



Unusual coexistence of cytomegalovirus and Epstein: Barr virus infection in an immunocompetent adult patient

Shiri Maymon, Oriane Globus, Inbal Friedman, Hilla Nochomovitz, Ronen Steinvil, Iris Bahir, Yoel Angel, Ori Rogowski, Ori Argov, Gideon Charach

Department of Internal Medicine C Tel Aviv Sourasky Medical Center, 6 Weizman Street, Tel Aviv, Israel, affiliated to the Sackler School of Medicine, Tel Aviv University, Israel

Abstract

Co-infection with EBV and CMV is extremely rare, however reactivation of EBV during an acute infection of CMV has been reported, most cases were observed in pediatric and immunocompromised patients.

Case presentation: A previously healthy, 33 year old male, was hospitalized in our ward as he came down with a fever of 38.3°C sustained over the preceding three weeks, fatigue, myalgia and night sweats. The physical examination was consisted with diffused papular abdominal rash and hepatosplenomegaly. Liver function tests were elevated. Serology tests were positive both for Cytomegalovirus (CMV) IgM and Epstein - Barr virus (EBV) IgM. However, they were negative for CMV IgG, Epstein- Barr nuclear Antigen (EBNA) IgG and EBV Viral Capsid Antigen (VCA) IgG.

Conclusion: We present a unique case of an adult patient who developed simultaneous acute coinfection of EBV and CMV. However, despite negative laboratory results of IgG, we cannot completely rule out the possibility of reinfection.

Keywords: EBV, CMV, EBNA, VCA

Introduction

Infectious mononucleosis (IM) is a common infection of childhood and young adulthood. It is most commonly caused by Epstein-Barr virus (EBV), and other etiologies include different viral agents such as Cytomegalovirus (CMV). Immunoreactivation of EBV by acute CMV infection is widely reported in the literature, while co-infection of the two etiological agents is a very rare condition, especially in immunocompetent adults. We encountered a patient with clinical and serological findings that were suggestive of acute coinfection by both viruses. Thus, we present this case as an example of an uncommon, yet possible, simultaneous infection in adult immunocompetent patients.

Case presentation

A normally healthy, 33 year old male, was hospitalized in our ward as he came down with a fever of 38.3°C sustained over the preceding three weeks. The fever was accompanied by fatigue, myalgia and occasional night sweats; no complaints of a sour throat were registered. He denied suffering from weight loss, chills, cough, dyspnea or dysphagia. He also denied suffering from abdominal pain, urinary complaints, change in bowel habit, and he did not travel abroad during that period. His physical examination yielded normal results except for a diffused non-specific papular abdominal rash and hepatosplenomegaly (spleen 14.4, liver 15.8cm). No pharyngitis or lymphadenopathy were found.

Laboratory tests showed anemia (Hb 11.5 g/dL, normal range 13.2-17 g/dL), MCV (80 fL, normal range 80-96 fL), elevated LDH (875 U/L, normal range 208-378 U/L), low levels of

Haptoglobin (< 80 mg/L, normal range: 360-1950 mg/L) indicating hemolytic anemia. Also, Leukocytosis (11.7 10³/μL, normal range 4-11 10³/μL), elevated CRP (26.34 mg/L, normal range 0-5 mg/L) and elevated liver enzymes: ALP 163 U/L (normal range: 46-116), GGT 222 U/L (normal range: 6-42 U/L), AST 95 U/L (normal range 7-40 U/L), ALT 121 U/L (normal range: 5-39 U/L). Other rheumatologic tests performed yielded negative results. Protein immunoelectrophoresis was not diagnostic. Serology tests were positive both for Cytomegalovirus (CMV) IgM and Epstein - Barr virus (EBV) IgM. However, they were negative for CMV IgG, Epstein- Barr nuclear Antigen (EBNA) IgG and EBV Viral Capsid Antigen (VCA) IgG. Hepatitis panel and testing for HIV were negative. Blood and Urine cultures were negative. Atypical lymphocytes were observed in blood smear.

Abdominal CT demonstrated hepatosplenomegaly (spleen span: 14.4, liver span: 15.8cm), without any other pathological findings albeit lymphadenopathy. During the seven day hospitalization the patient had a resolution of all the symptoms and liver function tests and LDH values showed a gradual decrease. The patient was diagnosed with infectious mononucleosis caused by an EBV and CMV co-infection.

Discussion

Infectious mononucleosis (IM) is a syndrome typically encountered in pediatric patients. EBV is the most common cause of IM and accounts for 90% of all cases. Many of the remaining cases are attributed to CMV. Other rare causes include toxoplasmosis, adenovirus, Human immunodeficiency

Virus (HIV), Human Herpes Virus (HHV) and Hepatitis B Virus (HBV) [1].

Symptoms of IM include: fever, cervical lymphadenopathy, pharyngitis and fatigue. Different viruses cause distinct clinical manifestations; CMV is predominantly associated with systemic symptoms whereas EBV is primarily associated with adenopathy, splenomegaly and exudative pharyngitis. Additionally, IM with EBV is associated with younger adults as compared to CMV [2]. The patient under study had systemic symptoms of fatigue and fever which correlate with CMV IM, and splenomegaly which is commonly associated with EBV IM.

Laboratory tests of IM include leukocytosis above 4500 cells/mm³ [3], with atypical lymphocytes that compose more than 10% of total cells. Elevated transaminases are encountered in most of the patients, and are frequently self-limited. Also, unusual hematological manifestations may include hemolytic anemia, thrombocytopenia, thrombotic thrombocytopenic purpura and disseminated intravascular coagulation [1, 3]. All laboratory abnormal results in this patient could be attributed to IM; Leukocytosis, atypical lymphocytes, hemolytic anemia and elevated transaminases were observed.

Diagnosis of IM is based on clinical symptoms and positive serology tests. Serological tests for IgM and IgG directed against EBV VCA have high sensitivity (97%) and specificity (94%) [4]. CMV serological tests show similar sensitivity and specificity (93% and 92%, respectively) [5]. Serological evidence of both acute CMV and EBV infection (IgM + and IgG -) was positive in the described case. Nonetheless, one must consider that there are other medical explanations that may be attributed to positive EBV IgM serology i.e. other herpes viruses that cause reactivation of EBV such as CMV [6, 7].

Acute CMV infection followed by EBV reactivation has been previously associated with EBV hepatitis [8] and rejection episodes and other adverse outcomes in post-transplant patients [9]. Although both co-infection with EBV and CMV and reactivation of EBV during an acute infection of CMV have been reported, most cases were observed in pediatric and immunocompromised patients [10]. Only two cases of co-infection of these viruses in immunocompetent adult patients have been described [1, 3].

In this unusual report we describe an adult patient who appears to have dual acute infection with EBV and CMV. Despite negative laboratory results, we cannot completely rule out the possibility of reinfection, unlikely as it might be. However, according to diagnostic definitions; EBV-infected patients- Primary infection: presence of IgM to viral capsid antigen (VCA) is conventionally used for diagnosing acute EBV infection. CMV-infected patients- Primary infection: positive for CMV-IgM. Thus, we consider this case more likely to be a result of co-infection rather than reactivation due to negative IgG titers for both viruses. Although treatment of EBV is primarily supportive, CMV in severe complicated cases can be treated with Ganciclovir or Foscarnet.

Conclusion

This unique case suggests that IM is a plausible differential

diagnosis in immunocompetent adults suffering from prolonged fever and showing characteristic clinical manifestations. Furthermore, atypical clinical presentation such as absence of cervical lymphadenopathy and serologically positive EBV tests prompt doctors to screen for other similar infections as CMV.

It is important to recognize the rare possibility of co-infection in healthy adults due to its possible complications.

Financial disclosure: None declared.

Funding sources: None

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the treatment of the patient and to the writing and final approval of the manuscript. All the authors work in a municipal university-affiliated hospital.

References

1. Bravender T. Epstein-Barr virus, cytomegalovirus, and infectious mononucleosis. *Adolesc Med State Art Rev.* 2010; 21(2):251-64.
2. Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988-1994. *Clin Infect Dis.* 2006; 43(9):1143-51.
3. Navetta B, Feldhamer K. Double Mono: A Case of Coinfection with Ebv and Cmv [abstract]. *Journal of Hospital Medicine.* (suppl 2), 2014, 9.
4. Bruu AL, Hjetland R, Holter E, Mortensen L, Natås O, Petterson W, *et al.* Evaluation of 12 commercial tests for detection of Epstein-Barr virus-specific and heterophile antibodies. *Clin Diagn Lab Immunol.* 2000; 7(3):451-6.
5. Van der Bij W, Torensma R, van Son WJ, Anema J, Schirm J, Tegzess AM, The TH Rapid immunodiagnosis of active cytomegalovirus infection by monoclonal antibody staining of blood leucocytes. *J Med Virol.* 1988; 25(2):179-88.
6. Oill PA, Fiala M, Schofferman J, Byfield PE, Guze LB. Cytomegalovirus mononucleosis in a healthy adult: association with hepatitis, secondary Epstein-Barr Virus antibody response and immunosuppression. *Am J Med.* 1977; 62(3):413-7.
7. Aalto SM, Linnavuori K, Peltola H, Vuori E, Weissbrich B, Schubert J, *et al.* Immunoreactivation of Epstein-Barr virus due to cytomegalovirus primary infection. *J Med Virol.* 1998; 56(3):186-91.
8. Rajwal S, Davison S, Wyatt J, McClean P. Primary Epstein-Barr virus hepatitis complicated by ascites with

- epstein-barr virus reactivation during primary cytomegalovirus infection. *J Pediatr Gastroenterol Nutr.* 2003; 37(1):87-90.
9. Hornef MW, Bein G, Fricke L, Steinhoff J, Wagner HJ, Hinderer W, *et al.* Coincidence of Epstein-Barr virus reactivation, cytomegalovirus infection, and rejection episodes in renal transplant recipients. *Transplantation.* 1995; 60(5):474-80.
 10. Wang X, Yang K, Wei C, Huang Y, Zhao D. Coinfection with EBV/CMV and other respiratory agents in children with suspected infectious mononucleosis. *Virology.* 2010; 7:247.