

CLINICAL VIGNETTE

An Uncommon Case of Infectious Mononucleosis

Danielle Ryba, MD and Phillip Brown, MD

Introduction

Infectious mononucleosis is relatively common, with an overall incidence of 5 per 1,000 people per year.^{1,2} Infectious mononucleosis is caused by infection with Epstein-Barr Virus (EBV), and it is estimated that 95% of the population will be infected with EBV in their lifetime.¹ Below, we discuss an interesting presentation of infectious mononucleosis.

Case

The patient was a 28-year-old male who initially presented in a video visit for upper abdominal discomfort. During his initial telemedicine appointment, the patient described 1-2 weeks of intermittent, sharp, right upper quadrant abdominal pain with deep breaths. There were no associated fevers, chills, nausea, or vomiting. A comprehensive metabolic panel was obtained same day, which demonstrated elevation of AST to 221 and ALT to 399. The patient was subsequently seen in person. Further history was negative for drug use, new sexual partners, recent travel, or significant alcohol use. The patient then reported mild symptoms suggestive of an upper respiratory tract infection about three weeks prior, with many sick contacts at work. At the time, he had tested negative for COVID. The physical exam was unremarkable. Repeat CMP showed increased AST to 287 and ALT to 543. Acute hepatitis panel was negative, however, heterophile antibody was positive. Additional tests included a positive EBV VCA IgG, and EBV DNA was greater than 2,000. Abdominal ultrasound demonstrated hepatosplenomegaly. The patient was diagnosed with acute infectious mononucleosis complicated by mild EBV hepatitis and advised to refrain from contact sports for the next month. Unfortunately, the patient was lost to follow up after completing initial evaluation.

Discussion

The typical presentation of infectious mononucleosis consists of sore throat, lymphadenopathy, and fevers.¹⁻³ Most individuals are infected between the ages of 15-24.¹ Epstein-Barr Virus can cause additional complications, including hepatitis, jaundice, and splenomegaly (which rarely can lead to splenic rupture).^{1,2} Older adults can present with jaundice without URI symptoms.¹ Elevated transaminases suggestive of hepatitis are relatively common in EBV infections, and about 75% of patients in one study developed subclinical hepatitis.³ Another report reported 10% of young adults with EBV infection will present with anicteric hepatitis.⁴ Liver transaminase elevation

is usually seen between week 2 and 4 of illness and may be up to four times the upper limit of normal.⁵ The diagnosis of infectious mononucleosis can be confirmed with heterophile antibody testing. However, false negatives can occur during the first week of illness. If there is a high clinical suspicion, testing for EBV viral capsid antigen IgM is advised.^{1,6} Treatment of infectious mononucleosis is primarily supportive and aimed at controlling symptoms. Imaging is not routinely necessary. Splenic rupture is a rare complication of the splenomegaly seen in EBV infections.^{1,6}

While it is common to see hepatitis in EBV infections, the virus is also associated with more complex liver pathology. A rare complication of EBV is cholestatic hepatitis.⁷ Jaundice is usually not reported but is more likely to occur in people over age 35. The underlying cause of cholestatic hepatitis due to EBV is unknown.⁷ Another rare complication of EBV is known as Chronic Active Epstein-Barr Virus infection (CAEBV). Similar to infectious mononucleosis, fever, lymphadenopathy, and splenic or liver enlargement are symptoms of CAEBV.⁸ More serious complications may include anemia, nerve damage, liver failure, and/or interstitial pneumonia. Although EBV is present in the B cells of healthy persons infected with EBV, in most cases of CAEBV reported in Asians or Native Americans, EBV has been surprisingly the opposite and instead detected in T or natural killer (NK) cells.⁸ Molecular approaches, such as EBV-DNA PCR or EBER-RISH, are frequently used to diagnose EBV-related hepatitis. EBV infection can also be detected with serological tests (including viral capsid antigen IgM and IgG, EBNA, and EA-D). However, this method is less reliable as the elderly population can have much higher titers than young adults.⁹ EBV may cause a temporary elevation of liver enzymes; and rarely can cause severe liver injury and acute liver failure (ALF).⁹ Acute liver failure occurs mostly in young adults without any known underlying liver disease. Only 0.21 % of adult ALF cases are attributed to EBV. This illness usually occurs in adults younger than 40 years of age.^{9,10} EBV is also associated with a variety of autoimmune diseases, and there is some evidence that it may play a role in the development of autoimmune liver disease and primary biliary cirrhosis.¹¹

There are multiple case reports of mild hepatitis occurring in young individuals with infectious mononucleosis. However, the presentation of some cases is quite different than that of our patient. As an example, one case reported a 22-year-old patient

who presented with mild scleral icterus, lymphadenopathy, and mild abdominal pain. She was diagnosed with a positive monospot test.⁴ Another 20yo male presented with fevers, vomiting, and sore throat. He had significantly elevated liver enzymes, and was ultimately diagnosed with EBV VCA IgM, as he had a negative heterophile antibody test.¹² Neither of these patients had hepatomegaly on ultrasound.^{4,12} Each of these patients had a more typical initial presentation of a viral illness, as compared to our patient. Our patient did not have a typical presentation of either acute infectious mononucleosis or hepatitis. His upper respiratory symptoms were quite mild, and he did not present with the typical fevers, lymphadenopathy, and sore throat. He also did not have severe abdominal pain, jaundice, nausea, or vomiting that can be seen with acute hepatitis. Since our patient's primary complaint was mild, intermittent right upper quadrant pain, we obtained a RUQ ultrasound as part of our initial evaluation. This confirmed the hepatosplenomegaly that can be seen in infectious mononucleosis. Given the atypical presentation, when the patient's lab results demonstrated elevated transaminases, a wide differential was considered, and we performed the heterophile antibody test, which confirmed a diagnosis of infectious mononucleosis. Interestingly, our patient had already produced EBV VCA IgG antibodies, which would typically suggest old infection. However, given EBV DNA PCR was still positive, and patient reported URI symptoms a few weeks prior to presentation, he was likely diagnosed after the peak of his illness. Additionally, since this patient did report a history of URI symptoms consistent with infectious mononucleosis, it was assumed he did not have isolated EBV hepatitis.

Infectious mononucleosis is a common illness.¹ However, it is important to recognize atypical presentations and keep a broad differential when encountering abnormal lab findings that are unexpected, such as acute LFT elevations. It is important to note, that in the absence of jaundice, abdominal pain, or obvious hepatomegaly, identifying mild hepatitis does not change management of infectious mononucleosis, and hepatic function is not routinely evaluated after a diagnosis of a typical presentation of infectious mononucleosis. In our review of the literature, we could not identify any guidelines on monitoring for resolution of liver function abnormalities. Rather, incidentally found LFT elevations can be used as a trigger to consider evaluation for infectious mononucleosis in the primary care setting.

REFERENCES

1. **Womack J, Jimenez M.** Common questions about infectious mononucleosis. *Am Fam Physician.* 2015 Mar 15;91(6):372-6. PMID: 25822555.
2. **Zhang L, Zhou P, Meng Z, Pang C, Gong L, Zhang Q, Jia Q, Song K.** Infectious mononucleosis and hepatic function. *Exp Ther Med.* 2018 Mar;15(3):2901-2909. doi: 10.3892/etm.2018.5736. Epub 2018 Jan 10. PMID: 29456696; PMCID: PMC5795407.
3. **Dunmire SK, Hogquist KA, Balfour HH.** Infectious Mononucleosis. *Curr Top Microbiol Immunol.*

- 2015;390(Pt 1):211-40. doi: 10.1007/978-3-319-22822-8_9. PMID: 26424648; PMCID: PMC4670567.
4. **Lawee D.** Mild infectious mononucleosis presenting with transient mixed liver disease: case report with a literature review. *Can Fam Physician.* 2007 Aug;53(8):1314-6. PMID: 17872846; PMCID: PMC1949255.
5. **Uluğ M, Celen MK, Ayaz C, Geyik MF, Hoşoğlu S.** Acute hepatitis: a rare complication of Epstein-Barr virus (EBV) infection. *J Infect Dev Ctries.* 2010 Oct 28;4(10):668-73. doi: 10.3855/jidc.871. PMID: 21045362.
6. **Lennon P, Crotty M, Fenton JE.** Infectious mononucleosis. *BMJ.* 2015 Apr 21;350:h1825. doi: 10.1136/bmj.h1825. PMID: 25899165.
7. **Herold J, Grimaldo F.** Epstein-Barr Virus-induced Jaundice. *Clin Pract Cases Emerg Med.* 2020 Jan 21;4(1):69-71. doi: 10.5811/cpcem.2019.10.45049. PMID: 32064430; PMCID: PMC7012545.
8. **Kimura H, Cohen JI.** Chronic Active Epstein-Barr Virus Disease. *Front Immunol.* 2017 Dec 22;8:1867. doi: 10.3389/fimmu.2017.01867. PMID: 29375552; PMCID: PMC5770746.
9. **Zhang W, Chen B, Chen Y, Chamberland R, Fider-Whyte A, Craig J, Varma C, Befeler AS, Bisceglie AM, Horton P, Lai JP.** Epstein-Barr Virus-Associated Acute Liver Failure Present in a 67-Year-Old Immunocompetent Female. *Gastroenterology Res.* 2016 Oct;9(4-5):74-78. doi: 10.14740/gr718e. Epub 2016 Sep 20. PMID: 27785330; PMCID: PMC5040549.
10. **Mellinger JL, Rossaro L, Naugler WE, Nadig SN, Appelman H, Lee WM, Fontana RJ.** Epstein-Barr virus (EBV) related acute liver failure: a case series from the US Acute Liver Failure Study Group. *Dig Dis Sci.* 2014 Jul;59(7):1630-7. doi: 10.1007/s10620-014-3029-2. Epub 2014 Jan 25. PMID: 24464209; PMCID: PMC4250929.
11. **Rigopoulou EI, Smyk DS, Matthews CE, Billinis C, Burroughs AK, Lenzi M, Bogdanos DP.** Epstein-barr virus as a trigger of autoimmune liver diseases. *Adv Virol.* 2012;2012:987471. doi: 10.1155/2012/987471. Epub 2012 May 28. PMID: 22693505; PMCID: PMC3368154.
12. **Kang MJ, Kim TH, Shim KN, Jung SA, Cho MS, Yoo K, Chung KW.** Infectious mononucleosis hepatitis in young adults: two case reports. *Korean J Intern Med.* 2009 Dec;24(4):381-7. doi: 10.3904/kjim.2009.24.4.381. Epub 2009 Nov 27. PMID: 19949739; PMCID: PMC2784984.