

DISSEMINATED CYTOMEGALOVIRUS INFECTION IN AN IMMUNOCOMPETENT ADOLESCENT: A CASE REPORT

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Abstract

CMV (Cytomegalovirus) is ubiquitous. In humans most CMV infections are asymptomatic. After primary infections, virus remains latent in most body cells and can be isolated from a variety of tissues under non pathological conditions. Mostly CMV dissemination was considered a feature of immunosuppressed state however serious life threatening disseminated infections are also manifested in immunocompetent patients as is highlighted in this case report. Literature review showed that serious infections with CMV in immunocompetent individuals are not as rare as were previously thought and can be as devastating as is depicted in this scenario leading to sudden bilateral hearing and visual loss. In our study immunosuppression was ruled out by absence of Diabetes Mellitus, chronic kidney disease, immunodeficiency disorders (congenital and acquired), hematological and non-haematological malignancies, treatment with steroids or immunomodulator / immunosuppressant agents and organ transplantation.

Key Words: Disseminated CMV Infection, Immunocompetent individual, Serial Antibody Serologies, Diagnostic and Therapeutic limitations.

Introduction

Primary CMV infection with mononucleosis like illness is a well known entity in immunocompetent individuals⁴. Congenital forms of infection are also well recognized.⁴ Morbidity and mortality in immunocompetent patients is also extensively reported in biomedical literature.⁵

Case Report

A 15 year old male student resident of Gujranwala (city of Pakistan) belonging to poor socioeconomic status presented via Emergency with presenting complaint of Fever and Headache for 15 Days and decreased Hearing for 02 Days.

Patient was in Usual state of health 15 days back when after having a bath in tube – well he developed high grade intermittent fever, sudden in onset, not associated with rigor and chills, relieved by medication (paracetamol) and associated with headache which was effecting whole circumference of head, moderate in severity, continuous, aggravated by fever not relieved by analgesics, associated with vertigo and neck pain but not associated with aura, hallucinations, altered sensorium or insomnia. No history of fits or black outs. Patient also complained of 1 episode of projectile vomiting which was not related to meals. Vomitus was not foul smelling, not containing any blood or clots, light yellow in color. History of (H/O) anorexia, fatigue, myalgia and arthralgia. There was no H/O watery eyes, rhinorrhea, cough, sputum, diarrhea, body

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rash and burning micturition.

There was complaint of (C/O) bilateral painless decreased hearing which was sudden in onset and progressive. Patient then developed sudden painless loss of vision first in left eye and then in right eye within 2 days with just perception of light intact.

C/O pain in abdomen initially localized to right hypochondrium which later subsided and patient then developed generalized abdominal pain with distention along with generalized body edema over a period of 1 month post admission.

Past medical and surgical history was insignificant. No H/O previous transfusion of blood or blood products. No H/O any sick contact or Tuberculosis contact, allergies, Hypertension, Diabetes Mellitus and Hikmat medication. H/O normal vaginal delivery, full term without any antenatal and post natal complications. Vaccination status was not well documented. Developmental milestones were achieved on time. Parents and all siblings of patient alive and healthy. School performance was satisfactory. Sleep wake cycle was normal and social history was non contributory.

Previously patient took various medications for fever including antibiotics (Ciprofloxacin) and Non Steroidal Anti Inflammatory Drugs but no improvement in symptoms which progressively worsened.

A sick looking young boy of average built and height, well oriented in time place and person with Pulse of 103 / min (regular), Blood Pressure of 100 / 60 mm-Hg (both arms) Temperature of 100°F and Respiratory Rate of 24/min. Patient had moderate pallor, but no, clubbing, cyanosis, koilonychia, leuconychia, and stigmata of chronic liver disease. Jugular venous pressure was in normal range. Thyroid and lymph nodes were not palpable. Glasgow coma scale was 15/15. Central nervous system showed grossly intact higher mental functions. Bilateral Babinski sign was equivocal. On Eye examination there was only perception of light intact bilaterally. Pupils were dilated. Fundoscopy showed bilateral clear media with significant disc swelling (+4.0D) and peri-papillary hemorrhages. On Ear examination bilateral decreased hearing was documented while rest of cranial nerves were intact. No signs of Meningeal Irritation. Power, tone, bulk and reflexes of all 4 limbs were normal. No cerebellar signs were present and gait was normal. Sensory system examination showed paraesthesia and dysaesthesia.

Average oral hygiene, abdomen soft, non-tender, umbilicus central inverted. No evidence of bruising, stria, scar marks, visible pulsations or dilated veins.

Spleen enlarged, tender and palpable two fingers below costal margin initially than became non-palpable after 2 weeks post admission. Liver tender and palpable three finger below costal margin initially than became non-palpable after almost 2 weeks post admission. Examination of chest (cardiovascular and respiratory) was unremarkable. Moderate swelling of face and feet with mild yellow discoloration of eyes later developed after almost 21 days post admission. Musculoskeletal examination was normal.

Complete blood picture showed pancytopenia, normocytic normochromic anemia with reticulocyte count of 1.4% while differential leucocyte count showed lymphocytic predominance. Blood films were negative for malarial parasite. Renal and liver functions were in normal range initially and then became deranged after 20 days post admission with decreased serum total proteins (albumin) while serum electrolytes and blood glucose levels remained in normal range throughout course of admission. On urine complete examination, there was sub-nephrotic range proteinuria with no growth on culture.

Cerebrospinal fluid (CSF) examination showed clear, colorless fluid with White blood cell count of 10/ul (90% lymphocytes & 10% neutrophils), Red blood cell count of 200/ul while Protein was 55.9 mg/dl, LDH (lactate dehydrogenase) was 74U/L and glucose was 49 mg/dl with no (AFB) Acid Fast Bacilli seen. Repeat CSF analysis after 2 weeks showed almost same picture.

Ultrasound abdomen showed hepatosplenomegaly (liver span was 17 cm and spleen size was 16 cm) initially but later liver and spleen regressed and became normal in size while gut wall thickening (oedema) and ascites developed. Ascitic fluid showed no AFB with decreased total fluid protein and increased LDH.

Bone marrow aspiration done 4 weeks post admission showed cellular elements with active erythropoiesis and leucopoiesis. There was predominance of lymphocytes with all stages of maturation seen. Bone marrow trephine biopsy showed normal bony trabeculae with cellular marrow. Erythropoiesis and leucopoiesis moderately active. Megakaryocytes present. Cellularity was around 70 to 75%. Blood and bone marrow culture showed no growth after 7 days of incubation.

On Magnetic resonance imaging (MRI) of brain, both optic nerves appeared swollen with signals of edema and possibility of optic neuritis. Rest of MRI was unremarkable. B – scan (brightness scan) of both eyes showed swollen ONH (optic nerve head) and swollen retro-bulbar optic nerves.

constituted haematological disorders caused by CMV.^{14,15} Less frequent manifestations comprised vascular thrombosis, ocular involvement, and pulmonary disease.¹⁶ Thrombosis of vascular system is attributable to intrinsic pro-coagulant properties of CMV.¹⁷ Eye infection manifested as uveitis, retinitis, corneal endothelitis, or papillitis.^{18,19} Chief symptoms and signs of presentation included loss or blurring of vision and redness of the affected eyes. PCR of aqueous humor or of the vitreous is indicated for diagnosing eye involvement.¹⁹

Impaired anti-CMV IgM response can occur in patients with asplenia (functional and anatomical). False positive results for CMV serology can be attributable to Measles, VZV (varicella zoster virus) and HSV (herpes simplex virus) due to antigenic cross reactivity within herpes virus family. EBV (Epstein barr virus) infection ruled out by negative monospot test. Seroconversion from negative to positive usually requires 3 to 4 weeks.

Perinatal disease in human embryo (host with immature immunologic responses) caused by CMV infection is characterized by jaundice, hepatosplenomegaly, thrombocytopenia, purpura, microcephaly, periventricular CNS calcifications, mental retardation and motor disabilities and blindness due to optic nerve atrophy (Inclusion disease). Hearing loss develops in more than half of infants symptomatic at birth but most infected neonates are asymptomatic. Neurologic deficit may occur later in life comprising of hearing loss (in 15%) and mental retardation (in 10 to 20%).⁴ Perinatal infections acquired through modes of transmission like breast feeding and blood products typically show a benign clinical course.²⁰ The plausible explanation precludes that our patient was not a late presentation of congenital infection asymptomatic at birth. Studies are in progress to conduct PCR assay for screening in newborns.^{21,22}

CMV meningoencephalitis can be observed in two forms in immunocompetent patients.^{23,24} Regarding paroxysmal type, which is characterized by headache, focal neurological symptoms or signs, alternating side of neurological deficits and symptoms lasting from minutes to hours. In monophasic type presentation is more frequent occurrence of seizures altered sensorium and symptoms lasting for days.^{25,26} Our patient somewhat exhibited paroxysmal symptomatology. Suggested hypothesis for suppression of haematopoiesis is direct inhibition by the virus of progenitor haematopoietic cell growth and stromal cell dysfunction as well as mediated by effects of inhibitory cytokines

released by CMV infected leukocytes.⁵ This accounts for probable explanation of pancytopenia in our study patient.

Over 95% of immunocompetent patients with acute infectious mononucleosis like illness recover without specific antiviral therapy and treatment is mainly symptomatic. Combinations of Ganciclovir and Foscarnet are considered effective in treating clinical resistant CMV retinitis but this efficacy is established only in immunocompromised individuals while toxicity remains the limiting factor for administration of these drugs. Second-line agents useful in resistant CMV infections include Leflunomide, Sirolimus – based therapy, and Artesunate. Adaptive immunotherapy is also under study.⁴ In pregnant women (immunosuppressed state) with primary CMV infections, passive immunization with hyper immune globulin is thought to be effective in both treatment and prevention of fetal infection. Controlled clinical trials are lacking and are deemed necessarily.²⁷ No US FDA approved regimen for therapy indicated (meningoencephalitis) in immunocompetent patients. Therapeutic options are debatable. Generally mortality rate of CMV in immunocompromised patients approaches up to 60 – 80%.⁴ Higher mortality in elderly patients (> 55 years – old) and in patients with diseases affecting immune response mechanisms.⁵ The possibility which need to be addressed in our patient was a re-activation versus re-infection.

Conclusion

The purpose of this case study is to highlight the incidence of disseminated CMV infection in immunocompetent individuals and the need to carry out randomized control trials for establishing efficacy of different antiviral drugs besides their toxic side effects and setting criterion to treat immunocompetent patient. Guidelines need to be established regarding drug regimens and protocols be set for establishing diagnosis and treating resistant viral strains of CMV. Prospective studies need to be carried out for a more conclusive answer to the need for development of vaccine for prophylaxis in different age groups.

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