



Case study

Cytomegalovirus infection in immunocompetent adults: Is observation still the best strategy?

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ABSTRACT

Cytomegalovirus (CMV) infection in immunocompetent patients generally resolves with few sequelae. However, it can cause severe and relapsing symptoms that can last for several weeks. Due to the self-limiting nature of CMV disease in immunocompetent individuals, criteria for specific antiviral therapy in this cohort are not well established. Additionally the adverse effect profile of currently available anti-CMV therapy limits its use in specific patient populations. We describe 3 immunocompetent adults who developed symptomatic CMV infection and were ill for several weeks. All patients had positive CMV viral assays and ultimately received anti-CMV therapy with significant improvement in symptoms within a few days of starting therapy. Choosing appropriate candidates for anti-CMV therapy, among immunocompetent individuals, requires further research.

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Introduction

Cytomegalovirus (CMV) infection is common among patients of all age groups, but it has traditionally been considered as a problem in neonatal and immunosuppressed patients. Cytomegalovirus infection in immunocompetent patients is usually subclinical, although the CMV mononucleosis like syndrome that can take many weeks to recover has been well described [1]. Severe CMV infection in immunocompetent patients has been described and may manifest with profound constitutional symptoms and multiple organ involvement.

Prior to the availability of polymerase chain reaction (PCR) assay, the diagnosis of CMV disease was based on cell culture, antigen detection assay, or on development of antibodies [2]. Polymerase chain reaction technology now allows physicians to detect circulating pathogens quickly and with great accuracy. With this new technology, individuals without the obvious severe manifestations of CMV disease are being more commonly reported and the spectrum of CMV disease needs to be reconsidered.

Symptomatic CMV infection in immunocompetent patients is usually considered to have a benign, self-limiting course and hence observation is almost universally recommended. One reason for

this recommendation may be related to the lack of safe and effective oral treatment option in CMV disease in the past. Oral valganciclovir has been shown to be effective in CMV disease in immunosuppressed patients [3]. However the appropriateness of treatment in immunocompetent but symptomatic patients who have CMV disease has yet to be clarified.

We report three cases of symptomatic CMV disease in immunocompetent adults. These individuals received anti-CMV therapy and demonstrated prompt improvement in their symptoms

Case 1

A 52-year old male with a history of hyperlipidemia, hypertension and remote history of pericarditis presented with two weeks of intermittent fever, photophobia, chills, and diaphoresis and progressively worsening neck stiffness. On admission, he also complained of intermittent non-radiating chest pain and lower quadrant abdominal cramps without constipation or diarrhea. The patient had no recent travel or sick contacts.

On admission, his temperature was 103.1°F. Computed tomography (CT) angiogram of the chest was negative for pulmonary embolism or infiltrates and CT of the head was unremarkable. The white blood count was $6.8 \times 10^3/\mu\text{L}$ (Normal $4\text{--}12 \times 10^3/\mu\text{L}$) with 56.6% Lymphocytes (Normal 14–41%) and the peripheral

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blood smear showed atypical lymphocytes. The aspartate aminotransferase (AST) was 138 U/l (Normal 10–40 U/L) and alanine aminotransferase (ALT) was 112 U/L (Normal 3–45U/L) with a negative viral hepatitis panel. The C-reactive protein was 3.8 mg/dL (Normal 0.0–1.0 mg/dL) and sedimentation rate was 10 mm/h (Normal 0–20 mm/h). An abdominal ultrasound was unremarkable except for mild splenomegaly. Influenza A and B PCRs, respiratory syncytial virus PCR, adenovirus, metapneumovirus, and parainfluenza viruses 1, 2 and 3 PCRs were all negative. A mononucleosis screen and Epstein-Barr virus viral capsid antigen (EBV VCA) IgM were negative while EBV VCA IgG and Anti-EBV nuclear antigen were positive. Rocky Mountain Spotted Fever Group IgG and IgM were negative. Additional negative tests included human immunodeficiency virus, syphilis, fungal precipitins and fungal complement fixation antibodies. Cerebrospinal fluid (CSF) revealed one white blood cell, glucose 64 mg/dL, and protein 69 mg/dL with negative bacterial culture. CSF herpes simplex virus (HSV) PCR was negative. Urine and blood cultures were negative.

The patient was initially started empirically on broad spectrum antimicrobials for possible meningitis. Antibacterials were discontinued after the lumbar puncture results were obtained. Additionally patient was started on acyclovir which was discontinued after the CSF HSV PCR result was negative. Cytomegalovirus antibodies were measured using solid-phase chemiluminescent immunometric assay and CMV IgG was 7.5 (normal < 0.9) and the IgM was 3.8 (normal < 0.9). CMV serum DNA quantitative measured at 825 IU/mL. The patient initially showed improvement with symptomatic therapy and acyclovir. However about 48hrs after stopping acyclovir, he started spiking fever up to 103.1°F associated with rigors and diaphoresis. CMV DNA was re-measured and was 4530 IU/mL. He was started on IV ganciclovir with improvement and resolution of fevers within 48 h. Patient was discharged on oral valganciclovir. On follow-up a week following discharge, his CMV DNA was undetectable and his liver enzymes had returned to the normal range.

Case 2

A 35-year-old male in excellent health presented with a three-week history of back pain, fever, chills, and worsening headache. On presentation, his temperature was 103°F. Physical examination was only remarkable for tenderness to palpation of the lower back. His white blood cell count was $7.2 \times 10^3 /\mu\text{L}$ with a normal differential. C-reactive protein was 2.3 mg/dL and sedimentation rate was normal. ALT was 99 U/L and AST was 58 U/L. The MRI of the lumbar spine was unremarkable.

The patient reported contact with a family member who was diagnosed with methicillin-resistant *Staphylococcus aureus* pneumonia about one month prior to admission. After admission patient was empirically started on IV vancomycin but he continued to be febrile. Blood cultures and urine cultures remained negative. A transthoracic echocardiogram was normal. Hepatitis and HIV tests were negative, rheumatoid factor was undetectable and ANA was negative. Other negative tests included for cryptococcal antigen, fungal precipitin, histoplasma urine antigen, and tuberculosis Quantiferon Gold. Epstein Barr virus antibodies revealed a positive EBV VCA IgG and negative EBV VCA IgM. CMV IgM was positive at 4.3 but CMV IgG was negative at 0.5.

He responded to symptomatic treatment and was stable to be discharged from hospital with close follow-up. However patient started to spike fever again at home with temperature to 102°F. Repeat labs about 2 weeks later showed increase in CMV IgM to 6.4 and CMV IgG to 6.3. CMV PCR was 1980 IU/mL. Liver enzymes remained elevated with ALT of 93 U/L and AST of 52 U/L. He was started on oral valganciclovir and responded within 48 h of initiation of antiviral therapy.

Case 3

A 72-year-old male with a history of gastroesophageal reflux disease and benign prostatic hypertrophy presented to the Emergency Department complaining of two week history of low grade fever (up to 101°F) at night, mild night sweats, generalized weakness, anorexia and weight loss of 3 pounds. He denied any recent travel or ill contacts.

His temperature on admission was 99.1°F and initial physical examination was unremarkable. His white count was $14.7 \times 10^3 /\mu\text{L}$ with 86% lymphocytes. Atypical lymphocytes were not noted on peripheral blood smear. ALT was 286 U/l and AST was 156 U/l. Viral hepatitis panel was negative. A CT scan of abdomen and pelvis showed trace pelvic ascites and mild splenomegaly. The patient was admitted and given supportive treatment. His maximum recorded temperature was 101.5°F. Patient responded to symptomatic treatment and was stable to be discharged from hospital after 3 days with close follow-up. CMV IgM and IgG antibodies were not performed, however CMV PCR was 15,034 IU/mL. Patient started spiking low grade fever at home associated with malaise, fatigue and generalized weakness. He was evaluated at follow-up and started on a 10 day course of oral valganciclovir. After five days of therapy, patient reported complete resolution of symptoms.

Discussion

Cytomegalovirus causes a wide spectrum of disease in healthy and immunosuppressed hosts. Initial descriptions of CMV disease referred to patients that were most severely afflicted. This included neonates and persons with immunosuppression. As the natural history of CMV infection was clarified it was noted that the majority of healthy individuals who acquire CMV infection are able to clear the infection within a short length of time with no adverse sequelae. However, symptoms can be prolonged with fever lasting for more than 3 weeks in immunocompetent patients with primary CMV infection [4]. Additionally severe CMV infection can present with several life-threatening complications [5]. In a review of 290 immunocompetent patients with severe CMV infection, gastrointestinal tract (primarily colitis) was most commonly affected. Central nervous system (CNS) (meningitis, encephalitis, transverse myelitis) and hematological abnormalities were also noted along with involvement of several other organ systems [5]. Another study from United Kingdom identified 124 immunocompetent patients with CMV infection with symptoms lasting for a mean duration of 7.8 weeks without treatment during the 2.5 year study period [6]. However 12% of patients had a relapsing illness with symptoms lasting up to 32 weeks. An earlier report of 34 immunocompetent patients with severe CMV infection noted a high mortality rate particularly among patients with multiple organ involvement [7].

Earlier studies used CMV culture or antibody seropositivity as the marker for CMV infection. With the advent of PCR technology, CMV viremia in symptomatic patients needs to be considered in the context of CMV infection. Severe and complicated CMV infection in immunocompetent patients has a significant health burden on this population and may have a higher prevalence than previously assumed [5,6].

The knowledge of management of CMV infection has expanded greatly in the last 20 years, particularly in the immunocompromised population. However few studies have evaluated the use of these antiviral agents for the treatment of severe CMV disease in immunocompetent patients. A review of severe CMV infection in immunocompetent patients published in 1997 reported use of antiviral drugs in only six of 24 patients with multiple organ involvement or non-CNS disease [7]. Five of the 6 patients who received anti-CMV therapy survived, while majority (14/18, 78%) of

patients who did not receive therapy died. There are several published case reports and reviews that highlight the significant mortality and morbidity associated with untreated CMV infection in immunocompetent patients with rapid clinical improvement after anti-CMV therapy [7–12].

Side effects remain the greatest concern in the utilization of anti CMV therapy. Ganciclovir and foscarnet may cause myelosuppression, renal toxicity and potential teratogenicity among other side effects. The availability of oral valganciclovir has enabled rapid transition from intravenous to oral therapy in suitable CMV infected patients to continue management in the out-patient setting.

Oral valganciclovir have been shown to be effective in CMV infection and disease in immunocompromised patients and generally supersedes management with intravenous therapy [3]. Newer and presumably safer pharmacologic agents for CMV disease are in late stage development [13]. These developments could make physicians reconsider possible therapy for immunocompetent patients especially those with severe symptoms or relapsing illness.

We report 3 previously immunocompetent adults who became ill with a similar pattern of fever, malaise and hepatitis. CMV PCR assay was positive in all patients and they improved within a few days after starting therapy with valganciclovir. The reason for this unique CMV process in these individuals remains unclear. However, improvement in the health outcomes of these patients was evident after starting anti-CMV therapy. Randomized controlled trials are required to assess the need for anti-CMV therapy in immunocompetent patients with symptomatic CMV infections.

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