# Reactivation of Cytomegalovirus in Critically Sick Patients

Yonit Wiener-Well MD[1], Amos M. Yinnon MD[1], Pierre Singer MD[3] and Moshe Hersch MD MSc[2]

[1]Infectious Disease Unit and [2]Intensive Care Unit, Shaare Zedek Medical Center, Jerusalem, Israel
Affiliated to Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
[3]Intensive Care Unit, Rabin Medical Center (Beilinson Campus), Petah Tiqva, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Cytomegalovirus is a ubiquitous virus that infects the majority of the human population. Primary infection, which usually occurs during childhood, is generally associated with benign febrile disease and compromises up to 20% of cases of infectious mononucleosis. Like other beta herpesviruses, CMV becomes latent after primary infection, being dormant until some unrelated stimulus precipitates reactivation. CMV is well recognized as a pathogen in immunosuppressed patients, manifesting as sight-threatening retinitis, hepatitis, pneumonitis or enterocolitis in patients with AIDS or in organ transplant recipients. In contrast, CMV reactivation in the immunocompetent host is less documented. Recent literature supports the possible pathogenicity of CMV in critically ill patients, though intensive care physicians rarely raise the possibility of this diagnosis in febrile immunocompetent critically ill patients. We present two critically ill patients with CMV reactivation in order to increase awareness of intensive care physicians to this entity.

## Patient Descriptions

### Patient 1

A 73 year old man was admitted with acute anterior myocardial infarction complicated by heart failure; immediate coronary balloon angioplasty with stent insertion was performed. During the procedure the patient was intubated and placed on ventilatory support. Two days after admission, the patient's temperature rose to 39°C, he remained on mechanical ventilation and there was clinical and radiologic evidence of pulmonary congestion. Fever continued for the next 3 weeks with no recognized origin although an extensive workup was done. Laboratory tests showed leukocytosis (11,300–19,000/mm$^3$) with normal platelets and erythrocyte counts, and fluctuating elevated hepatic transaminases (from normal to 10–20 times the upper limit of normal). Multiple blood, urine and sputum cultures were taken. Extensive serology and immunology tests were performed, which were all negative except for Epstein-Barr virus and CMV, with positive immunoglobulin G and negative IgM antibodies, indicating past infection. Concurrently, the patient received empiric broad-spectrum antibiotics but he remained febrile.

The chest radiogram and computerized tomography scan suggested adult respiratory distress syndrome, and a trial of intravenous corticosteroids was given (from hydrocortisone 100 mg 3 times a day to solumedrol 40 mg twice a day). Four days after initiation of corticosteroids, mild thrombocytopenia (124,000/mm$^3$) appeared. Thrombocytopenia progressed gradually and 10 days later the platelets count reached 44,000/mm$^3$. The peripheral smear and bone marrow biopsy showed only reactive changes, and other common causes for thrombocytopenia were excluded. Leukopenia appeared with a total white cell count of 1,000/mm$^3$, with normal differential and anemia, requiring multiple blood transfusions. At this point, CMV reactivation was suggested as the reason for the continuing fever, pancytopenia and elevated hepatic enzymes. A CMV pp65 antigenemia test was performed and indeed showed a strongly positive result (200 positive cells per 200,000 cells), and real-time polymerase chain reaction for CMV revealed more than 140,000 copies/ml. CMV viruria was not tested. Antiviral therapy was initiated with foscarnet. Ganciclovir was avoided because of preexisting pancytopenia. Several days later, an improvement in all blood count values was observed, and one week after treatment was begun the RT-PCR showed 1250 copies/ml while CMV antigenemia had decreased to 1 infected cell per 200,000 cells. Subsequently, the patient defervesced, blood counts normalized and a repeat CMV antigen test was negative. The patient was weaned and extubated. Several weeks later the patient died due to a recurrent acute cardiac event.

### Patient 2

A 74 year old man was referred for emergency coronary artery bypass grafting and aortic valve replacement. Due to chronic obstructive lung disease, the patient was treated with corticosteroids before and after surgery. The postoperative period was complicated by sigmoid volvulus, dislocation of a percutaneous gastrostomy and critical care neuromyopathy. He was febrile from the second postoperative day and suffered three episodes of bacteremia and respiratory infections. Laboratory tests showed leukocytosis and mildly elevated liver enzymes. Serology for CMV was tested and showed positive IgG and negative IgM antibodies.

CMV = cytomegalovirus

Ig = immunoglobulin

RT-PCR = real-time polymerase chain reaction

Fever continued despite appropriate antibiotic therapy and with no further obvious bacterial or fungal infection. Five weeks after surgery CMV antigenemia was tested and found to be positive with two infected neutrophils among 200,000 cells. CMV viruria was not tested. Although there was no bone marrow involvement and hepatic abnormalities were considered to be fluconazole-related, ganciclovir treatment was initiated because of the persistent fever. The patient defervesced within days. A CMV antigenemia test was again obtained after one week of antiviral therapy and had become negative. The patient was discharged to a rehabilitation unit.

## Comment

CMV has been recognized for many years as an important pathogen in immunosuppressed transplant or AIDS patients and has received little attention as a potential pathogen in the non-immunosuppressed critically ill. The prevalence of this phenomenon is not clear. Reactivation of CMV was found in 15% of surgical intensive care unit patients when respiratory cultures were tested, and 5.8% of patients had CMV viremia by viral cultures [1]. In other studies the prevalence of CMV reactivation in ICU or septic patients was tested by advanced virologic methods like PCR or pp65 antigenemia and found to be as high as 17–35% [2-4]. Patients with active CMV infection had a higher mortality rate than those without CMV infection (55% vs. 36%, respectively), longer duration of intensive care treatment (30 vs. 23 days, respectively) [3,4] and longer periods of ventilator dependence (33 vs. 13 days) [1,4]. Signs preceding or following positive viral cultures included persistent fever (95%), lymphopenia (100%), thrombocytopenia (60%) [5] and hepatic dysfunction (70%) [1]. Several risk factors found to be independent predictors of CMV reactivation in ICU patients include previous CMV exposure (IgG+), female gender, presence of a bacterial infection/sepsis, and steroid exposure [1,4]. Renal failure was also associated with CMV reactivation [4].

We describe two ICU patients with CMV reactivation, both of whom had a prolonged and complicated course with unexplained fever and both had been given corticosteroids. Therefore, we may consider critically ill patients with a protracted hospitalization as moderately immunocompromised even if they do not receive corticosteroids and/or chemotherapy. CMV reactivation should be included in the differential diagnosis of critically ill patients with unexplained fever, especially if cytopenia is present and/or liver enzyme tests are elevated. Optimal tests for diagnosing reactivation are determination of antigenemia and PCR.

Three antiviral drugs that act to inhibit the viral DNA polymerase have proven effective in the treatment of CMV disease – ganciclovir, foscarnet and cidofovir. These drugs have been used to treat CMV disease in AIDS and in other immunocompromised patients. Although there are many reports of immonocompetent patients treated with antiviral drugs for severe CMV infections, no recommendation can be made regarding treatment in the special group of patients described here.

ICU = intensive care unit

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**Correspondence:** Dr. Y. Wiener-Well, Infectious Disease Unit, Shaare Zedek Medical Center, P.O. Box 3235, Jerusalem 91301, Israel.

Phone: (972-2) 655-5076

Fax: (972-2) 666-6840

email yonitw@zahav.net.il