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## Severe cytomegalovirus infections in immunocompetent patients at admission as dengue mimic: Successful treatment with intravenous ganciclovir

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### ABSTRACT

Cytomegalovirus (CMV) infection is associated with adverse clinical outcomes in immunosuppressed persons. The incidence and association of CMV reactivation with adverse clinical outcomes in critically ill persons lacking evidence of immunosuppression at ICU admission has received great attention in the practice of critical care medicine. Critically ill patients in ICU who had associated risk factors such as mechanical ventilation, severe sepsis, or blood transfusion are more prone to CMV activation, which in turn led to increased mortality and morbidity in terms of increased ICU stay, longer duration of mechanical ventilation, and higher rates of nosocomial infections. However, severe CMV as initial presentation mimicking dengue infection is rare. We recently came across seven cases with positive CMV serology at ICU admission, which we discuss in the light of current literature.

## 1. Introduction

Cytomegalovirus (CMV) reactivation in apparently immunocompetent individuals with critical illness is becoming an area of emerging clinical significance<sup>[1,2]</sup>. CMV reactivation is associated with a significant 81% higher mortality rate than that in critically ill patients without active CMV infection and also higher morbidity in terms of increased duration of ICU stay, longer duration of mechanical ventilation and higher rates of nosocomial infection<sup>[1]</sup>. However, severe CMV as initial presentation mimicking dengue infection is rare. We recently came across seven cases with positive CMV serology at intensive care unit (ICU) admission, of which initial three patients succumbed. Hence early administration of ganciclovir was decided in subsequent patients. One patient left the hospital

against medical advice. Here we describe three cases of severe CMV who were successfully treated with intravenous ganciclovir. This drug was well tolerated and progressive improvement of organ function was observed after antiviral therapy.

## 2. Case report

### 2.1. Case 1

A 20 year old female patient, primigravida, 36 weeks pregnant, presented with high grade fever associated with chills and rigors, progressively increasing shortness of breath for 1 week. Her antenatal period was otherwise uneventful and there were no associated co-morbid conditions. On admission to ICU she was febrile (101.5 °F), and tachypnic (respiratory rate=35/min). Preliminary investigations revealed low platelet count (88 000/mm<sup>3</sup>) and elevated liver enzymes. (SGPT–88 IU/L, SGOT–130 IU/L) and negative for malaria parasite. Chest radiograph revealed bilateral infiltrates. Patient was intubated and mechanically

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ventilated in view of deteriorating oxygen saturation and low PaO<sub>2</sub> on ABG. Ultrasound revealed a single live fetus with tachycardia (FHR=180/min). Obstetrician's opinion was sought and emergency cesarian section was done. A 1.8 kg female child with APGAR score 8/10 delivered and admitted to neonatal ICU. Detailed infectious diseases work-up revealed negative dengue NS1 Ag, Ig M, Ig G, leptospira Ig M. CMV IgM (ELISA method and MEIA by automated system Abbott Axysm) was positive. She started on IV gancyclovir in addition to IV antibiotics. Patient became afebrile. Upon improvement in chest X-ray and ABG she was weaned off the ventilator and extubated on 3rd post operative day. Hepatopathy was resolved. Subsequently she was shifted to ward and discharged a week later.

### 2.2. Case 2

A 45 year old female patient, nil comorbid, presented with high grade fever, with chills and shortness of breath. Initial ABG revealed severe hypoxemia on 8 L oxygen with Hudson mask (PaO<sub>2</sub> 50 mmHg). She was connected to BiPAP, noninvasive ventilator with oronasal mask. Biochemical investigations were unremarkable except for raised liver enzymes (SGOT 132 IU/L and SGPT 122 IU/L. CRP 302 mg/L. She had mild thrombocytopenia (platelet 1.3 lakhs/mm<sup>3</sup>). Dengue, malaria, leptospira, typhoid, hepatitis serology were negative. CMV IgM was positive on day 3 of ICU admission. CT chest revealed bilateral airspace consolidation. Apart from antibiotics, she started on IV gancyclovir. After four days of antiviral therapy she was improved clinically. CRP decreased to 28 mg/L. She was shifted to ward and discharged subsequently. Gancyclovir was continued for 2 weeks.

### 2.3. Case 3

19 year old male patient, with no prior comorbidity, presented with fever chills and rigors, altered consciousness, GCS 6. Mechanical ventilation was instituted. Liver enzymes and serum bilirubin was very high (SGOT 553 IU/L, SGPT 1 772 IU/L, total bilirubin 11.8 mg/dL, conjugated 9.6 mg/dL and unconjugated 2.2 mg/dL) INR 2.2 s. X ray chest revealed bilateral patchy consolidation. Platelets count 1.6 lakhs/mm<sup>3</sup>. Anti HAV and CMV IgM were positive. IV gancyclovir was started. The liver enzymes and the INR decreased eventually but bilirubin remained high and the patient could be extubated on day 5 and shifted out of ICU on day 7. Gancyclovir was given for 8 d.

Three out of initial seven patients died. All of them presented with thrombocytopenia, hepatic dysfunction, breathlessness, fever with chills and rigors. One patient was 17 year old male and the second one was 30 year old female and the third one was 27 year old female patients. In our medical ICU, we don't routinely screen for CMV on admission. As all these young otherwise immunocompetent patients tested negative for dengue, malaria, hepatitis,

they were screened for CMV serology as add-on laboratory investigations. All the three patients succumbed before laboratory results became available (within 2nd day of ICU admission) and antiviral therapy could not be instituted.

## 3. Discussion

CMV infection is among the most common opportunistic infections in immunocompromised patients such as solid organ transplant recipients, patients receiving chemotherapy for cancer or patients with human immunodeficiency virus. Even the critically ill patients considered non-immunocompromised, once admitted to the intensive care units, present features consistent with immunosuppression, such as reactivation of latent viral infections, such as CMV[3]. CMV reactivation occurs in critically sick patients admitted in ICUs and the reported prevalence ranges from 0%–35% in different studies[4]. According to a systematic review by Osawa *et al*, potential risk factors for CMV reactivation included sepsis, requirement of mechanical ventilation, and transfusions. Prolonged mechanical ventilation (21 to 39 d *vs.* 13 to 24 d) and duration of ICU stay (33 to 69 d *vs.* 22 to 48 d) correlated significantly with a higher risk of CMV infection[5]. Mortality rates in patients with CMV infection were higher in some but not all studies[5]. Heininger *et al* assessed the clinical outcomes of nonimmunosuppressed critically ill patients with severe sepsis who had CMV reactivation. They found that intensive care unit stay, hospital stay and mechanical ventilation were all significantly prolonged in patients with CMV reactivation compared with those without reactivation, but the mortality rate was not different between groups[6]. The inclusion of an imbalanced proportion of patients with active cytomegalovirus infection may severely compromise the reliability of outcome results of severe sepsis trials independent of their design. Even randomized trials could have a much higher probability of false-negative rates for a new therapy than designed. Future severe sepsis trials should consider including active cytomegalovirus infection as a prospective covariate[7].

The mechanism(s) underlying the observed association between CMV and adverse clinical outcomes are not completely understood. Because most people are infected with this ubiquitous virus by adulthood, confirming pathogenicity has now become a clinical priority[8]. Cytomegalovirus-mediated immunosuppression leading to an increased risk of secondary infections and CMV-mediated lung injury are the most plausible mechanisms in these clinical settings[9]. In the pathogenesis immunodysfunction and imbalance in immunomodulatory mediators principally tumor necrosis factor and nuclear factor  $\kappa$  B are involved[2]. However, we encountered patients who presented with high grade fever, thrombocytopenia, deranged liver enzymes and progressive shortness of breath requiring mechanical ventilation and had positive CMV serology within day 1 of ICU admission.

Clinical spectrum of CMV disease ranges from a mild mononucleosis-like syndrome to very severe multivisceral involvement<sup>[4]</sup>. All types of visceral involvement *eg.* interstitial pneumonitis, hematological disorders, hepatitis and several others have been observed in critically ill patients admitted in ICUs<sup>[4]</sup>. CMV can virtually affect any organ even in otherwise immunocompetent individuals and thus should be kept in the differential diagnosis of critically ill patients admitted in ICUs with unexplained fever and multi-system involvement.

Diagnosis of CMV infection in such critically ill but immunocompetent cases is another area of controversy and there are no uniform guidelines available. The conventional methods for the diagnosis of CMV infection/disease are viral isolation by viral culture, serology which includes CMV specific antigen and IgM antibody detection, and molecular method for detection of viral DNA from blood and other clinical specimens<sup>[4]</sup>. Viral isolation done by either tissue culture or shell vial culture is the most specific diagnostic test and until now is regarded as the gold standard, but its availability is restricted to reference research laboratories. We limited our diagnostic testing to CMV serology and accept this limitation. Real time PCR assays have substituted other diagnostic methods for CMV reactivation/invasive disease, as it is more sensitive and specific for early detection of CMV disease, is helpful in monitoring the virus load and is a more reliable marker for monitoring the clearance of the virus from blood<sup>[10–13]</sup>.

Another debatable area is issues of treating CMV infection in cases of immunocompetent individuals<sup>[4]</sup>. In both solid organ and haematopoietic stem cell transplant recipients, clearance of viraemia is shown to be helpful in guiding the duration of therapy<sup>[14]</sup>, however very few studies have addressed this issue in critically ill patients with CMV reactivation<sup>[8]</sup>. Out of the seven patients with CMV reactivation at our hospital, the initial three patients who did not receive antiviral treatment died; subsequent three patients who received intravenous ganciclovir in the dose of 5 mg/kg twice a day survived. One patient who started on ganciclovir left the hospital against medical advice. The improvement seen in some patients in a few other studies who received ganciclovir could also be due to the self-limiting nature of CMV disease and therefore can't alone be attributed to antivirals with certainty<sup>[4,15]</sup>.

The current report of seven cases with positive CMV serology within day one of ICU admission adds a few questions to the issue of CMV reactivation in immunocompetent patients. Given the significant impact of critical illness, limited current diagnostic options, the paucity of clinical data supporting a possible pathogenic role for CMV and the increasing dilemma over starting specific antivirals, there is a strong rationale for a large, prospective, randomised controlled trial to resolve such an important issue for our critically ill patients.

## Conflict of interest statement

We declare that we have no conflict of interest.

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