020 **Revised:** 22-06-2020
**Accepted:** 30-06-2020 **Published Online:** 29-08-2020

Access this article online

Quick Response Code:

Website: www.ijmm.org

DOI: 10.4103/ijmm.IJMM_20_291



**How to cite this article:** Dharsandiya M, Shah K, Patel K, Patel T, Patel A, Patel A. SARS-CoV-2 viral sepsis with meningoencephalitis. Indian J Med Microbiol 2020;38:219-21.

**Table 1: Serial changes in laboratory parameters after hospitalization**

| Day of hospitalisation | 1 | 3 TCZ | 5 | 7 TCZ | 9 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|
| Hb (g/dl) | 15.1 | 15 | 13.9 | 14.6 | 16.3 | 14.8 | 15.7 | 9.7 |
| WBC (Poly/Lym) | 6200 (70/20) | 6150 (87/10) | 10,610 (87/7) | 22,570 (91/6) | 19,300 (86/8) | 10490 (91/5) | 31290 (95/3) | 27460 (86/09) |
| NLR | 3.5 | 8.7 | 12.4 | 15 | 10.75 | 18.2 | 31 | 9.5 |
| Platelets/cmm | 73 K | 71.4 K | 138 K | 203 K | 237 K | 150 K | 190 K | 125.6 K |
| CRP (mg/dl) | 4.6 | 6.3 | 2.2 | 0.8 | 0.5 | <0.5 | <0.5 | <0.5 |
| Ferritin (ng/ml) | 1373 | 1274 | 814 | 842 | 630 | 4920 | 10690 | 4392 |
| D-dimer (ng/ml) | 1602 | 535 | 367 | 1652 | | 2778 | 3925 | 2699 |
| Serum creatinine (mg/dl) | 1.52 | 1.6 | 1.6 | 1.1 | 1.47 | 1.7 | 2.8 | |
| PT (s)/INR | 15.3/1.07 | 16.7/1.18 | | 14.2/1.0 | 15.9/1.13 | | | |
| APTT (s) | 49 | >120 | | 36 | 34.6 | 47 | | |
| Procalcitonin (ng/dl) | | 0.22 | | | | | 0.9 | |
| IL-6 (pg/ml) | | 45.5 | | | | | >1000 | |

Serum fibrinogen: 223 and fibrinogen degradation product was<5. NLR: Neutrophil-to-lymphocyte ratio, Hb: Haemoglobin, WBC: White blood cells, TCZ: Tocilizumab, CRP: C-reactive protein, PT: Prothrombin time, INR: International normalised ratio, APTT: Activated partial thromboplastin time, IL-6: Interleukin-6

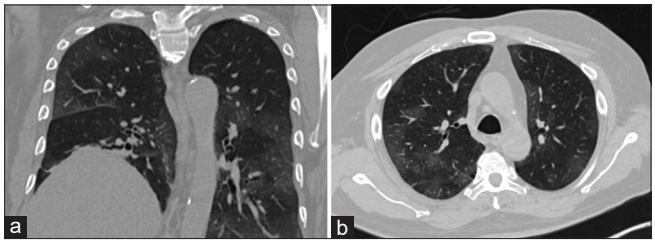


**Figure 1:** a coronal and b axial computed tomography scan of the thorax showing bilateral ground-glass opacities

anticoagulant (injection enoxaparin 60 mg subcutaneous twice a day (BID)) and an antiplatelet soluble aspirin 300 mg ½ tablet once daily. Antihypertensives and insulin were continued. He had progressive worsening dyspnoea on day 2 of hospitalisation despite support and was put on non-rebreathing mask with 14 l of oxygen and injection methylprednisolone 80 mg stat dose was given. He remained hypoxic and breathless despite these measures and was shifted to the intensive care unit and started on high-flow nasal cannula (HFNC). His serial inflammatory markers progressively worsened along with clinical deterioration. Injection tocilizumab 640 mg (8 mg/kg) was given in view of worsening clinical and laboratory parameters on day 3 of hospitalisation. His oxygenation status improved with HFNC and dyspnoea decreased with improvement in appetite. The patient appeared confused and talked irrelevantly during morning round on hospitalization day six. He received second dose of Tocilizumab on hospitalization day seven in view of clinical worsening with progressive hypoxia on HFNC with rising D-dimer and serum ferritin. The patient required mechanical ventilator the next day due to progressive hypoxia. The patient had one episode of seizure while on invasive ventilation. A physical examination revealed normal sized pupil reacting to light and there was no focal neurological deficit. A CT scan examination of the brain revealed age-related cortical atrophy. A cerebral spinal fluid analysis showed raised total cells – 20/cmm (100% lymphocytes), with normal protein – 39 g/dl and sugar – 137 mg/dl. His antibiotics were upscaled to meropenem. On day 9 of hospitalisation, the patient developed autonomic disturbances with paroxysmal episodes of tachycardia–bradycardia and hypertension–hypotension; physical examination showed cold peripheral extremities with discoloured feet despite a high blood pressure (180/100 mmHg) [Figure 2]. In view of the autonomic dysfunction, low-dose propranolol (20 mg BID) was started and there was a reduction in the frequency of autonomic disturbances. On hospitalisation day 7, a repeat dose of tocilizumab was given. His condition continued to deteriorate and on day 11 of hospitalisation, he developed oliguric renal failure with very high ferritin levels (more than 10,000 ng/ml) and also D-dimer levels (3925 ng/ml). A repeat C-reactive protein (<0.5 mg/dL) and procalcitonin (0.9 ng/dL) were normal. He had leucocytosis (Total white cells count (TC) – 31290/cmm) and the blood cultures were repeatedly sterile. There were few treatment options left for probable worsening MAS despite two dosage of tocilizumab and ongoing low-dose steroid therapy. Intravenous gamma globulin in 50% of calculated dose (i.e., 200 mg/kg) was given and the empiric antimicrobials were upscaled (injection linezolid 600 mg IV BID and injection caspofungin 70 mg IV Once a day (OD)) and repeat blood cultures from an arterial line and serum beta-D-glucan (BDG) test were sent. Renal replacement therapy (haemodialysis) was initiated, followed by sustained low-efficiency dialysis. Despite all the measures, the patient succumbed on day 13 of hospitalisation. The last blood culture that had been drawn before he died grew Enterococcus faecium sensitive to vancomycin (minimum inhibitory concentration MIC <0.5), linezolid (MIC 2) and his serum BDG came 201 pg/ml.

## Discussion

Bacterial and fungal pathogens are most commonly associated with sepsis and septic shock in clinical practice, whereas viruses are infrequently a cause of sepsis. The diagnosis of viral sepsis is also challenging as there are no specific diagnostic criteria.

**Figure 2:** Bilateral lower limbs showing colour changes suggestive of peripheral shock

Exclusion of bacterial or fungal sepsis by sterile blood cultures as well as some laboratory features may suggest a viral sepsis. Li *et al*. define viral sepsis as life-threatening organ dysfunction due to a dysregulated host response to viral infection in both adult and paediatric populations in the presence of viral infection diagnosed clinically along with viral culture, antigen detection, molecular diagnostics, histopathology or immunohistochemistry.[7] Dengue virus is commonly identified as a cause of viral sepsis, followed by rhinovirus and influenza virus. Neonates and young children, pregnant women, elderly people and immunocompromised patients are considered vulnerable for severe infection and sepsis.[7] The SARS-CoV-2 virus evades killing by the immune system on the one side and on the other side, its continuous high replication induces severe inflammatory responses from the host with high levels of tumour necrosis factor-alpha and interleukin-6 (IL-6) that can damage organs. The prolonged inflammation can then result in an immunosuppressed state (state of immune dysregulation), further reducing the body's capacity to clear infections and increasing the risk of death from the viral infection and/or a newly acquired superinfection.[2,8]

Our patient succumbed to viral sepsis due to his age and the fact that male gender with comorbidities such as diabetes and hypertension put him at a higher risk for endothelial dysfunction resulting from SARS-CoV-2 infection.[9] Clinicians have noticed that many severe or critically ill SARS-CoV-2 patients develop the typical clinical manifestation of shock like cold extremities and weak peripheral pulses, even in the absence of overt hypotension.[10] Many of these patients have severe metabolic acidosis, suggesting possible microcirculatory dysfunction with multiorgan failure. Our patient also developed hyperlactataemia and progressive renal failure over the last 2 days. There were several unusual clinical and laboratory features in our patient; he had low platelet with high total CPK on admission and an NLR of 3.5. During hospitalisation, he developed features of severe sepsis and CNS involvement, possibly due to very high SARS-CoV-2 viral load-viraemia leading to sepsis and meningoencephalitis. His D-dimer remained elevated throughout the course of hospitalisation with normal fibrinogen and fibrinogen degradation product level with normal platelets suggesting persistent intrapulmonary coagulopathy. The last 2 days of hospital course were complicated by sudden worsening of probable MAS suggested by a rising serum ferritin level. IL-6, a pro-inflammatory cytokine, has been shown to play a role in generating a cytokine release storm by reducing natural killer/CD8 cell cytolytic function to kill infected cells. As a result, the antigen-presenting cells get an opportunity for prolonged cell-to-cell interaction with the host immune cells. This cytokine storm results in the activation of macrophages and MAS. Our patient received two dosage of tocilizumab at 4 days' interval and we did check his repeat IL-6 level showing >1000 ng/ml suggesting effective blockade of IL-6 receptor. Despite that the patient showed features of progressive MAS, which probably started responding to intravenous immunoglobulin. Towards the end, he probably developed candidaemia (high BDG) and enterococcus faecium bloodstream infection.

## Summary

Severe SARS-CoV-2 infection can induce multiple immunopathological processes simultaneously or sequentially leading to a variety of multisystem complications not restricted to the pulmonary system. Patients can have progressive MAS-like features with clinical worsening despite anti-inflammatory treatment.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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