

# Cytomegalovirus Coinfection in Critically Ill Patients with Novel Coronavirus-2019 Disease: Pathogens or Spectators?

Suhail S Siddiqui<sup>1</sup>, Soumyadip Chatterjee<sup>2</sup>, Ambuj Yadav<sup>3</sup>, Nitin Rai<sup>4</sup>, Avinash Agrawal<sup>5</sup>, Mohan Gurjar<sup>6</sup>, Geeta Yadav<sup>7</sup>, Shantanu Prakash<sup>8</sup>, Amit Kumar<sup>9</sup>, Syed N Muzaffar<sup>10</sup>

## ABSTRACT

Coronavirus disease-2019 (COVID-19) pandemic is raging all over the world. As we are delving more into management of COVID-19, certain new challenges are emerging. One of these is emergence or reactivation of viral infections belonging to Herpesviridae family, especially cytomegalovirus (CMV). Although we have come across the threat of fungal and resistant bacterial infections, experience regarding reactivation or coinfection with concomitant viral infections like CMV during the COVID pandemic is still limited. Whether CMV is a bystander or pathogen is difficult to say categorically and needs further research. In this case series, we intend to describe three patients of COVID-19 with CMV coinfections. To our knowledge, this is the first case series from India.

**Keywords:** Coronavirus disease-2019, Critically ill, Cytomegalovirus, Viral coinfection.

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## INTRODUCTION

Coronavirus disease-2019 (COVID-19) pandemic has affected the whole world. In COVID, many superimposed infections may emerge during the course of disease secondary to lymphopenia, use of immunosuppressants (like steroids, tocilizumab etc.), underlying comorbidities, and immune dysregulation.<sup>1,2</sup> Emergence or reactivation of viral infections belonging to Herpesviridae family, especially cytomegalovirus (CMV) is one of these threats, which may aggravate the end-organ damage caused by COVID. Unravelling whether CMV is a bystander or pathogen is difficult to say explicitly and requires further research. Timely management of CMV infections in COVID-19 may influence the outcome of patients. We hereby describe three patients of COVID-19 with CMV coinfection and share our learning experience gained from these cases. To our knowledge, this is the first case series from India.

## CASE DESCRIPTIONS

### Case 1

Fifty-four-year-old man, chronic smoker, overweight, and hypertensive, got admitted with 1-week history of fever, cough, and breathlessness. SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test was positive. At admission, he had hypoxemia (SpO<sub>2</sub> 86% on room air) and respiratory rate up to 35–40/minute, suggestive of severe COVID-19 pneumonia. Chest X-ray showed ground-glass opacities involving 50% of the lung parenchyma bilaterally. He was managed with lung protective invasive mechanical ventilation (MV), restrictive fluid strategy, 16–18 hour/day proning sessions (4–5), intravenous (IV) remdesivir, IV dexamethasone 6 mg 12 hourly, and enoxaparin thromboprophylaxis. After 2 weeks of ICU stay, weaning was tried, but all the weaning attempts failed due to underlying neuromuscular weakness. On examination, bilateral cranial nerve palsies, areflexia, and muscle power grade up to 0/5 in bilateral upper and lower limbs were present. A possibility of Guillain-Barre syndrome (GBS) was kept after ruling out other differentials, for which IV immunoglobulin therapy (IVIg) was administered for

<sup>1,4,5,10</sup>Department of Critical Care Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India

<sup>2</sup>Department of Infectious Diseases, Tata Medical Centre, Kolkata, West Bengal, India

<sup>3,9</sup>Department of Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India

<sup>6</sup>Department of Critical Care Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

<sup>7</sup>Department of Pathology, King George's Medical University, Lucknow, Uttar Pradesh, India

<sup>8</sup>Department of Microbiology (Virology), King George's Medical University, Lucknow, Uttar Pradesh, India

**Corresponding Author:** Syed N Muzaffar, Department of Critical Care Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India, Phone: +91 9648084011, e-mail: muzaffarnabeel@gmail.com

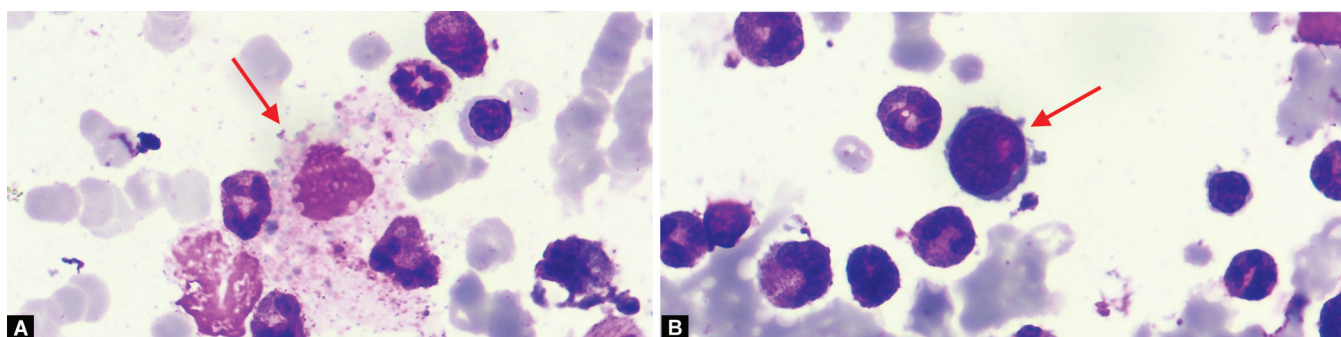
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5 days with subtle improvement in muscle strength up to 1/5 grade in both upper limbs.

By 5th–6th week of hospitalization, he started experiencing gut dysfunction (abdominal distension, diarrhea, feed intolerance) along with features of refractory shock requiring persistent vasopressor support to maintain target mean arterial pressure (MAP). Labs revealed pancytopenia with deranged liver function, high serum triglyceride and ferritin levels. Bone marrow aspiration and biopsy had features of hemophagocytosis and hemopoiesis along with presence of CMV inclusion bodies (Fig. 1). In addition, PCR for CMV DNA in blood (sent in pancytopenia panel) turned out to be positive. So, a possibility of hemophagocytic lymphohistiocytosis



**Figs 1A and B:** (A) Histiocyte showing hemophagocytosis with engulfment of many neutrophils (red bold arrow, Leishman stain, 1000 $\times$ ) in bone marrow; (B) Pronormoblast showing nuclear inclusions of CMV (red bold arrow, Leishman stain, 1000 $\times$ ) in bone marrow

(HLH) secondary to CMV was kept and IV ganciclovir initiated along with steroids, but the patient continued to deteriorate and succumbed to his illness in 8th week of ICU stay.

### Case 2

Fifty-seven-year-old man, on rituximab maintenance therapy for autologous bone marrow transplant done 2 years ago (for mantle cell lymphoma), was admitted in COVID ICU with moderate COVID pneumonia. He initially showed improvement after IV remdesivir, IV dexamethasone 6 mg OD, and subcutaneous enoxaparin thromboprophylaxis and was discharged after 10 days of ICU stay. A few days post discharge, he presented again to the ICU in shock and hypoxemic respiratory failure, which was managed with high flow nasal oxygenation (HFNO), vasoactive drugs, broad-spectrum antibiotics and antifungals. Workup showed RT-PCR for COVID positive, along with raised CRP and d-dimer levels. DVT screening of lower limbs and 2D echocardiography did not reveal any evidence of thromboembolism. In next 2 days, invasive MV had to be initiated in view of worsening hypoxemia. Following intubation, mini-bronchoalveolar lavage (mini-BAL) was done, and samples were sent for cytology, gram stain, bacterial and fungal cultures and PCR *Pneumocystis jirovecii* (PCP) workup, in which carbapenem-resistant *Pseudomonas aeruginosa* was detected and accordingly managed. In addition, serum galactomannan (GM) antigen turned out to be positive (GM index 0.97/0.5 by Platelia™ *Aspergillus* kit) for which antifungals were continued. HRCT chest revealed bilateral ground glass opacities (GGO) with consolidation in lower lobes suggestive of severe COVID pneumonia (CTS: 24/26). In view of persistent fever, hypoxemia, worsening organ functions, and rising inflammatory markers, two units of convalescent plasma, IV steroids, and IVIG were added. However, there was a progressive downhill course in his illness, and he started to have abdominal distension with malena. Besides other differentials, a possibility of CMV infection was considered. PCR for CMV DNA in blood turned out to be positive following which IV ganciclovir was added, but the patient continued to deteriorate and developed multiple organ failures [encephalopathy, worsening hypoxemia, refractory shock, and acute kidney injury (AKI) requiring renal replacement therapy (RRT)] and eventually succumbed to his illness.

### Case 3

Sixty-two-year-old man, known diabetic and hypertensive patient, was admitted in COVID ICU with severe COVID pneumonia (RT-PCR for COVID positive) following a 3-week history of fever, dry

cough, myalgia, and recent onset breathlessness. After 10 days of management in COVID ICU (with intermittent HFNC/NIV and anti-COVID medications), he was transferred to non-COVID ICU facility following a negative RT-PCR COVID test. However, at ICU admission, he sustained hypoxemic cardiac arrest for which cardio-pulmonary resuscitation (CPR) was done and return of spontaneous circulation (ROSC) immediately achieved. Post-resuscitation, he was managed with cerebral protective strategy, lung protective invasive MV, and vasopressor support. During ICU stay, there were recurrent events of sepsis attributed to gram-negative bacteremia (*Burkholderia cepacia*) and multi-drug-resistant *Pseudomonas aeruginosa* VAP. Meanwhile, he started developing pancytopenia by 4th week of illness. In work up, labs showed high ferritin levels, raised serum triglycerides and features of transaminitis. Peripheral blood smear (PBS) revealed atypical medium to large-sized lymphocytes (Fig. 2A) and bone marrow aspiration done simultaneously showed features of hemophagocytosis (Fig. 2B). In addition, PCR for CMV DNA turned out to be positive in blood. IV ganciclovir was thereafter initiated along with steroids in view of HLH secondary to CMV after which gradual clinical improvement was noted and patient got liberated from MV and was discharged from ICU.

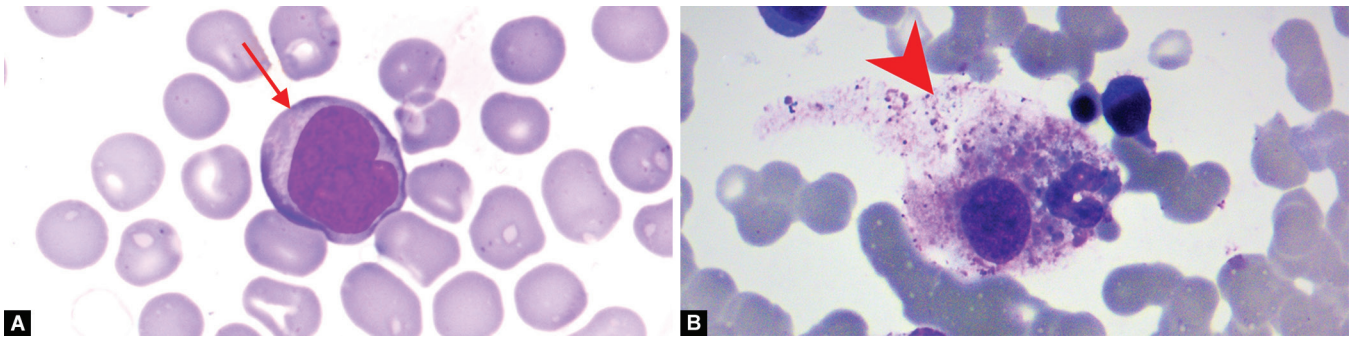
Table 1 shows a description of these cases in detail.

## DISCUSSION

Herpesviridae family is the most important group of viruses responsible for persistent viral infections in humans, of which CMV contributes to 60–90% infections in adults, especially in developing countries.<sup>3</sup> In healthy individuals, these viruses are kept dormant by body's immune mechanisms but in immunocompromised population, reactivation from a latent state can occur.

SARS-CoV2 infection predisposes patients to concomitant viral coinfections, owing to T-cell lymphopenia, decreased NK cell number and use of immunosuppressive medications.<sup>4</sup>

The first case of CMV co-infection with COVID-19 was first reported by D'Ardes and coworkers in Italy in 2020.<sup>5</sup> Since then, many studies have been emerging to explore this area. In an observational study from France, 38 COVID-19 patients on more than 7 days of MV were studied for HSV and CMV pulmonary coinfections (by quantitative real time PCR in tracheal samples) out of which 47% patients had one of these infections (24% HSV, 5% CMV, 18% both).<sup>6</sup> A case series looking for CMV infection (by PCR in plasma or BAL) in COVID-19, also found CMV reactivation between day 7 and 45 of illness. Most of these patients were above 60 years of age and immunosuppressed (HIV, diabetes mellitus, medications).<sup>7</sup> In a recent retrospective study on 34 critically ill COVID patients from France,



**Figs 2A and B:** (A) Peripheral blood smear showing atypical medium- to large-sized lymphocyte with moderately condensed chromatin, prominent nucleoli, and moderate to deep basophilic cytoplasm (red bold arrow, Leishman stain, 1000×); (B) Bone marrow aspirate smear showing hemophagocytosis with engulfment of neutrophil (red bold arrow head, Leishman Stain, 1000×)

**Table 1:** Case descriptions

	Case 1	Case 2	Case 3
At ICU admission			
Age (years)/gender	54/M	57/M	62/M
Comorbidities	Hypertension Type 2 DM Obesity COPD Hypothyroidism	Mantle cell lymphoma Post bone marrow transplant (on rituximab)	Hypertension Type 2 DM (uncontrolled; HbA1C 10.6)
SOFA admission	6	10	8
Severity of hypoxemia	Severe ARDS	Severe ARDS	Severe ARDS
Laboratory values at ICU admission			
Hb (g/dL)	14.6	12.2	11.1
TLC (/mm <sup>3</sup> )	12,300	17,700	15,400
PLT (lac/mm <sup>3</sup> )	4	1.1	1.3
CRP (mg/L)	91	20	132
IL-6 (pg/mL)	15	193	NA
D-dimer (µg/mL)	8.5	1.7	1.25
Serum ferritin (ng/mL)	1,045	4,171	264
LDH (U/L)	966	613	1,071
INR	1.07	1.3	1.4
T.bil/D.bil (mg/dL)	0.37/0.23	0.4	0.8/0.5
SGOT/SGPT (IU/L)	23/17	58/53	67/87
Urea (mg/dL)	48	41	72
S. Creatinine (mg/dL)	0.9	1.03	1.1
Procalcitonin (ng/mL)	0.5	1.06	<0.05
Clinical course during ICU stay			
Duration of MV (days)	61	26	51
Duration of vasopressor therapy (days)	54–55	7–10	3–4
Need for RRT	No	Yes	No
Diagnosis of CMV			
Time of CMV workup (in week of illness)	6th week	4th week	3rd week
Risk factors	Uncontrolled DM, Steroids, Prolonged MV	Bone marrow transplant, Steroids	Uncontrolled DM, Steroids
Clinical presentation	Refractory septic shock, Pancytopenia, Gut and Hepatic dysfunction	Refractory septic shock, Gut dysfunction	Refractory sepsis

Peripheral blood smear	Mixed picture of RBCs with microcytic and macrocytic forms, neutrophils with hypersegmentation and coarse granules	—	Normocytic normochromic RBCs, few macrocytes and spherocytes and atypical lymphocyte (medium to large sized) with moderately condensed chromatin, prominent nucleoli, basophilic cytoplasm.
Bone marrow workup	HLH; (CMV intranuclear inclusion bodies)	—	HLH
Serology: IgM CMV antibody (positive OD ratio >1.1; Calbiotech USA)	—	—	IgM CMV antibody OD = 1.24
CMV viremia: TaqMan (Real time PCR CMV DNA) in Blood (copies/mL): IU/mL (approximate)	3,870	8,036	2,480
Histology: Bone marrow biopsy	CMV intranuclear inclusion bodies seen in bone marrow (Fig. 1)	—	—
Other workups Ophthalmological examination	Normal funduscopy Exposure Keratopathy	—	Normal funduscopy Keratopathy (suspicion of viral keratitis)
Specific treatment			
Medications	IV Remdesivir/IV Steroids/ Enoxaprain thromboprophylaxis subcutaneous Antibiotics, antifungals, IV gancyclovir IVIg	IV Remdesivir/IV Steroids/Enoxaprain thromboprophylaxis subcutaneous CP, pulse steroids Antibiotics, antifungals, IV gancyclovir IVIg	IV Remdesivir/IV Steroids/ Enoxaprain thrombo- prophylaxis subcutaneous IV gancyclovir
Outcome			
LOS ICU	8 weeks	5 weeks	10 weeks
Survival at ICU discharge	Non-survivor	Non-survivor	Survivor

COPD, chronic obstructive pulmonary disease; T2DM, type 2 diabetes mellitus; SOFA, sequential organ failure assessment; ARDS, acute respiratory distress syndrome; TLC, total leukocyte count; PLT, platelet count; CRP, c-reactive protein; IL-6, interleukin-6; T. bil, total bilirubin; D.bil, direct bilirubin; MV, mechanical ventilation; RRT, renal replacement therapy; HLH, hemophagocytic lymphohistiocytosis; CMV, cytomegalovirus; DNA, deoxyribonucleic acid IV, intravenous; IVIG, intravenous immunoglobulin; LOS ICU, length of stay intensive care unit; Data not available

Epstein-Barr virus (EBV), human herpes virus 6 (HHV-6), and CMV viremia were seen in 82, 22 and 15% patients, respectively. Median age of these patients was 59 years and around 88% of them were on invasive MV and 18% on both extracorporeal membrane oxygenation (ECMO) and invasive MV. CMV viremia was detected after 12 days (median) of ICU admission and in around 20% patients, it was not quantifiable. No association between viral coinfections and mortality was found in this study.<sup>8</sup> Till date, no case of CMV coinfection in COVID has been reported from India, and we aim to highlight the first such case series from India.

In our patients, clues favoring CMV infection included predisposing risk factors [like multiple comorbidities including bone marrow transplantation, usage of immunosuppressive medications, elderly population (mean age 58 years), and prolonged ICU stay] and a clinical picture significant of hematological dysfunction (HLH in cases 1 and 3) and refractory organ failures (all cases). A high index of suspicion for CMV should be kept in COVID patients with similar risk factors and clinical presentation.<sup>9,10</sup> Even though HLH

has been described in COVID-19 *per se*,<sup>11,12</sup> it still seems imperative to study whether a viral coinfection like CMV has proclivity to develop profound hematological anomalies. As far as diagnosis of CMV is concerned, it is not necessary that all patients with CMV infection develop CMV disease, which are two distinct entities. CMV disease refers to the presence of CMV antigen or nucleic acid along with attributable clinical features (either CMV syndrome or tissue invasive disease), which may not be seen in all patients with CMV infection.<sup>13</sup> In addition, nonspecific clinical presentation and lack of established cut offs for the diagnostic tests make the diagnosis even more challenging.<sup>14</sup> Besides, tissue-invasive disease may be present even if the plasma or whole-blood PCR is negative.

CMV viremia was seen in all our cases and a direct histological evidence of infection was also seen in the form of CMV nuclear inclusion bodies in bone marrow in case 1. Additionally, assessment of viral load kinetics (which depends upon patient's immunity, stage of disease, site of infection and clinical and virological response to drug therapy) and sampling from other organs (like CSF, BAL,

gastrointestinal tract, urine) would have been more representative of the actual viral burden and may have correlated better with active CMV disease.<sup>13,14</sup> Thus, it is difficult to comment conclusively whether CMV was a bystander or a pathogen in our cases.

But, still we would like to emphasize that interplay between SARS CoV-2 and CMV may pose challenging questions and needs prompt attention in critical care settings to timely manage the end organ damage (EOD) caused by concomitant CMV infections in COVID.<sup>15,16</sup> Timely management of CMV infection may influence the outcome of patients, which needs large scale research.<sup>17</sup>

## CONCLUSION

CMV coinfection is an emerging threat in critically ill COVID-19 patients and may aggravate the damage caused by an underlying COVID infection, especially in critical care settings. Clues to diagnosis may be patients with refractory organ failures and hematological dysfunction and to pick up these cases timely, early, and serial testing for CMV from blood and other tissues may be helpful. Understanding the intricacies of interaction between SARS CoV-2 and CMV infections is quintessential to tackle the upcoming challenges posed by CMV in COVID pandemic.

## ORCID

Suhail S Siddiqui  <https://orcid.org/0000-0001-7109-0566>  
 Soumyadip Chatterjee  <https://orcid.org/0000-0002-5291-1901>  
 Ambuj Yadav  <https://orcid.org/0000-0003-1471-6539>  
 Nitin Rai  <https://orcid.org/0000-0003-3351-4553>  
 Avinash Agrawal  <https://orcid.org/0000-0003-0345-4166>  
 Mohan Gurjar  <https://orcid.org/0000-0002-8489-0324>  
 Geeta Yadav  <https://orcid.org/0000-0001-8193-8436>  
 Shantanu Prakash  <https://orcid.org/0000-0002-5881-6921>  
 Amit Kumar  <https://orcid.org/0000-0001-8056-3468>  
 Syed N Muzaffar  <https://orcid.org/0000-0001-5643-7314>

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