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(CASE REPORT)

PRIMARY CYTOMEGALOVIRUS INFECTION IN A TODDLER

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ABSTRACT

Cytomegalovirus is a human herpesvirus, which is very spread in nature, its global seroprevalence varies from 40-100%. CMV is transmitted from person to person via close contact with an individual who is excreting the virus, through infected bodily fluids such as saliva, urine, blood, breast milk, semen, and tears, particularly during childbirth. CMV have a broad cellular tropism, allowing it to infect epithelial cells, endothelial cells, fibroblasts, macrophages, and neural stem cells. After the primary infection, the host immune response suppresses lytic replication, but fails to eradicate the virus, establishing so permanent latency. We report a toddler who presents with primary Cytomegalovirus infection. His symptoms and signs included prolonged fever, fatigue and enlarged liver and spleen. Laboratory was remarkable for lymphocytosis and abnormal liver function. Treatment was supportive followed by complete recovery. Humans may become infected with CMV at any age. Although primary infection is usually asymptomatic, it may present clinically as a mononucleosis- like illness.

Keywords: Cytomegalovirus; Primary; Infection; Toddler; Mononucleosis.

1 INTRODUCTION

Cytomegalovirus (CMV) is a member of the family Herpesviridae, also known as Human Herpesvirus 5 (HHV-5). CMV is the largest, 220 nm in diameter, and the most complex herpesvirus, with a 235,000 double-stranded DNA genome which encodes over 200 viral proteins. It is ubiquitous in nature and humans can be infected at any age. The global seroprevalence of CMV varies from 40-100% [1].

Cytomegalovirus was first observed in 1881, by German pathologist Hugo Ribbert, when he noticed enlarged cells with enlarged nuclei present in the cells of an infant [2]. Many years later, in 1956, Thomas Huckle Weller isolated the virus, known afterwards as "cytomegalovirus" [3]. In 1990, the first draft of human cytomegalovirus genome was published, which was the biggest contiguous genome sequenced at that time [4, 5].

CMV is transmitted from person to person via close contact with an individual who is excreting the virus, through infected bodily fluids such as saliva, urine, blood, breast milk, semen, and tears, particularly during childbirth. Intermittent viral shedding occurs frequently in infants, children, and pregnant women. It can be spread through the placenta, blood transfusions, organ transplantation, and breast milk feeding [6, 7].

CMV have a broad cellular tropism, allowing it to infect epithelial cells, endothelial cells, fibroblasts, macrophages, and neural stem cells. The virus uses a pH-independent fusion pathway directly at the plasma membrane in the fibroblasts, while in the epithelial and endothelial cells it enters through a pH-dependent endocytic pathway. Once inside the host cell, the virus initiates a cascade of lytic replication by hijacking host cellular machinery, suppressing apoptosis, and initiating viral DNA synthesis. This process cause the cell to swell dramatically, from which has derived the name "*cytomegaly*". After the primary infection, the host immune response suppresses lytic replication, but fails to eradicate the virus, establishing so permanent latency[8]. CMV infects a wide range of human organs and tissues. CMV is the most frequent congenital viral infection, approximately 20% of the infants symptomatic at birth, suffer from permanent sequelae, commonly sensorineural hearing loss [9].

This report aims to present a primary CMV infection in a previous healthy toddler.

2 CASE REPORT

An otherwise healthy 20-months old toddler was admitted with a two-week history of persistent fever, anorexia and fatigue. On physical examination, the child appeared moderately ill, he was active and vivid despite persistent fever at moderate degree 38,5-39°C and reported anorexia and fatigue reported by his parents.The conjunctiva and mucous membranes were normal, no pharyngeal injection or cervical lymphadenopathy were observed. Respiratory and cardio-vascular systems displayed no abnormalities. No edema on the extremities or rash on the skin were founded. The abdominal examination was remarkable for the enlargement of liver and spleen, which were palpable 4-5cm under the costal margin.

The child attended child-care facilities. He was the only child. Both parents were healthy. The child was fully vaccinated. The family did not keep domestic animals at home and consumed safe foods.

Laboratory investigations on admission revealed; lymphocytosis, abnormal liver function (elevated hepatic enzymes), decrease of CD4+ (helper T cells), increase of CD8+ (cytotoxic T cells) (Table 1).

Table 1: Laboratory values

WBC	**17,300 cells/ml**	**5,000-12,000 cells/ml**
Neutrophyls	2,100 cells/ml	650-4,800 cells/ml
Lymphocytes	13,600 cells/ml	2,300-9,120 cells/ml
RBC	4,360,000 cells/mL	3,800,000-5,000,000 cells/ml
hemoglobin	11.0 g/dL	9.7-12 g/dL
PLT	197,000 cells/ml	150,000-400,000 cells/ml
ALT	130 U/L	9-25 U/L
AST	97 U/L	21-44 U/L
LDH	640 U/L	192-321 U/L
C reactive protein	0.23 mg/dL	< 0.5 mg/dL
Ferritin	113.94 ng/mL	5.3-99.9 ng/mL
Fibrinogen	179 mg/dL	160-390 mg/dL
T helper CD4＋	18%	31.0%-54.0%
T cytotoxic CD8＋	54%	16.0%-38.0%

Abdominal ultrasonography demonstrated enlarged liver (10.5 cm in longitudinal diameter), and enlarged spleen (11.5 cm in longitudinal diameter) with normal echo-structure.

Microbial cultures obtained from throat, blood, urine, and stool specimens yielded no bacterial growth. Serological evaluations for Leishmania visceral, Brucellosis, Rickettsiosis, Salmonellosis, Human Immunodeficiency Virus (HIV), Epstein-Barr virus (EBV) were negative. Serology for CMV resulted positive both IgM and IgG, CMV IgM 20.70 AU/mL (<0.84), CMV IgG 26.1 AU/mL (<5.9). Diagnosis of primary CMV infection was done based on positive results of polymerase chain reaction (PCR) in urine smear.

The treatment was supportive, fever gradually abated, the total days with fever was estimated 20 days. In the follow-up schedule after 3-weeks the spleen and liver were withdrawn into normal size, and the child was playful and energetic again. Serology conversion of IgM occurred at week six, whereas IgG remained in high titer. (Table 2)

Table 2: Serology titer of CMV immunoglobulins.

	Week 0	**Week 3**	**Week 6**
IgM	20.70 AU/mL	3.72 AU/mL	0.64 AU/mL
IgG	26.1 AU/mL	90.5 AU/mL	178.5 AU/mL

3 DISCUSSION

The reported child presents in his second year of life and frequents day-care facilities which classify him a risk group in contacting CMV. Children in day-care institutions are in close contact and share toys or other items such as bottles, and utensils which are a way of exchanging saliva. Acquisition of CMV may occur at any time during life [1]. Most adults eventually become infected with CMV, the epidemiology of this infection is complex, and the age at which an individual acquires CMV greatly depends on geographic location, socioeconomic status, cultural factors, and child-care practices. In early childhood, CMV can be acquired via saliva in family or day care settings. Especially in developing countries, most children acquire CMV infection early in life.

Due to its potential to evade the immune system, CMV shows a multi-systemic distribution, affecting various tissues and organs, including the lungs, liver, retina, muscles, brain, and gastrointestinal tract. Thus CMV is not a single-disease virus. Its impact ranges from mild illness in healthy people to severe, life-threatening conditions in unborn children, transplant patients, and through its potential links to chronic diseases like cancer and vascular illness. In healthy children, primary CMV infection often presents as a self-limiting febrile illness resembling Epstein-Barr virus (EBV) mononucleosis [10]. However CMV- Mononucleosis differs by less frequently presenting with pharyngitis, adenopathy, and splenomegaly. Symptoms include fever, malaise, myalgia, headache, and fatigue. Some patients experience splenomegaly, hepatomegaly, adenopathy, and rash [11]. In our case, the child presented with prolonged fever (approximately three weeks) accompanied with fatigue, which is much longer than any other common viral infection of childhood. Pharyngitis and lymphadenopathy which are dominant signs in EBV-mononucleosis were absent. The great enlargement of spleen and liver prompt an accurate differential diagnosis with other infectious diseases such as Leishmanial visceral, Brucellosis, Rickettsiosis, Salmonellosis, HIV, EBV, and noninfectious diseases such as systemic inflammatory diseases and malignant hematologic diseases.

Laboratory tests in our case revealed lymphocytosis, abnormal liver function (elevated hepatic enzymes), decrease of CD4+ (helper T cells), increase of CD8+ (cytotoxic T cells). The generation of cytotoxic T-cell (CTL) responses against CMV may be a more important host immune response in control of infection. In general, these CTLs involve major histocompatibility complex (MHC) class I restricted $CD8^+$ responses [12, 13]. Diagnosis of CMV infection was confirmed by detection of IgM and IgG specific antibodies on blood tests and detection of antigen by polymerase chain reaction (PCR) in urine smear. Serology results dismissed other infectious etiologies. The absence of increased inflammatory markers did not support the diagnosis of systemic inflammatory diseases. Immunophenotype of peripheral blood smear detected only decrease of CD4+ and increase of CD8+, and no other abnormal cell lineage, so malignant hematologic diseases were dismissed too.

After the primary infection, a complex host response tries to limit CMV replication. Multiple defense systems sense the foreign presence of the virus very early after contact. The specific pathogen-associated molecular patterns include virion glycoproteins and the viral genome itself [8, 14]. Among the earliest responses are production of interferon and cytokines that help establish an antiviral state [15]. Both the innate and the adaptive immune systems play a crucial role in virus clearance. Depletion of NK cells in mice results in higher titers of murine CMV in tissues and increased mortality [16]. In humans, NK cell deficiency has been linked to severe CMV disease. Adaptive T cell responses are critical for keeping the virus inactive, so restoration of CD8+ and CD4+ T cells is a strong correlate of control of the virus after transplant. Moreover, adoptive transfer of CMV-specific T cells protects against clinical reactivation [12]. In seropositive individuals, a strikingly high fraction (10% or more) of circulating T lymphocytes target CMV, it tends to increase with age, which supports the hypothesis that CMV contributes to immune system exhaustion and dysfunction

associated with aging [17]. Antibodies in CMV-infected individuals have been useful for establishing serostatus, only antibodies to gB or gH neutralize the virus [18].

Despite the vigorous host system defense, CMV has evolved multiple viral evasion strategies. Proteins delivered with infecting virion block intrinsic cellular defenses, including induction of apoptosis, production of interferon and interferon-stimulated genes, and shutoff of protein synthesis [19]. CMV also interferes with the cellular immune responses [20. 21]. At least seven genes are able to modulate, and in many cases inhibit, NK cell function. CMV encodes chemokines, chemokine receptors, and cytokines that likely participate in immune evasion [22].

4 CONCLUSION

Our child presented in his second year of life with primary cytomegalovirus infection, which caused a mononucleosis-like syndrome accompanied by fever, fatigue and hepato-splenomegaly.

Humans may become infected with CMV at any age. Although primary infection is usually asymptomatic, it may present clinically as a mononucleosis- like illness.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed Consent was taken from the parents of the hospitalized child, reported in the study, for using the data of the medical records, providing anonymity.

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