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Case Report

Chronic active Epstein-Barr exacerbated by COVID-19 co-infection

David B Villafuerte^{*,*}, Olga Lavrynenko[#], Rayan Qazi, Marco F Passeri, Fernando L Sanchez

University of the Incarnate Word School of Osteopathic Medicine, Texas Institute of Graduate Medical Education and Research at Laredo Medical Center, Laredo, US

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ABSTRACT

A 60-year-old Hispanic female was admitted with recurrent fevers, altered mental status, lymphadenopathy, hepatosplenomegaly, and pancytopenia. Initially, sepsis was presumed because of recurrent urinary tract infection with extended-spectrum beta-lactamase *Escherichia coli*. Despite appropriate therapy, her clinical condition continued to decline. An extensive workup was obtained to determine the source of her ailments. Bone marrow biopsy was negative for leukemia, lymphoma, and myelodysplastic syndrome; fluorescence *in situ* hybridization and a cytogenetic panel were normal; a lumbar puncture was negative. However, peripheral blood was remarkable for elevated titers for Epstein-Barr virus (EBV) consistent with chronic active EBV. Treatment with valganciclovir showed early positive results, but the patient became co-infected with COVID-19, and her EBV titer increased again, resulting in a precipitous health decline and death.

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Introduction

The Epstein-Barr virus (EBV) is a double-stranded DNA virus belonging to the human *Herpesviridae* family (Dunmire et al., 2018). It infects over 90% of adults worldwide. Typically, it is transmitted through the oral route through the exchange of saliva, where it targets B-cells and epithelial cells in the tonsils. It then undergoes an incubation where it sheds intermittently into the blood and saliva. When the immune system tries to neutralize it, the virus becomes latent and remains in B-cells for the individual's lifetime (Dunmire et al., 2018). Usually, infection is asymptomatic, but when it is not, it commonly causes infectious mononucleosis, which presents as fatigue, fever, sore throat, and hepatosplenomegaly (Cohen, 2000). Rarely, chronic infection, known as chronic active EBV (CAEBV), occurs (Cohen, 2000). Herein, we report a case of such and the first to show exacerbation by SARS-CoV-2.

Case report

A 60-year-old Hispanic woman was brought to the hospital by her daughter because of a 2-day history of nausea, vomiting, poor

appetite, fever, and altered mental status. This was her third admission in the previous 3 months for similar complaints.

On her first admission (early fall 2021), she experienced 2 days of progressive weakness, fatigue, confusion, decreased appetite, and recurrent emesis. Her vitals were remarkable for fever, hypotension, and tachycardia. Physical exam revealed an ill appearance, generalized weakness, orientation to person and place only, paranoia, and suprapubic tenderness. Computed tomography (CT) of the chest and abdomen revealed enlarged peri-aortic, iliac, axillary, and aortopulmonary lymph nodes along with hepatosplenomegaly (Figure 1A–B). Laboratory findings revealed pancytopenia, anemia, and a urine culture positive for extended-spectrum beta-lactamase (ESBL) *Escherichia coli*. She was placed on sepsis protocol with a 14-day course of meropenem. Eventually, she was discharged home on ertapenem. The fever had subsided, but her altered mental status was persistent.

On her second admission (over a month later), she returned because of recurrence of her previous symptoms. Vital signs revealed fever, tachycardia, and tachypnea. Physical exam demonstrated pale skin, ill appearance, generalized weakness, hepatosplenomegaly, and altered mental status with orientation to self only. A CT of the head was negative. The chest x-ray was unremarkable. Laboratory findings reflected persistent anemia, pancytopenia, and lactic acidosis. A viral respiratory and gastrointestinal panel was obtained too. Bone marrow biopsy was negative. A lumbar puncture was performed because of concerns for meningitis given the persistent

* Corresponding author.

E-mail address: dbvillafuerte@gmail.com (D.B. Villafuerte).

Co-first authors: Villafuerte, DB and Lavrynenko, O.

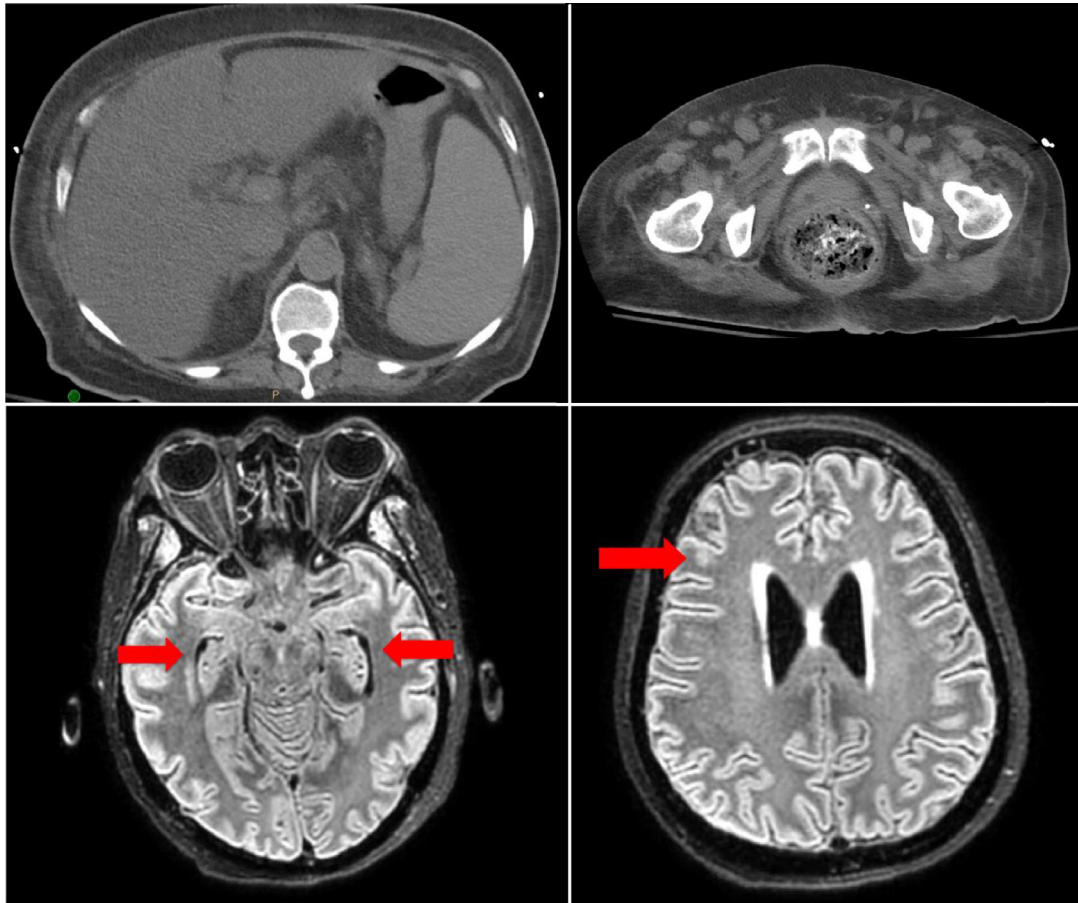


Figure 1. (A) Top left: coronal section CT abdomen and pelvis with contrast grossly observed hepatosplenomegaly with the liver measuring 21.7 cm in length and the spleen measuring 14.6 cm in length. Mild to moderate ascites was noted with fluid surrounding the liver and spleen and layering dependently within the pelvis. (B) Top right: coronal section CT abdomen and pelvis with contrast bilateral enlarged inguinal lymphadenopathy that continued inferiorly and extensively from chains of the para-aortic and iliac lymph nodes that were infectious in origin. (C) Bottom left: MRI brain/head bilateral medial temporal lobe hyperintensity with associated atrophy has been previously described in EBV encephalitis as a source of seizures. Mild medial temporal lobe atrophy likely from chronic microvascular ischemic change. (D) Bottom right: MRI brain/head microvascular ischemic change in the right frontal lobe that abuts the cortex, increasing the likelihood of seizure focus because of the involvement of the cortex.

CT = computed tomography; EBV = Epstein-Barr virus; MRI = magnetic resonance imaging.

fever and altered mental status. Cerebrospinal fluid (CSF) analysis, Gram stain, cytology, and meningitis PCR panel results were negative. Peripheral blood was positive for EBV viral capsid antigen antibody (VCA Ab) (immunoglobulin G [IgG]) of >750.00 (reference range, <18.00 negative, 18.00 to 21.99 equivocal, and >21.99 positive), and EBV Epstein-Barr nuclear antigen antibody (EBNA Ab) (IgG) of 18.5 (reference range, <18.00 negative, 18.00 to 21.99 equivocal, and >21.99 positive) and a quantitative DNA PCR of $92,422$ copies/ml (reference range, <200 copies/ml negative) with 4.98 log copies/ml (reference range, <2.30 log copies/ml negative). There was a reduced CD4 count of 172 (reference range, 501 – 1500 cells/ μ l) and CD8 of 69 (reference range, 145 – 900 cells/ μ l) with negative HIV.

She was initially given meropenem because of her history of ESBL *E. coli*. However, on day 5, acyclovir was started empirically because there was no recovery. Six days later, acyclovir was changed to valganciclovir for potential cytomegalovirus because of lack of improvement. Shortly after, results from the initial EBV PCR returned. Over the next few days, she began to experience fewer fevers and had an improved mental status. Quantitative EBV DNA PCR obtained 5 days after starting valganciclovir showed a viral load of $3,763$ copies/ml and 3.58 log copies/ml. She was discharged on a 10-day course of valganciclovir and instructions to follow up as an outpatient with an infectious disease.

Unfortunately, 13 days later, she returned with the same chief complaint. She had not attended outpatient follow-up. Vital signs revealed fever, hypotension, tachycardia, and tachypnea. Physical exam noted pale skin, ill appearance, generalized weakness, an inflamed throat, swollen neck lymph nodes, hepatosplenomegaly, and leukoplakia. Laboratory exams reflected anemia, pancytopenia, and lactic acidosis. COVID-19 PCR was positive, unlike previous admissions. Quantitative EBV DNA PCR demonstrated an increased viral load of $146,524$ copies/ml and 5.17 log copies/ml. The next day she went into status epilepticus, requiring intubation for airway protection. Postseizure magnetic resonance imaging (MRI) revealed bilateral, symmetric subtle medial temporal lobe T2 hyperintensities and punctate, nonspecific T2 hyperintensities predominantly seen in the right frontal lobe (Figure 1C–1D). Despite intensive treatment, she continued to deteriorate, which led to her death 8 days later.

Discussion

CAEBV is an extremely rare disease where the body's immune response cannot control a reactivated EBV infection (Kimura and Cohen, 2017). Geographically, it is most frequently seen in Asia, but cases in the US have been described (Kimura and Cohen, 2017).

Our patient was Hispanic and lived most of her life along the US and Mexico border.

Latent EBV can reactivate into lytic replication after various precipitating causes, among them another infection (Odumade et al., 2011). Our patient was afflicted with ESBL *E. coli* and SARS-CoV-2, which led to reactivation confirmed through EBV antibody IgM and IgG titers plus PCR viral load.

Clinically, CAEBV presents as a chronic or recurrent infectious mononucleosis-like illness (Kimura and Cohen, 2017). Our patient manifested classic symptoms and laboratory presentation, including fever, fatigue, inflamed throat, leukoplakia, swollen lymph nodes, pancytopenia, transaminitis, and hepatosplenomegaly. EBV encephalitis is also considered given MRI findings of medial temporal lobe hyperintensities, seizures, and altered mental status. Albeit rare, cases exist with normal CSF findings, alongside seizures and multiorgan failure (Khanal et al., 2016).

CAEBV may be indolent with asymptomatic periods or persistent or fulminant, with death occurring within a few weeks and sometimes associated with opportunistic infections (Kimura and Cohen, 2017). Although our patient had a period of improvement with valganciclovir, her rapid death associated with COVID-19 follows the latter pattern.

In 2018, the World Health Organization established the latest standard for the diagnosis and classification of CAEBV (Willemze et al., 2019). Our patient met all four parameters of diagnosis. First, she presented with severe recurrent symptoms for at least 3 months. Second, there was elevated EBV genome load in peripheral blood confirmed through positive EBV VCA Ab (IgG), EBV EBNA Ab (IgG), and DNA PCR, which followed the parameters of viral reactivation (Hess, 2004; Kimura and Kwong, 2019). Third, infection of T-cells presented as a reduced CD4 and CD8 count. Fourth, other diagnoses were excluded with negative tests for primary EBV, HIV, and other immunodeficiencies.

There is no established treatment protocol, and only hematopoietic stem-cell transplantation has been shown to be curative (Bollard and Cohen, 2018). However, our patient was not a candidate because of her unstable health. Attempts to treat using typical EBV antiviral therapy, including acyclovir, ganciclovir, and vidarabine, have shown a poor response (Schooley et al., 1986; Ishida et al., 1993; Kimura et al., 2001b) because replication of latent EBV in most proliferating immune cells does not require the viral DNA polymerase that these pharmaceuticals target (Bollard and Cohen, 2018). Our experience was similar when using acyclovir but opposite with valganciclovir, which showed recovery and a reduced PCR viral load. Sadly, 2 weeks later, she contracted COVID-19, and her health worsened. PCR viral load increased again. Unfortunately, because of co-infection and subsequent death, it is unknown whether she would have shown remission with valganciclovir or at least improved to where she could have received hematopoietic transplantation.

Conclusions

Ultimately, because cases of CAEBV are rare, physicians must have a greater awareness of the condition and its diagnostic cri-

teria (Kimura et al., 2001a). Antiviral therapy must be started early with the intent of proceeding to hematopoietic transplantation. Future research will be necessary to develop more effective therapeutic strategies.

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Author contributions

All authors contributed to all aspects of this project.

Patient consent

No consent is required as no identifiable patient data is included in this case report.

Data availability

Upon request to the corresponding author.

Declaration of Competing Interest

The authors have no competing interests to declare.

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Dr. Lavrynenko and Dr. Villafuerte are equal first authors. Therefore, Dr. Qazi is the second author, and so forth.

References

- Bollard CM, Cohen JL. How I treat T-cell chronic active Epstein-Barr virus disease. *Blood* 2018;131:2899–905.
- Cohen JL. Epstein-Barr virus infection. *N Engl J Med* 2000;343:481–92.
- Dunmire SK, Verghese PS, Balfour Jr HH. Primary Epstein-Barr virus infection. *J Clin Virol* 2018;102:84–92.
- Hess RD. Routine Epstein-Barr virus diagnostics from the laboratory perspective: still challenging after 35 years. *J Clin Microbiol* 2004;42:3381–7.
- Ishida Y, Yokota Y, Tauchi H, et al. Ganciclovir for chronic active Epstein-Barr virus infection. *Lancet* 1993;341:560–1.
- Khanal D, Singh T, Rabinstein A. Epstein Barr virus encephalitis in adults: a case series (P1.293). *Neurology* 2016;86 P1.293.
- Kimura H, Cohen JL. Chronic active Epstein-Barr virus disease. *Front Immunol* 2017;8:1867.
- Kimura H, Hoshino Y, Kanegane H, et al. Clinical and virologic characteristics of chronic active Epstein-Barr virus infection. *Blood* 2001a;98:280–6.
- Kimura H, Kwong YL. EBV viral loads in diagnosis, monitoring, and response assessment. *Front Oncol* 2019;9:62.
- Kimura H, Morita M, Tsuge I, et al. Vidarabine therapy for severe chronic active Epstein-Barr virus infection. *J Pediatr Hematol Oncol* 2001b;23:294–9.
- Odumade OA, Hogquist KA, Balfour Jr HH. Progress and problems in understanding and managing primary Epstein-Barr virus infections. *Clin Microbiol Rev* 2011;24:193–209.
- Schooley RT, Carey RW, Miller G, et al. Chronic Epstein-Barr virus infection associated with fever and interstitial pneumonitis. Clinical and serologic features and response to antiviral chemotherapy. *Ann Intern Med* 1986;104:636–43.
- Willemze Rein, Cerroni Lorenzo, Kempf Werner, Berti Emilio, Facchetti Fabio, Swerdlow Steven, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood* 2019. doi:10.1182/blood-2018-11-881268.