Mild infectious mononucleosis presenting with transient mixed liver disease

Case report with a literature review

David Lawee MD CCFP FCFP

The Epstein-Barr virus (EBV) causes the clinical syndrome commonly known as infectious mononucleosis (IM). The classic presentation of IM in young adults consists of the triad of fever, oropharyngitis, and a bilateral and symmetrical lymphadenitis in the posterior triangle of the neck. While laboratory evidence of hepatocellular involvement is invariably associated with EBV IM, clinical evidence of hepatitis is rarely the presenting feature of the infection. There are no evidence-based guidelines for the diagnosis or treatment of EBV; however, several diagnostic and therapeutic strategies are recommended.[1] The management of suspected EBV infection is outlined by the Guidelines and Protocols Advisory Committee in British Columbia.[2]

I report a patient with mild EBV infection associated with mixed liver disease. The initial diagnosis was of hepatitis A. The true etiology became apparent only after laboratory testing confirmed EBV infection and ruled out the common causes of hepatitis.

Case description

A 22-year-old woman, a second-year English major, visited the office complaining of feeling unwell for the past 7 days with low-grade fever, asthenia, pruritus, generalized weakness, nausea but no vomiting, mild sore throat, and mildly swollen glands.

Her vital signs were normal. She was afebrile. Her physical examination was entirely normal except for mild bilateral mid-jugular lymph nodes enlargement, mild scleral jaundice, and mild tenderness in the right upper quadrant. She did not have hepatosplenomegaly. The pharynx and tonsils looked normal without exudate. There were no pharyngeal petechiae and no swollen uvula. The axillary and inguinal lymph nodes were physiologic. The urine was tea coloured and frothed upon shaking. A dipstick showed a large amount of bilirubin.

History failed to show risk factors for hepatitis A, B, or C (no piercing, tattooing, or needle sharing). She had been immunized against hepatitis B in high school. She'd had unprotected intercourse 3 days before the onset of her illness with the same partner of 4 months. There was no history of travel. She lived by herself. She hadn't had any contact with anyone who had sore throat or flulike illness over the past 4 to 6 weeks. The initial diagnosis was of viral hepatitis of unknown etiology, possibly hepatitis A.

The investigation included a complete blood count. It showed neutropenia (1.37 x 10^9/L) and reactive lymphocytes (4.55 x 10^9/L). There were no atypical lymphocytes reported. The result of a monospot test was positive. Findings for hepatitis C screen, hepatitis A, immunoglobulin G (IgG), and immunoglobulin M (IgM) were negative. The hepatitis B surface antigen result was positive (>100 U/L). Test results for autoimmune diseases were negative. Results from an abdominal ultrasound were normal.

Three days after her initial presentation, most of her symptoms resolved.

Table 1 tracks changes in liver enzymes throughout the course of the illness. This patient's clinical presentation suggested a viral illness. The moderate pain in the right upper quadrant, mild jaundice, and frothy urine suggested obstructive jaundice as demonstrated by elevated alkaline phosphatase and mildly elevated total bilirubin levels. The elevated γ-glutamyl transpeptidase, aspartate aminotransferase, and alanine aminotransferase indicated hepatocellular involvement. Thus, the laboratory profile indicated a mixed liver disease. The result of the monospot test confirmed the EBV infection.

Discussion

The unusual presentation led me to conduct a literature search of PubMed MEDLINE back to 1966 and *PubMed*

Table 1. Progress of liver enzymes throughout patient's illness

LABORATORY TESTING	19/05/2006	24/05/2006	06/06/2006	LABORATORY RANGE
Alkaline phosphatase	270	441	91	35-122 U/L
γ-Glutamyl transpeptidase	83	162	25	<36 U/L
Aspartate aminotransferase	165	132	23	<31 U/L
Alanine aminotransferase	140	266	18	<36 U/L
Total bilirubin	34	23	7	<23 µmol/L

Central (all years) using 4 MeSH terms and key words (*human herpesvirus*, *hepatitis*, *Epstein-Barr virus infections*, and *liver diseases*). The following points might be of clinical interest to family physicians.

Transmission. Epstein-Barr virus infection is transmitted via intimate contact of oropharyngeal secretions. In susceptible patients, EBV invades the epithelial cells of the salivary glands and the white blood cells known as B cells of the oropharynx, and spreads to the entire lymphoreticular system.

Seroepidemiological survey indicates that most primary infection of EBV occurs in early childhood and is asymptomatic with a prevalence of more than 90% in adults. Only 10% of adults older than 40 years are susceptible to EBV infections. Infants become susceptible to EBV when maternal antibody protection wanes.

Human beings are the primary reservoir for person-to-person transmission with a healthy individual shedding the virus intermittently. Depending on the response of the body's immune system, EBV infection might establish a lifelong dormant infection in some cells in the body's immune system.[3] The reactivation of these dormant cells plays an important role in the emergence of Burkitt lymphoma and nasopharyngeal carcinoma.[4]

Clinical features. Exudative pharyngitis occurs in 30% of cases with EBV infection. When present, the exudate is commonly confused with group A streptococcal pharyngitis. A third of patients with EBV carry group A streptococcal organisms; concomitant infection is also common.[5] Because of this overlap, laboratory support is essential to establish exact diagnosis.

Macular, petechial, scarlatiniform, urticarial, or erythema multiforme can be associated with EBV infection in 5% of patients.[3] Of those patients with EBV who receive amoxicillin, 90% to 100% will develop a pruritic maculopapular rash 7 to 10 days after administration of the first dose.[3] The rash appears when a suspected case of strep throat is, in fact, a primary EBV infection. Circulating IgG and IgM antibodies to ampicillin are demonstrable.[5]

Laboratory diagnosis. Laboratory diagnosis of acute IM is suggested when leukocytosis with an absolute lymphocytosis (>50% of the total white blood count) and at least 10% atypical lymphocytes are apparent on peripheral blood smear. Mild thrombocytopenia occurs in 25% to 50% of patients.

Standard testing. The standard testing for EBV infection relies on measurement of the heterophil antibody (nonspecific antibodies that agglutinate sheep erythrocytes). These antibodies are present in 40% to 60% of patients with IM in the first week of the illness and in 80% to 90% of cases by the third or fourth week. Repeated testing might be required in patients with the clinical syndrome whose test results are negative early in the course of the illness.

As few as 50% of patients who are younger than 4 years might develop the heterophil antibody.[1] The heterophil response (Paul-Bunnell test) persists for up to 3 months, although it might be present for as long as a year after onset. While the Paul-Bunnell test is a quantitative assay, the various monospot tests are qualitative. They are slightly more sensitive (85%) than the heterophil assay, but false-positive findings could occur in children or in patients with other viral illnesses. A substantial number of pseudo-outbreaks have been linked to laboratory error.[5]

Antibody testing. Testing for specific antibodies to antigenic components of the virus that appear at different stages of infection is costly and seldom required. The antibodies include viral capsid antigen (VCA), early antigens (EAs), and Epstein-Barr nuclear antigen (EBNA). The interpretation of EBV serology is beyond the scope of this report. Suffice it to say that the primary acute EBV infection is associated with VCA-IgM, VCA-IgG, and absent EBNA antibodies. Recent infection (3 to 12 months) includes positive VCA-IgG and EBNA antibodies, negative VCA-IgM antibodies, and usually positive EA antibodies. After 12 months, the pattern is the same as recent infection, except EA antibodies are absent. Interpretation of these results will allow one to categorize the EBV infection as chronic, reactivation, past, primary infection, or susceptibility to infection. The direct detection of EBV in blood or lymphoid tissues is a research tool and is not available for routine diagnosis.[3]

Epstein-Barr virus and the liver. Epstein-Barr virus infections are associated with hepatocellular hepatitis. The frequency of this association varies with age. It is estimated to be 10% in young adults and 30% in the elderly where it presents itself as an anicteric viral hepatitis.[5] The hepatocellular disease is usually mild. It could go undetected clinically and it resolves spontaneously. An early transient mild increase in serum transaminases might be present and is the only precursor for positive results for a heterophil test.[5]

Only a few cases of cholestatic liver disease have been reported.[5-7] While cholestasis can occur during the convalescent phase of any severe form of viral hepatitis, elevated alkaline phosphatase and elevated bilirubin levels are not typically associated with EBV infection. The mechanism for the obstructive component is unknown; it is assumed to be related to a "mildly swollen bile duct"[8] rather than an infection of the epithelial cells of the bile ducts.[9]

Except in transplantation or among patients with immunodeficiency, such as HIV, X-linked lymphoproliferative disease, or cancer chemotherapy, EBV infections are rarely associated with acute fulminant hepatic failure. Epstein-Barr virus infection can trigger autoimmune hepatitis in susceptible individuals.[10]

The underlying pathogenesis and immunologic mechanisms of acute and chronic hepatitis associated with EBV infection are unknown. Immunohistochemistry identified CD3- and CD8-positive T-lymphocytic infiltrate as possible underlying causes.[8]

Complications. Apart from the risk of splenic rupture, complications of EBV infection are rare.[1] There does appear to be a causal relationship between EBV infection and chronic fatigue syndrome.[11]

In 1983 the first case of a solitary penile ulcer associated with infectious mononucleosis was reported.[12] Since then several cases of genital, oro-genital, and digital ulcer complicating EBV infections have been reported.[13-16] Recognition of this etiology in the differential diagnosis for the genital ulcer syndrome can avoid an erroneous diagnosis of genital herpes and its implications.

Conclusion

There are several points to be made about EBV. In primary care, particularly when there is a high level of viral upper-respiratory infections or group A streptococcal pharyngitis in the community, diagnosis of mild EBV infection is difficult if not impossible. Diagnosis requires a high level of suspicion and supporting of laboratory data. Several etiological agents cause overlapping clinical presentation, such as viral hepatitis (A, B, and C), herpes simplex virus infection, human herpesvirus 6 infection, cytomegalovirus, HIV, drug-induced hepatitis, autoimmune hepatitis, and toxoplasmosis.

Epstein-Barr virus's exudative pharyngitis is often confused with streptococcal pharyngitis. If treated with penicillin it results in a non-itchy maculoerythematous rash. The rash could be misdiagnosed as allergy to penicillin.

The degree of liver involvement associated with EVB infections always varies. Mild self-limited hepatocellular liver disease is common. It manifests by a transient elevation of alanine aminotransferase levels. Cholestatic liver disease is less frequent and is also self-limited. Misdiagnosed, it could lead to costly and lengthy investigation. Fulminant liver disease is extremely rare; it affects liver-transplant and immune-compromised patients.

And, finally, unlike genital herpes, EBV genital ulcers are not necessarily sexually transmitted.

Dr Lawee *is a Professor Emeritus in the Department of Family and Community Medicine at the University of Toronto in Ontario.*

Acknowledgment

I am thankful for the assistance provided by **Mr David Le Sauvage** *of the Canadian Library of Family Medicine:* **dlesauv1@uwo.ca**.

Competing interests

None declared

EDITOR'S KEY POINTS

- Epstein-Barr virus does not always present with the classic triad of fever, oropharyngitis, and cervical lymphadenitis. Exudative pharyngitis occurs in only 30% of cases.
- Epstein-Barr virus infection is associated with hepatocellular hepatitis. The frequency is estimated to be 10% in young adults and 30% in the elderly.
- This hepatocellular hepatitis is usually mild and resolves spontaneously.

POINTS DE REPÈRE DU RÉDACTEUR

- Le virus d'Epstein-Barr ne se présente pas toujours avec l'habituelle triade de fièvre, oropharyngite et lymphadénite cervicale. La pharyngite exsudative ne se produit que dans 30% des cas.
- L'infection au virus d'Epstein-Barr est associée à l'hépatite hépatocellulaire. On estime sa fréquence à 10% chez les jeunes adultes et à 30% chez les personnes âgées.
- Cette hépatite hépatocellulaire est habituellement légère et disparaît spontanément.

Correspondence to: Dr David Lawee, *101—1910 Yonge St, Toronto, ON M4S 3B2; telephone 416 789-2027; fax 416 483-3422; e-mail* **davidlawee@sympatico.ca**

References

1. Ebell MH. Epstein-Barr virus infectious mononucleosis. *Am Fam Physician* 2004;70(7):1279-87.
2. Guidelines and Protocols Advisory Committee. *Diagnosis and management of sore throat: reviewed 2003*. Victoria, BC: British Columbia Medical Association; 2007. Available from: **www.health.gov.bc.ca/gpac/pdf/throat.pdf**. Accessed 2007 Mar 23.
3. Centers for Disease Control and Prevention. *Epstein-Barr virus and infectious mononucleosis*. Atlanta, GA: Centers for Disease Control and Prevention; 2007. Available from: **http://www.cdc.gov/ncidod/diseases/ebv.htm**. Accessed 2007 Mar 26.
4. Nova: Science in the News. *Kissing the Epstein-Barr virus goodbye*. Canberra, Aus: Australian Academy of Science; 1997. Available from: **http://www.science.org.au/nova/026/026key.htm**. Accessed 2007 Mar 26.
5. Cunha BA. *Infectious mononucleosis*. Omaha, NE: eMedicine; 2006. Available from: **http://www.emedicine.com/MED/topic1499.htm**. Accessed 2006 Aug 21.
6. Hinedi TB, Koff RS. Cholestatic hepatitis induced by Epstein-Barr virus infection in an adult. *Dig Dis Sci* 2003;48(3):539-41.
7. Bernstein CN, Minuk GY. Infectious mononucleosis presenting with cholestatic liver disease. *Ann Intern Med* 1998;128(6):509.
8. Nelson RS, Darragh JH. Infectious mononucleosis hepatitis: a clinicopathologic study. *Am J Med* 1956;21(1):26-33.
9. Feranchak AP, Tyson RW, Narkewicz MR, Karrer FM, Sokol RJ. Fulminant Epstein-Barr viral hepatitis: orthotopic liver transplantation and review of the literature. *Liver Transpl Surg* 1998;4(6):469-76.
10. Vento S, Guella L, Mirandola F, Cainelli F, Di Perri G, Solbiati M, et al. Epstein-Barr virus as a trigger for autoimmune hepatitis in susceptible individuals. *Lancet* 1995;346(8975):608-9.
11. Rea TD, Russo JE, Katon W, Ashley RL, Buckwald DS. Prospective study of the natural history of infectious mononucleosis caused by Epstein-Barr virus. *J Am Board Fam Pract* 2001;14(4):234-42.
12. Lawee D, Shafir MS. Solitary penile ulcer associated with infectious mononucleosis. *Can Med Assoc J* 1983;129(2):146-7.
13. Sisson BA, Glick L. Genital ulceration as a presenting manifestation of infectious mononucleosis. *J Pediatr Adolesc Gynecol* 1998;11(4):185-7.
14. Taylor S, Drake SM. Dedicoat M, Wood MJ. Genital ulcers associated with acute Epstein-Barr virus infection. *Sex Transm Infect* 1998;74(4):296-7.
15. Cheng SX, Chapman MS, Margesson LJ, Birenbaum D. Genital ulcers caused by Epstein-Barr virus. *J Am Acad Dermatol* 2004;51(5):824-6.
16. Bennett NJ, Domachowske J. *Mononucleosis and Epstein-Barr virus infection*. Omaha, NE: eMedicine; 2006. Available from: **http://www.emedicine.com/PED/topic705.htm**. Accessed 2007 Mar 26.