

Epstein-Barr Virus Coinfection in COVID-19

Journal of Investigative Medicine High Impact Case Reports
Volume 9: 1–3
© 2021 American Federation for Medical Research
DOI: 10.1177/23247096211040626
journals.sagepub.com/home/hic


Asim Nadeem, MD¹, Krithika Suresh, MD¹ , Hassan Awais, MD¹, and Saba Waseem, MD¹

Abstract

Epstein-Barr virus (EBV), a member of the herpes virus family, is a causative agent for infectious mononucleosis in young adults. It has an asymptomatic and subclinical distribution in about 90% to 95% of the world population based on seropositivity. EBV is associated with various lymphomas, nasopharyngeal carcinoma, and in immunocompromised states can give rise to aggressive lymphoproliferative disorders. Symptomatic patients mostly present with mild hepatitis, rash, oral symptoms, lymphadenopathy, and generalized malaise. Recently with the COVID-19 (coronavirus disease-2019) pandemic, hepatitis has been found to be related to acute EBV and cytomegalovirus reactivation versus acute infection in the absence of other major causes. We describe a case of EBV coinfection in a patient with resolving mild COVID-19 infection.

Keywords

EBV, COVID-19, hepatitis

Case Description

A 62-year-old male with past medical history of hypertension, hyperlipidemia, coronary artery disease, and arthritis was readmitted via emergency department for worsening chest pain, productive cough, and shortness of breath. His chest pain was pleuritic. He was discharged a week earlier from a 1-day hospital stay on a 10-day course of dexamethasone for coronavirus disease-2019 (COVID-19) infection, which he was unable to take. He was maintaining oxygen saturation of 88% on 6 L nasal cannula. Initial blood work was remarkable for leukocytosis 25.86 (ref: 3.1–8.50 × 10³/uL) with bands elevated at 9%, anion gap 15, lactic acid elevated 3.3 (ref: 0.5–2.0 mmol/L), mild transaminitis with aspartate aminotransferase (AST) 113, and alanine aminotransferase (ALT) 153. Physical examination was remarkable for decreased air entry with bilateral crepitation. Computed tomography pulmonary embolus study confirmed presence of bilateral acute pulmonary emboli with possible right heart strain and bilateral infiltrates consistent with COVID-19 pneumonia. He was treated with heparin infusion, remdesivir, dexamethasone, 1 dose of vancomycin, and piperacillin-tazobactam as well as supportive breathing treatments consisting of albuterol nebulization as needed. He was then admitted to the medical floors for further management.

Echocardiogram obtained later was resulted as normal left ventricular function with ejection fraction 55% to 65% with normal right ventricular pressure and no evidence of right ventricular dysfunction. Heparin infusion, remdesivir, and

dexamethasone were continued. Vancomycin and piperacillin-tazobactam were given the initial 2 days to cover for superimposed bacterial pneumonia and later deescalated to amoxicillin-clavulanic acid on days 3 and 4 of hospitalization. Ultrasound abdomen done on day 4 showed no abnormalities within the liver or gallbladder.

During hospitalization, patient was noticed to have worsening of liver enzymes which peaked at ALT 721 IU/L (normal <55 U/L) and AST 305 IU/L (normal value < 35 U/L). Other laboratory values were γ -glutamyl transferase 114 IU/L (ref: 12–64 IU/L), albumin 2.7 g/dL (ref: 3.4–4.8 g/dL), alkaline phosphatase 49 IU/L (ref: 56–119 IU/L), and international normalized ratio 1.5. Further workup showed procalcitonin minimally elevated at 0.28 (ref: <0.05 ng/mL), d-dimer elevated at 12.89 (ref: <0.5 mg/dL), and fibrinogen was normal. His blood alcohol and acute hepatitis panel were negative on day 2 of hospital admission. Acetaminophen levels obtained on hospital day 4 were <0.6 (ref 0.00–50.0 μ g/mL). At that point, remdesivir was discontinued on day 2 of admission as it was thought to have contributed to

¹Conemaugh Memorial Medical Center, Johnstown, PA, USA

Received March 18, 2021. Revised July 27, 2021. Accepted July 31, 2021.

Corresponding Author:

Asim Nadeem, MD, Department of Internal Medicine, Conemaugh Memorial Medical Center, 1086 Franklin Street, Johnstown, PA 15905, USA.

Email: drasimnadeem@gmail.com



Table 1. The trend of LFTs during patient's hospitalization.

	Hospital day										
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
Total bilirubin (ref: 0.3-1.2 mg/dL)	0.9	0.6	0.6	0.7	0.6	0.8	1.1	1.2	1.1	1.1	0.9
AST (ref: 5-34 U/L)	113	141	169	249	286	305	274	244	260	244	216
ALT (ref: <55 U/L)	153	190	289	452	580	712	721	674	706	645	624
Albumin (ref: 3.4-4.8 g/dL)	3.3	2.7	2.7	2.8	2.7	3.0	2.9	2.8	2.9	2.8	2.8
ALP (ref: 53-141 U/L)	67	49	55	59	53	66	74	84	89	89	100

Abbreviations: LFTs, liver function tests; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline-phosphatase.

worsening of liver function. Antibiotics were discontinued as bacterial infection was less likely and it was thought amoxicillin-clavulanic acid could also have contributed to liver enzyme abnormalities. Computed tomography abdomen and pelvis with contrast (day 8) showed mild splenomegaly with no abnormalities noted in the liver or gall bladder.

Despite discontinuation of remdesivir, antibiotics, and improving oxygen requirements, his liver function continued to worsen (see Table 1) and additional workup including autoimmune work up with anti-smooth muscle antibodies, systemic lupus erythematosus, and vasculitis panel were done and reported negative. Further testing with EBV and cytomegalovirus (CMV) serology were done, which revealed EBV viral capsid antigen (VCA) IgM positivity. He was also positive for EBV VCA IgG, EBV early antigen (EA) IgG, and EBV nuclear antigen (NA) IgG. EBV polymerase chain reaction was reported positive. CMV IgM antibody was negative; however, CMV IgG antibody was positive with reported value >10 (ref: 0.00-0.059). He remained stable with improving oxygen requirements and was eventually discharged home without the need for supplemental oxygen.

Discussion

In December 2019, a pneumonia associated with the 2019 novel coronavirus emerged in Wuhan, China, and subsequently spread in many countries becoming a pandemic.¹ Common clinical features consisted mainly of respiratory symptoms and consisted of fever, cough, shortness of breath with associated radiological feature of interstitial pneumonia on imaging.²

COVID-19 has also been associated with acute liver injury as manifested by increased liver enzymes in case reports and studies worldwide. In a study by Phipps et al,³ acute liver injury was common in those patients who tested positive for severe acute respiratory syndrome coronavirus disease-2 (SARS CoV-2) but was mild; however, about 6.4% had severe liver injury and were also found to have a severe disease course.

A systematic review and meta-analysis published by Kunotsur et al,⁴ which was a pooled analysis of 10 studies,

noted the prevalence of hepatic manifestations to be elevated AST 37.2%, elevated ALT 26.6%, low albumin 45.6%, and elevated total bilirubin 18.2%.

A study of 5700 COVID-19 patients conducted in New York by Richardson et al⁵ noted a pattern of liver injury with AST elevation in 58.4% patients and ALT elevation in 39%.

Bongiovanni et al⁶ reported a case of acute hepatitis in a 30-year-old-woman with asymptomatic COVID-19 infection where her liver enzymes were increased and noted to be AST 1531 IU/L and ALT 893 IU/L.

Primary EBV infection can cause a mild self-limited hepatitis that typically resolves without clinical sequelae. In the study by Mellinger et al,⁷ primary EBV infection accounted for <1% of consecutive adult acute liver failure cases.

SARS-CoV-2 and EBV coinfection was reported by Garcia-Martinez et al,⁸ where a 19-year-old female patient presented with fever, bilateral eyelid edema, and right hemifacial swelling. She was also noted to have splenomegaly, bilateral cervical lymphadenopathy, and elevation of transaminases with AST 239 and ALT 264 U/L. A study by Anirvan et al⁹ noted pattern of liver injury to be AST predominant compared with ALT in COVID-19 infection and, if ALT > AST was noted, recommended to rule out non-COVID-19-related causes of elevated liver enzymes including hepatitis A, B, C, E, and other viral causes.

Our patient had mild COVID-19 infection; however, due to his worsening transaminitis prompted further evaluation. Common causes of hepatitis such as Tylenol toxicity, viral hepatitis, and alcohol exposure were ruled out. Ultrasound abdomen or computed tomography abdomen and pelvis did not reveal gallstones or liver abnormalities except for mild splenomegaly. Autoimmune panel was negative. EBV viral panel was positive for EBV VCA IgM as well as EBV VCA IgG, EBV EA IgG, and EBV NA IgG. EBV was confirmed positive by EBV polymerase chain reaction as well. This led us to believe our patient most likely had reactivation of EBV infection leading to acute hepatitis. Primary COVID-19 infection also could have contributed to liver enzyme derangements; however, based on our literature review COVID-19 infections were associated with greater elevations of AST than ALT, making EBV a more likely cause of

our patient's hepatitis than COVID-19. Although it is hard to prove causality of elevated liver function test (LFTs) in our patient, our case highlights the importance of testing for other viral coinfections in patients with resolving COVID-19 infection. A limitation of the case report was to ascertain the temporal association of EBV infection in relation to COVID; however, we believed underlying EBV infection was contributory to his transaminitis, although causality was not established.

Conclusion

Mild to moderate elevation of LFTs below 200 U/L in the setting of COVID-19 pneumonia is quite common. Worsening transaminase elevations should be further evaluated with significant importance given to other viral causes of hepatitis such as CMV and EBV secondary to possible reactivation/coinfection. Based on our case report in any patient with worsening LFTs, EBV serologies should be performed to rule out reactivation or coinfection of the virus. As the understanding seems to evolve regarding the COVID-19 pandemic, prospective observations will provide further evidence on this important aspect.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

The Conemaugh Memorial Medical Center Office of Research Administration reviewed the case and determined that it does not meet the definition of human subject research as defined by the 45 CFR 46; therefore, institutional review board review is not required.

Informed Consent

Verbal informed consent was obtained from the patient for anonymized information to be published in this case report.

ORCID iD

Krithika Suresh  <https://orcid.org/0000-0003-2573-832X>

References

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506. doi:10.1016/S0140-6736(20)30183-5
3. Phipps MM, Barraza LH, LaSota ED, et al. Acute liver injury in COVID-19: prevalence and association with clinical outcomes in a large US cohort. *Hepatology*. 2020;72:807-817. doi:10.1002/hep.31404
4. Kunoutsuor SK, Laukkanen JA. Hepatic manifestations and complications of COVID-19: a systematic review and meta-analysis. *J Infect*. 2020;81:e72-e74. doi:10.1016/j.jinf.2020.06.043
5. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323:2052-2059. doi:10.1001/jama.2020.6775
6. Bongiovanni M, Zago T. Acute hepatitis caused by asymptomatic COVID-19 infection. *J Infect*. 2021;82:e25-e26. doi:10.1016/j.jinf.2020.09.001
7. Mellinger JL, Rossaro L, Naugler WE, et al. Epstein-Barr virus (EBV) related acute liver failure: a case series from the US Acute Liver Failure Study Group. *Dig Dis Sci*. 2014;59:1630-1637. doi:10.1007/s10620-014-3029-2
8. García-Martínez FJ, Moreno-Artero E, Jahnke S. SARS-CoV-2 and EBV coinfection. *Med Clin (Engl Ed)*. 2020;155:319-320. doi:10.1016/j.medcle.2020.06.010
9. Anirvan P, Bharali P, Gogoi M, Thuluvath PJ, Singh SP, Satapathy SK. Liver injury in COVID-19: The hepatic aspect of the respiratory syndrome - what we know so far. *World J Hepatol*. 2020;12:1182-1197. doi:10.4254/wjh.v12.i12.1182