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CASE REPORT

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Epstein–Barr virus infection leading to multiorgan involvement in an immunocompetent man

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Key Clinical Message

Epstein–Barr virus (EBV) is a commonly asymptomatic widespread human herpes virus affecting over 90% of the population. It mostly originates complications like simple sore throat and infectious mononucleosis but severe manifestations are rare. Herein we report a 30-year-old immunocompetent man who presented with fever, sore throat, general weakness, and drowsiness. The diagnosis was formulated based on the positive RT-PCR test for EBV DNA and serological detection of IgM antibody against viral capsid antigen. The patient developed severe meningoencephalitis, myocarditis, and bowel perforation and passed away after 72 days of hospitalization.

KEYWORDS

bowel perforation, Epstein–Barr virus (EBV), meningoencephalitis, multiorgan failure, myocarditis

1 | INTRODUCTION

Epstein–Barr virus (EBV) is a common human herpes virus that involves more than 90% of people.[1] The enormous spread of EBV is probably related to the long incubation period and disparate transmission routes through bodily fluids, especially saliva. However, EBV can also spread in blood and semen during sexual contact, blood transfusions, and organ transplantations.[2] Primary infection with EBV occurs commonly during childhood with mild viral symptoms or asymptomatic infections. Nevertheless, in adults, it often presents with infectious mononucleosis. The acute phase is almost always self-limiting, and afterward, EBV remains latent in the memory cells of B lymphocytes.[3] Scattered cases of severe EBV complications have been reported in the literature; however, these cases are extremely rare and mostly affect immunocompromised individuals. Both the acute primary infection and the activation of latent EBV are reported to be associated with neurological disorders, cardiac complications, severe organ damage, autoimmune processes, and malignancy.[4] Even when severe complications occur, the prognosis is good in the majority of patients, and fatal consequences are not common.[5]

Since most infected patients remain asymptomatic throughout their lives, clinical suspicion of EBV in the first place as a causative agent for the severe manifesting picture is of great importance. Herein, we report a severe case of EBV, complicated simultaneously with encephalitis, myocarditis, and intestinal perforation, in a 30-year-old immunocompetent male.

This manuscript has two first authors. "Saina Paymannejad" and "Kiana Shirani" are cofirst authors.

2 | CASE PRESENTATION

A 30-year-old man presented to the Department of Infectious Diseases and Tropical Medicine affiliated with Isfahan University of Medical Sciences with fever, sore throat, general weakness, and drowsiness. He had a past medical history of a seizure episode at the age of 4, and Guillain-Barre syndrome at the age of 10 but was otherwise healthy.

Physical examination noted an emaciated individual compatible with his age. He had a body temperature of 38.4°C (101.1°F), a pulse rate of 130 beats/min, and a respiratory rate of 24 breaths/min. We detected splenomegaly, axillary lymphadenopathy, and tonsillar enlargement. The patient was confused and dull. Neurological examination revealed bradykinesia and cogwheel rigidity, predominantly on the right side. Furthermore, nuchal rigidity as well as positive Kernig's sign and Brudzinski's sign were identified. Other systems' examinations were unremarkable.

Initial laboratory data included pancytopenia, elevated liver enzymes, direct hyperbilirubinemia, and high erythrocyte sedimentation rate (ESR).

To further evaluate the cytopenic state, we requested a peripheral blood smear (PBS), which revealed mild hypochromic RBCs with anisocytosis, severe leukopenia, and 15% atypical lymphocytes. Nonetheless, further evaluation revealed that the patient's condition could not be explained by hematological disorders.

Based on the clinical and paraclinical findings, EBV-specific serological antibody assays were tested, resulting positive for viral capsid antigen IgM. Moreover, EBV DNA was detected by reverse transcription polymerase chain reaction (RT-PCR) test. Since the admission occurred during the COVID-19 pandemic, an RT-PCR test was also performed for COVID-19 to determine whether the symptoms were associated with this infection; however, the result was negative. Moreover, the patient was evaluated and resulted negative for human immunodeficiency virus (HIV) infection by ELISA and P24 antigen testing.

At this point, EBV encephalitis was considered; nevertheless, due to the rare incidence of severe complications in EBV infection, justifying the patient's symptoms with this diagnosis alone did not seem rational. As a result, we expedited a thorough workup in order to identify any other possible etiological factor that could be associated with the altered mental status either individually or concurrently with EBV infection.

Brain magnetic resonance imaging (MRI) with and without administration of contrast medium injection was performed. T2/FLAIR images showed bilateral hyperintensities in the medial temporal lobe as well as the basal ganglia, and diffusion-weighted imaging/apparent diffusion coefficient (DWI/ADC) revealed diffusion restriction in cortical regions. Besides, diffused meningeal enhancement was observed following the contrast injection (Figure 1). The findings were in favor of viral meningoencephalitis, ischemia, or trauma; however, the two latter differential diagnoses were ruled out by history and physical exam.

A lumbar puncture was done and analysis of the cerebrospinal fluid (CSF) indicated mild pleocytosis with 20 WBCs/mm^3 and 95% lymphocytic dominance, a protein level of 74 mg/dL, and a glucose level of 53 mg/dL. On the 8th day of hospitalization, intravenous acyclovir (700 mg, q 8 h) and corticosteroid therapy with dexamethasone (8 mg, q 8 h) were initiated. The autoimmune panel, paraneoplastic panel, and polymerase chain reaction (PCR) multiplex of CSF were all negative except for the EBV-PCR, ruling out other possible differential diagnoses. Acyclovir was discontinued after a negative result for HSV-PCR.

On the 20th day of hospitalization, the patient developed mild nonradiating chest pain, dyspnea, and persistent tachycardia, and therefore, underwent a cardiologic evaluation. Laboratory levels of troponin and creatinine kinase MB were within the normal range. An electrocardiogram (ECG) did not indicate any pathology other than sinus tachycardia, whereas echocardiography revealed an ejection fraction (EF) of 40%, global hypokinesia, and mild systolic dysfunction. Diagnosis of myocarditis was entertained based on the presence of viral infection and ruling out other differential causes of heart failure by echocardiography. The patient was placed under ECG monitoring and follow-up echocardiography. Afterward, on the 21st day of hospitalization, the patient was put on captopril and metoprolol for the management of acute heart failure.

Since the patient's condition was gradually worsening over the hospitalization course and he had developed two major complications due to the underlying EBV infection, on the 23rd day of hospitalization, we planned to add an antiviral therapy with ganciclovir (350 mg, q 12 h) to the patient's pharmaceutical regimen in order to decrease the viral load and possibly slow down the progression of the disease.

Two days later, the patient suddenly experienced episodes of severe nausea and vomiting, abdominal discomfort, and obstipation. There was tenderness and guarding on the left lower quadrant area, as well as generalized abdominal distension. Abdominopelvic multidetector row computed tomography (MDCT) scan with contrast detected pneumoperitoneum and mild ascites. Jejunal and proximal ileal loops were severely dilated and multiple air bubbles were observed on the left quadrants. Accordingly, small bowel obstruction

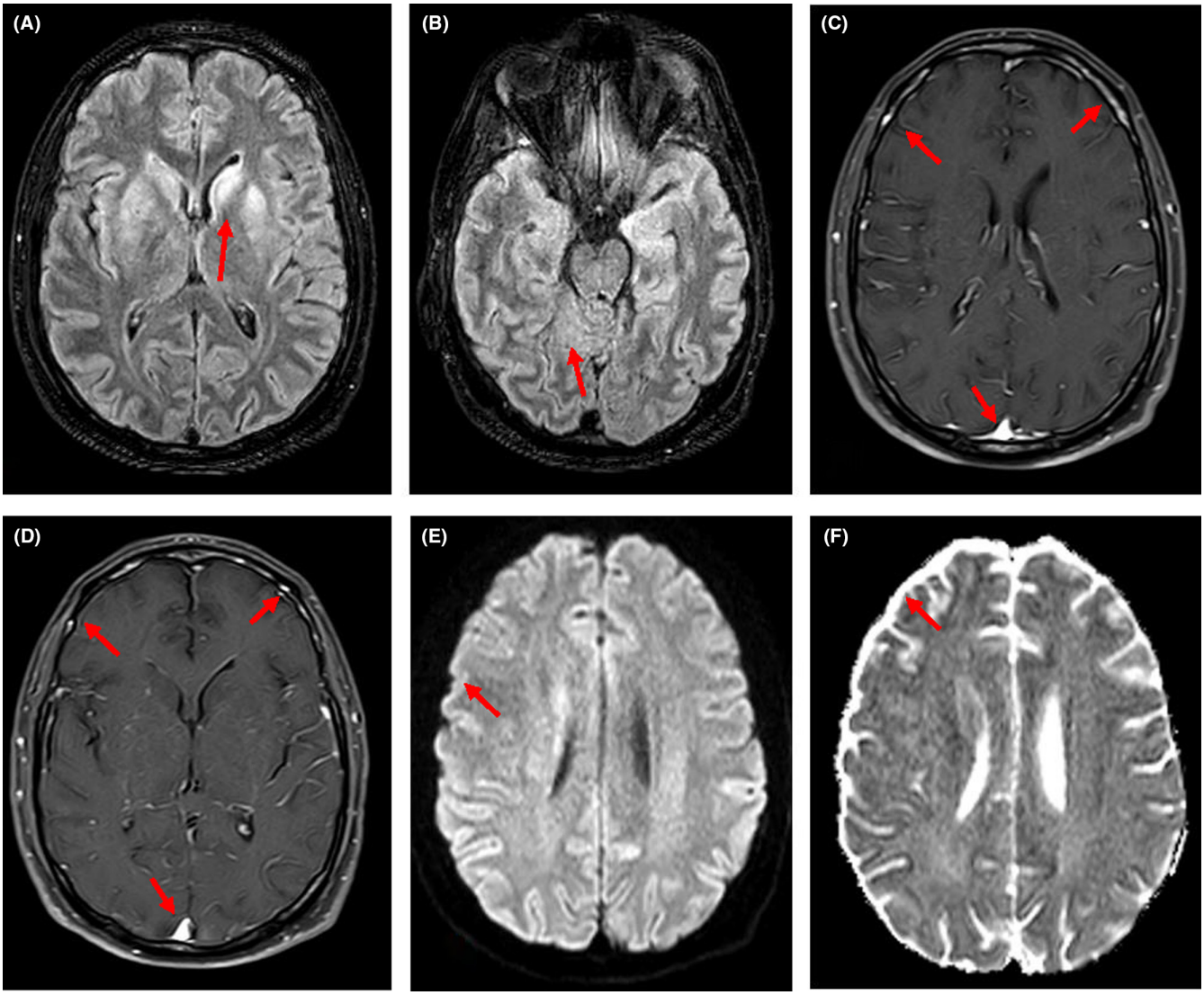

FIGURE 1 Axial FLAIR MRI showing high signal intensities in the bilateral caudate and lentiform nuclei (A) and left medial temporal lobe (B). Postcontrast brain MRI shows diffuse meningeal enhancement (C and D). Axial diffusion-weighted imaging (DWI) (E) and apparent diffusion coefficient (ADC) (F) show restriction diffusion in cortical regions.

and microperforation were suggested, and the patient was prepared for emergency surgery. After general anesthesia, in the supine position, the small intestine was approached with a midline laparotomy. Approximately 150 cm distal to the ligament of Treitz, more than half of the lumen was perforated. Ten centimeters of the small intestine was resected, and the two sides were connected by end-to-end anastomosis. Pathological evaluation of the resected specimen revealed submucosal and vascular congestion with extensive acute inflammation and necrosis of the serosal surface. One month later, the patient suffered from another episode of acute abdomen. Bowel perforation was proposed based on radiological imaging and the patient underwent colostomy as well as the resection of the distal ileum, right hemicolon, and appendix. While histopathological examination showed similar characteristics of acute inflammation and congestion, immunohistochemical analysis stained positive for EBV DNA. The findings were in favor of EBV-associated lymphoma and granulomatous formation (Figure 2).

During the postoperative period, the patient's condition sustained to deteriorate. He developed arterial fibrillation and eventually passed away after 72 days.

3 | DISCUSSION

3.1 | Multiorgan involvement

The prognosis for EBV infection is very favorable, and the majority of cases self-limit spontaneously in a short

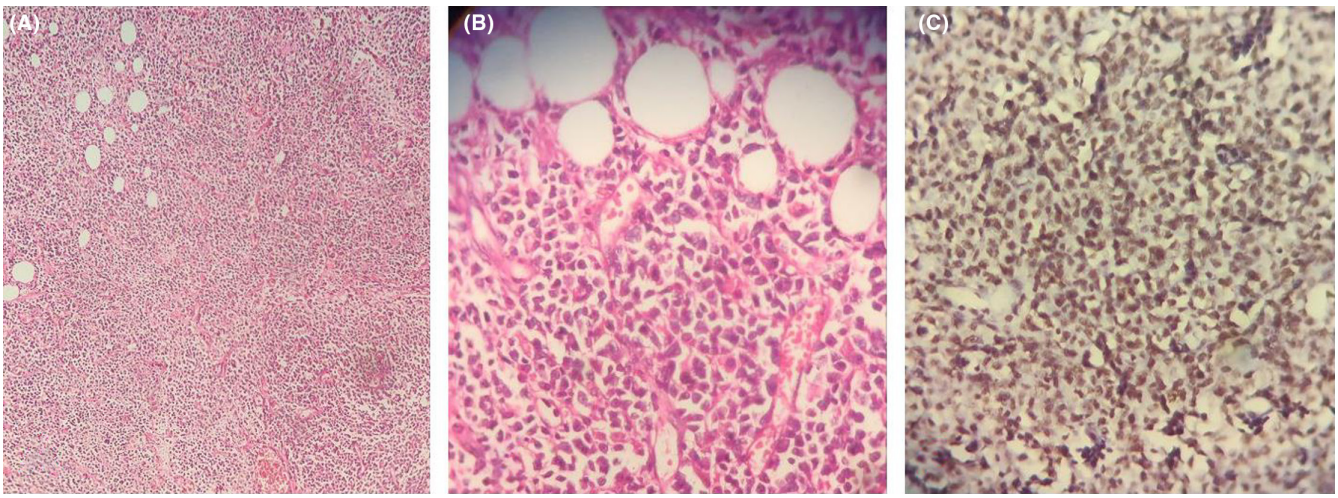

FIGURE 2 (A) Histopathological examination of the surgical specimen with hematoxylin and eosin exhibiting acute inflammation, lymphocytic infiltration, and areas of necrosis (×10). (B) Note the presence of nucleolus and large nuclei in some lymphocytes (×40). (C) Immunohistochemical stain for Epstein–Barr virus. Strong positive membranous/cytoplasmic staining is demonstrated in several cells (×40).

period without sequelae. Nevertheless, EBV can affect almost all organs in the body, revealing a thousand faces of the disease.[3] While isolated single-organ involvement is more frequently documented, multiorgan failure is extremely rare.[6–9] The mechanism of severe organ damage is not yet fully understood; however, an in vitro study on rats proposed that either EBV-transformed B lymphocytes could secrete antibodies against host tissues or that natural antibodies against EBV proteins could cross-react with tissue antigens.[10] Patnaik et al. described a case of fulminant EBV encephalitis who developed multi-organ failure on the second day and succumbed within 52 h.[6] One possible speculation for the disseminated EBV involvement could be the uncontrolled lymphoproliferative response, which might be related to the virus-associated hemophagocytic syndrome (HLH), or reflect an underlying immunodeficiency. This was well illustrated by van der Woude et al. who described an EBV infection leading to HLH with progressive hepatic and renal failure.[7] Wang et al. reported a 59-year-old female with EBV-positive diffuse large B-cell lymphoma who died precipitously due to lymphomatosis and fulminant organ dissemination.[8] Contrary to the mentioned articles, in our patient, the symptoms appeared more gradually over a longer period of time. Although he died eventually as in the previous literature, the course of the deterioration was less acute and lasted 72 days. In addition, one of the interesting features of our report is the intact immunity of the case. Our patient was a previously healthy young male with no history of predisposing factors that could contribute to the catastrophic course of the disease. He neither had an impaired immunodeficiency panel nor did he consume immune suppressive medication, which adds novelty to the literature.

3.2 | Meningoencephalitis

Severe neurological complications occur in about 1% of EBV infections, with encephalitis being the most frequent manifestation.[11] We initially diagnosed the EBV meningoencephalitis based on the clinical and radiological findings and confirmed the diagnosis by detecting EBV PCR in the CSF. Nevertheless, CSF investigation for evidence of EBV DNA revealed negative results in some cases.[12,13] The inconsistency of the findings could possibly support the suggestion that EBV encephalitis could result from both immunotoxicity and direct neuronal invasion.[14] Radiological imaging, especially MRI, is a useful tool in diagnosing and evaluating the prognosis of the disease. Approximately 60% of EBV meningoencephalitis contain abnormal CT or MRI findings, most frequently in cerebral hemispheres, cerebellum, or basal ganglia. The highest mortality rate is related to brain stem involvement, whereas the involvement of the basal ganglia is very rarely associated with sequela.[15] Koning et al. reported a 21-year-old immunocompetent female with EBV encephalitis whose only radiological abnormality was leptomeningeal enhancement along the cerebellar folia. Despite not receiving adequate treatment, she made a good neurological recovery.[13] In another case reported by Çelik et al, involvement of substantia nigra was associated with a full recovery within 2 weeks.[16] The severe and fetal course that happened in our patient could be elucidated by the expanded neuroanatomic distribution of the radiological abnormalities, as MRI revealed pathology in bilateral cortical regions, basal ganglia, and medial temporal lobes, as well as the diffused meningeal enhancement following contrast administration. Di Carlo et al. suggested that

a negative DWI sequence in MRI is associated with favorable improvement in severe EBV meningoencephalitis.[17] The role of viral infections in causing cytotoxic edema and, therefore, an alteration in water diffusion supports this interesting statement.[18] Since DWI provides image contrast that is dependent on the molecular motion of water, special attention should be paid upon this sequence, when viral encephalitis is speculated. In our case, DWI images revealed considerable restriction diffusion in cortical regions, backing up the aforementioned assertion.

3.3 | Myocarditis and atrial fibrillation

Viral infections have long been associated with the development of myocarditis. Despite the rare incidence of less than 1%, EBV-related myocarditis should not be underestimated as the natural history is severely heterogeneous: it varies from sudden death due to fulminant heart failure or malignant ventricular arrhythmias, to complete recovery or long-term evolution into dilated cardiomyopathy.[19,20] Sui et al. reported a 17-year-old male with fulminant EBV myocarditis and rhabdomyolysis who developed extensive calcification of left ventricular walls. Despite the severe progression of the disease, he survived eventually with favorable follow-up evaluations.[21] Watanabe et al. described acute EBV myocarditis in a young female, complicated with malignant ventricular arrhythmias and cardiac arrest. She was discharged after 20 days on pharmacological therapy.[19] By contrast, an asymptomatic face of EBV myocarditis is illustrated by Maiese et al, whose patient presented with neurological symptoms and passed away due to EBV encephalitis. Myocarditis was not diagnosed until postmortem histopathological evaluations.[22] Progression of the cardiac complications in our case passed a unique course. The initial presenting picture of myocarditis was nonradiating chest pain, dyspnea, and persistent tachycardia, which completely resolved within a few days, and follow-up echocardiograms revealed considerable improvement. Nevertheless, after about 1 month of recovery, a sudden severe attack of atrial fibrillation and consequent cardiac arrest resulted in the expiration of the patient. A similar case of sudden cardiac arrest preceded by fever, symptoms of upper respiratory infection, and altered mental status was reported in a pediatric patient with EBV-induced HLH.[23] Definitive diagnosis of EBV myocarditis could only be formulated with an invasive endomyocardial biopsy and identifying the viral genome by PCR techniques.[24] Nevertheless, electrocardiography and especially MRI techniques could provide valuable information.[25] In our case, since acute EBV infection was well established and the patient had already developed confirmed EBV-related neurological complications, a biopsy was not performed as it was invasive and could not change our treatment approach. Moreover, an endomyocardial biopsy is only indicated in patients with acute deterioration of heart function of unknown origin who are not responding to medical treatment.[26]

3.4 | Bowel perforation

Data regarding EBV-related bowel perforation is scars and a review of the literature detected only six cases with this complication. One of the distinguishing points of our case is that the patient experienced two separate episodes of bowel perforation. The first one was subtler involving only a small portion of the small intestine, but in the second episode distal part of the ileum, right hemicolon, and appendix were all perforated. The possible cause of the difference in severity could be clarified based on the histopathological analysis. While inflammation and necrosis were the only detected pathologies in the first surgical specimen, the second one revealed evidence of malignant EBV-associated lymphoma. Takahashi et al. described lymphoma cell infiltration as the possible cause of bowel perforation.[27] Supporting this statement, other presented cases of bowel perforations were observed in patients with EBV-associated lymphoproliferative disorders.[28–30] Due to the rare nature of this complication, diagnosis is usually not correctly formulated. Xiao et al. described a sudden perforation of ileocecal in an EBV-positive Natural Killer/T-cell lymphoproliferative disorder who was misdiagnosed as an inflammatory bowel disease for a relatively long time due to his prominent digestive disorders.[28] Although we managed to detected EBV DNA in the immunohistochemical analysis ascertaining the diagnosis, some cases failed to achieve positive results.[30]

3.5 | Management

Corticosteroids are generally recommended to alleviate symptoms in certain complicated cases of EBV infection.[31] Since our patient suffered from CNS involvement and thrombocytopenia, corticosteroids were indicated. Antiviral therapy even in severe cases of EBV infection is debated, as on one hand, no definitive consensus confirms its efficacy,[32] and on the other hand, a number of studies reported significant improvement in the symptoms and prognosis.[5,33] In our case, since the patient's condition was continuing to deteriorate and new complications appeared, we planned to initiate an adjuvant antiviral

treatment. Our choice is supported by an in vitro study suggesting that antivirals suppress EBV DNA amplification in infected cells.[34] Trevillyan et al. reported considerable clinicopathological recovery and reduction in CSF EBV DNA following valganciclovir administration.[35] In addition, a case of good recovery on acyclovir alone, even without administrating the recommended corticosteroid therapy has been stated.[13] A significantly lower viral load has been reported in immunocompromised patients with EBV encephalitis who received ganciclovir compared to those who were only receiving supportive treatment.[36,37] In addition, successful use of ganciclovir in immunocompetent patients with severe EBV hepatitis has been stated before.[38] It should be noted that symptomatic management is required in all cases.

4 | CONCLUSION

We report a very rare case of EBV infection with severe neurological, cardiac, and gastrointestinal complications causing multiorgan dysfunction. Since our patient was a young, healthy, immunocompetent man, thinking of EBV as the assumed etiological factor originating all of the complications was tricky. This article aims to lead the audiences' minds toward the unusual presenting faces of EBV infections so that one would be able to provide timely accordant management.

AUTHOR CONTRIBUTIONS

Kiana Shirani: Conceptualization; project administration; resources; supervision; validation. **Saina Paymannejad:** Data curation; investigation; methodology; visualization; writing – original draft; writing – review and editing. **mohammad amin najafi:** Methodology; project administration; validation; writing – review and editing. **Farzin Khorvash:** Conceptualization; project administration; resources; supervision. **Farid Shamlou:** Data curation; investigation; methodology; visualization; writing – original draft.

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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