

RESEARCH NOTE

Cytomegalovirus mononucleosis as a cause of prolonged fever and prominent weight loss in immunocompetent adults

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ABSTRACT

Four immunocompetent adults presented with protracted fever lasting >6 weeks and severe weight loss, associated with primary cytomegalovirus (CMV) infection. Each patient had spleen enlargement, lymphocytosis and hypertriglyceridaemia, but recovered spontaneously. A further 20 immunocompetent patients with primary CMV infection were also reviewed, and all presented the usual clinical picture of CMV mononucleosis. It was concluded that CMV mononucleosis should be considered in the differential diagnosis in patients with prolonged fever and weight loss if lymphocytosis is present.

Keywords Cytomegalovirus, diagnosis, lymphocytosis

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Symptomatic primary cytomegalovirus (CMV) infection in immunocompetent adults usually presents as a mild self-limited mononucleosis [1]. In some cases, fever is prolonged and may be considered in the differential diagnosis of fever of

unknown origin [2]. However, to our knowledge, CMV infection has not been described as a cause of prominent weight loss in immunocompetent adults. In this study, the medical charts of all immunocompetent adults diagnosed with primary CMV infection in our unit in the period 1997–2002 were reviewed. Patients were considered to have CMV mononucleosis if they presented with a fever plus absolute ($> 5 \times 10^9/\text{mm}^3$) or relative ($> 50\%$) lymphocytosis with atypical lymphocytes, and (a) isolation of CMV from blood or (b) isolation of CMV from urine, plus one of the following: CMV-IgM seroconversion [3]; or positive CMV-IgM in two serum samples taken 2 weeks apart with a four-fold increment in CMV-IgG titres [4]. Other causes of mononucleosis (e.g., Epstein-Barr virus (EBV), *Toxoplasma*, HIV infection, and others if clinically indicated) were always excluded [5]. Exclusion criteria were: age of <14 years, HIV infection, renal failure, cirrhosis, neoplasia, transplantation, use of steroids or other immunosuppressive drugs, and blood product transfusion or heart surgery in the previous 6 months. In total, 24 patients were diagnosed with CMV mononucleosis. Among these, four patients presented with a more protracted clinical course, including fever lasting ≥ 6 weeks, and body weight loss of $\geq 10\%$. The laboratory data for these four patients (group 1) are shown in Table 1. The remaining patients with spontaneous primary CMV infection were analysed as the reference group (group 2). No statistical comparisons were performed, as only four patients were included in group 1. Detection of CMV in cell culture was performed by spin amplification shell vial assay [6]. Anti-CMV IgM and IgG antibodies were determined in serum using the enzyme-linked fluorescent assay (Vidas; bioMérieux, Hazelwood, MO, USA).

The clinical presentations of the four patients in group 1 were as follows.

1. A male aged 66 years with arterial hypertension was admitted with a 4-week history of malaise, fatigue, fever (38.8 °C), night sweats and weight loss (25 kg). He looked moderately ill. Ultrasonography disclosed hepatosplenomegaly. Blood and urine cultures for bacteria, purified protein derivative tests for tuberculosis, and serological tests for *Brucella*, *Treponema pallidum*, *Coxiella burnetii*, *Chlamydia*, *Toxoplasma*, EBV and HIV were all negative. CMV-IgM was positive in two serial serum samples, and CMV

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Table 1. Laboratory data on admission for patients in group 1

	Normal values	Case 1	Case 2	Case 3	Case 4
WBC × 1000/μL	4.0–11.0	9.6	11.7	12.8	19.8
Lymphocytes (%)	16–45	55	54	70	86
Haemoglobin (g/dL)	12.0–17.5	10.8	11.3	14.0	14.1
ESR (mm/h)	< 15	87	56	15	10
AST (U/L)	< 37	74	54	176	60
ALT (U/L)	< 40	77	81	396	60
Alkaline phosphatase (U/L)	90–258	102	49	105	72
Total bilirubin (mg/dL)	< 1.0	0.7	0.6	0.7	1.0
Triglycerides (mg/dL)	70–170	286	229	258	280

WBC, white blood cell; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

was isolated from blood. The fever subsided spontaneously after 5 weeks and the patient started to recover weight. The patient was asymptomatic 2 years later.

- A male aged 32 years presented with a 3-week history of fever, fatigue, scanty cough and weight loss (13 kg). Physical examination was normal except for splenomegaly. Blood cultures and serological tests for *Brucella*, *C. burnetti*, EBV, *Toxoplasma* and HIV were negative. CMV-IgM was negative in the first serum sample, but positive after a further 2 weeks, and CMV was isolated from urine. The fever resolved spontaneously after 7 weeks. The patient regained his previous weight 7 weeks after the fever subsided.
- A male aged 35 years was admitted because of fever, headache, fatigue, weight loss (8 kg), cough and thoracic pain which had begun 1 month earlier. Physical examination disclosed hepatosplenomegaly. A chest X-ray disclosed a bilateral interstitial infiltrate. Sputum and blood cultures, purified protein derivative test and serology for *C. burnetti*, *Chlamydia*, *Mycoplasma pneumoniae*, influenza viruses, *Legionella*, EBV, HIV, *Toxoplasma*, hepatitis viruses A, B and C, and *Brucella*, were all negative. CMV-IgM was negative in the first serum sample, but positive after a further 2 weeks. CMV was isolated from urine (blood culture was not done). Fever and the other symptoms subsided spontaneously after 4 weeks, but the previous weight was only regained after a further 10 weeks.
- A male aged 32 years presented with a 3-week history of fever, fatigue and malaise, with a 10-kg loss of body weight. Splenomegaly was felt. The rest of the physical examination was unremarkable and chest X-ray was normal. Blood cultures and serological studies, including *C. burnetti*, *T. pallidum*, HIV, EBV and

Toxoplasma, were negative. The first serum sample was negative for CMV-IgM, but a second sample was positive. CMV was isolated from urine and blood. The patient recovered uneventfully after 8 weeks without treatment, and the previous weight was recovered 3 weeks after the disappearance of the fever.

The other 20 patients (group 2) were diagnosed with CMV mononucleosis. Their data are shown in Table 2 in comparison with those of group 1.

Several complications or associated manifestations have been described in immunocompetent patients with CMV infection, including severe pneumonia, granulomatous hepatitis [7], Guillain-Barré syndrome [8], meningoencephalitis [9], myocarditis [10], thrombocytopenic purpura [11], erythema nodosum [12], crioglobulinaemia [13], vasculitis [14], vascular thrombosis [15] and colitis [16]. Protracted CMV infections with malaise, fever and persistent lymphocytosis have been described in infants [17], but we are not aware of reported cases of CMV mononucleosis as a cause of protracted fever with prominent weight loss in immunocompetent adults.

Table 2. Demographic, clinical and laboratory features of patients

	Group 1 (n = 4)	Group 2 (n = 20)
Mean age in years (range)	41.2 (32–66)	26.3 (13–44)
Male gender (%)	100	65
Duration of fever (days)	69.2 (± 15.9)	29.7 (± 5)
Lymphadenopathies (%)	0	45
Hepatomegaly (%)	50	30
Splenomegaly (%)	100	35
Abdominal pain (%)	0	15
Cough (%)	25	25
WBC × 1000/μL	13.4 (± 2.2)	10.8 (± 1.0)
Percentage of lymphocytes	66 (± 7)	58 (± 2)
ESR (mm/h)	37 (± 17)	25 (± 4)
ALT (U/L)	91 (± 28)	161 (± 40)
AST (U/L)	156 (± 80)	291 (± 619)
Triglycerides (mg/dL)	263 (± 12)	192 (± 25)

Data are expressed as mean values except where indicated. Abbreviations as in Table 1.

In this study, the clinical manifestations and laboratory data for patients in group 2 were similar to those described previously for CMV mononucleosis in healthy adults [1,4,5], but four patients presented with a more protracted clinical course in which fever and significant weight loss were the prominent symptoms. All of these patients had splenomegaly, but none had peripheral lymphadenopathies. The main diagnostic considerations were lymphoma, other occult neoplasia, systemic vasculitis, or a chronic infection. The clue for diagnosis was the presence of lymphocytosis with activated lymphocytes.

The four patients had hypertriglyceridaemia. The cytokines that mediate the immune response to infection are known to induce changes in lipid metabolism, particularly hypertriglyceridaemia [18]. With the available data, it can be speculated that weight loss in these immunocompetent patients was cytokine-mediated. In summary, CMV infection should be considered in previously healthy patients with protracted fever and weight loss when lymphocytosis is present. In such patients, CMV serology and blood culture should be performed if possible, bearing in mind that, in some cases, it may take 4–6 weeks before specific antigens can be detected. In the case of positive results, other expensive or aggressive diagnostic tests that are usually performed in cases of fever of unknown origin can be avoided.

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