EJCRIM
European Journal
of Case Reports
in Internal Medicine

CYTOMEGALOVIRUS VIREMIA AS A CAUSE OF FEVER OF UNKNOWN ORIGIN IN AN IMMUNOCOMPETENT ADULT

Aaron Naveen Joseph[1], Samuel VanBeck[1], Nooria Saif[2], Tahreem Ahmad[3], Islam Younes[3]

[1] West Virginia University, School of Medicine, Morgantown, USA
[2] Allama Iqbal Medical College, Lahore, Pakistan
[3] Department of Medicine, West Virginia University School of Medicine, Morgantown, USA

Corresponding author's e-mail: anj0016@mix.wvu.edu

Received: 25/08/2025
Accepted: 15/09/2025
Published: 25/09/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent for publication (text and images) was obtained from the patient.
This article is licensed under a Commons Attribution Non-Commercial 4.0 License

How to cite this article: Naveen Joseph A, VanBeck S, Saif N, Ahmad T, Younes I. Cytomegalovirus viremia as a cause of fever of unknown origin in an immunocompetent adult. *EJCRIM* 2025;**12**:doi:10.12890/2025_005777

ABSTRACT

Background: Cytomegalovirus (CMV) infection in immunocompetent adults is usually mild; severe hyperinflammatory phenotypes occur rarely. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterised by uncontrolled immune activation; cytomegalovirus is a recognised but uncommon trigger. Overlapping features with other inflammatory disorders complicate timely diagnosis and management.

Case description: We report a 28-year-old previously healthy male with several days of gastrointestinal and upper respiratory symptoms followed by persistent fevers and a transient petechial, later salmon-pink, macular rash. Vital signs showed tachycardia and tachypnoea as well as SpO2 of 93%. Initial broad infectious work-up was negative. Laboratory tests revealed leucocytosis with lymphocytic predominance, transaminitis (ALT 138 U/l, AST 103 U/l), elevated ferritin, C-reactive protein 20 mg/l, triglycerides 166 mg/dl and splenomegaly. Cerebrospinal fluid showed mild lymphocytic pleocytosis. H-score suggested moderate probability for HLH; bone marrow biopsy demonstrated rare haemphagocytosis without malignancy. The differential included adult-onset Still's disease given the Yamaguchi criteria. Indomethacin improved fevers, but leucocytosis persisted. Serum cytomegalovirus polymerase chain reaction returned positive on day 5 and was corroborated by plasma cell-free DNA testing; the Epstein-Barr virus polymerase chain reaction became negative. Valganciclovir was initiated, with prompt clinical and laboratory improvement.

Conclusion: Cytomegalovirus can precipitate a hyperinflammatory state mimicking adult-onset Still's disease and secondary hemophagocytic lymphohistiocytosis in immunocompetent hosts. Early consideration of cytomegalovirus with timely molecular testing in fever of unknown origin, paired with parallel evaluation for hemophagocytic lymphohistiocytosis, may expedite therapy and improve outcomes.

KEYWORDS

Cytomegalovirus, fever of unknown origin, hemophagocytic lymphohistiocytosis, immunocompetent adult-onset Still's disease

LEARNING POINTS

- Cytomegalovirus may cause hyperinflammation that mimics adult-onset Still's disease.
- Cytomegalovirus infection may trigger hemophagocytic lymphohistiocytosis.
- Clinical improvement after antiviral therapy supports the diagnosis of cytomegalovirus infection.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

INTRODUCTION

Cytomegalovirus is highly prevalent worldwide, with seropositivity estimates ranging from 56 to 94% depending on age and socioeconomic context[1,2]. In immunocompetent adults, primary cytomegalovirus infection typically causes asymptomatic or mononucleosis-like illness; severe organ disease is uncommon but increasingly recognised[1,3]. Hemophagocytic lymphohistiocytosis is a life-threatening hyperinflammatory syndrome; infections, malignancy and autoimmunity are common triggers in adults, with cytomegalovirus an established yet infrequent cause[3,4]. We present an immunocompetent adult with cytomegalovirus viremia and overlapping features of adult-onset Still's disease and secondary hemophagocytic lymphohistiocytosis, highlighting the diagnostic complexity and value of early molecular testing.

CASE DESCRIPTION

A 28-year-old previously healthy male developed several days of nausea, vomiting, diarrhoea and upper-respiratory symptoms followed by persistent fevers, fatigue and a transient petechial rash. Empiric ciprofloxacin had been prescribed before admission. On presentation, his vital signs were as follows: temperature 38°C, heart rate 133, respiratory rate 25, blood pressure 116/72, oxygen saturation (SpO_2) 93% on room air. This presentation fits the national early warning score (NEWS) of 8[5]. Laboratory testing showed leucocytosis with lymphocytic predominance, transaminitis (ALT 138 U/l, AST 103 U/l), elevated ferritin, C-reactive protein 20 mg/l, triglycerides 166 mg/dl and splenomegaly. A peripheral smear showed reactive lymphocytosis and smudge cells without cytopenia. A broad infectious evaluation including HIV, hepatitis A/B/C, Epstein-Barr virus, Lyme disease and other tick-borne pathogens was negative. Cerebrospinal fluid revealed mild lymphocytic pleocytosis. Given persistent fevers and hyperinflammatory markers, hemophagocytic lymphohistiocytosis was considered: the H-score indicated a moderate probability[6]. Bone marrow biopsy showed rare haemophagocytosis without malignancy.

During hospitalisation, the patient developed a transient salmon-pink macular rash with febrile episodes (*Fig. 1*), meeting Yamaguchi criteria for adult-onset Still's disease; indomethacin led to defervescence, but leucocytosis persisted[7]. On hospital day 5, a serum cytomegalovirus polymerase chain reaction test returned positive, and plasma cell-free microbial DNA testing confirmed cytomegalovirus viremia; the Epstein-Barr virus polymerase chain reaction became negative. Oral valganciclovir was started, with prompt clinical and biochemical improvement. The final working diagnosis was cytomegalovirus viremia precipitating a hyperinflammatory response resembling adult-onset Still's disease with secondary hemophagocytic lymphohistiocytosis features.



Figure 1. Transient salmon-pink macular rash during febrile episodes.

DISCUSSION

Severe cytomegalovirus disease in immunocompetent adults, though rare, is increasingly reported across organ systems and can mimic rheumatologic or hyperinflammatory conditions[1,3]. Adult hemophagocytic lymphohistiocytosis requires high clinical suspicion; HLH-2004 criteria and tools such as the H-score help stratify probability and guide marrow evaluation[3,6].

This case underscores three points:

1) cytomegalovirus should be considered early in fever of unknown origin with systemic inflammation;

2) hemophagocytic lymphohistiocytosis evaluation should proceed in parallel given the morbidity of delayed treatment;

3) targeted antivirals can both treat cytomegalovirus and clarify causality when inflammatory features overlap with adult-onset Still's disease[1,8,9].

Further work is needed to define when immunocompetent adults with severe cytomegalovirus benefit from antivirals and to refine algorithms integrating cytomegalovirus testing with hemophagocytic lymphohistiocytosis diagnostics in this population[4].

REFERENCES

1. Schattner A. The wide spectrum of presentations of cytomegalovirus infection in immunocompetent hosts: an exhaustive narrative review. *Pathogens* 2024;**13**:667. doi:10.3390/pathogens13080667
2. Gantt S, Orem J, Krantz EM, Morrow RA, Selke S, Huang ML, et al. Characterization of the risk factors for transmission and symptoms of primary human herpesvirus infections among Ugandan infants. *J Infect Dis* 2016;**214**:36–44. doi:10.1093/infdis/jiw076
3. Lancini D, Faddy HM, Flower R, Hogan C. Cytomegalovirus disease in immunocompetent adults. Med J Aust 2014;**201**:578–580. doi:10.5694/mja14.00183
4. Chevalier K, Schmidt J, Coppo P, Galicier L, Noël N, Lambotte O. Hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection: 5 cases and a systematic review of the literature. *Clin Infect Dis* 2023;**76**:351–358. doi:10.1093/cid/ciac649
5. Williams B. The National Early Warning Score: from concept to NHS implementation. *Clin Med (Lond)* 2022;**22**:499–505. doi:10.7861/clinmed.2022-news-concept
6. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014;**66**:2613–2620. doi:10.1002/art.38690
7. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992;**19**:424–430.
8. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet* 2014;**383**:1503–1516. doi:10.1016/S0140-6736(13)61048-X
9. Boomer JS, To K, Chang KC, Takasu O, Osborne DF, Walton AH, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA* 2011;**306**:2594–2605. doi:10.1001/jama.2011.1829