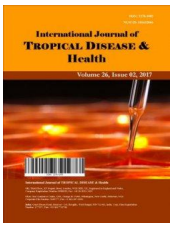

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Multiorgan Failure Associated with Epstein-Barr Viremia-An Elusive Diagnosis: A Case Series

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Authors' contributions

This work was carried out in collaboration between all authors. Author AA designed the study and was the primary consultant in first two cases. He contributed to the conception, draft, analysis, revision and final approval of the work to be published. Author MA was involved with data acquisition, tabulation, grammar and literature search for the study. Author AS contributed to data acquisition of images and was actively involved in the critical care management of the cases reported. Author SBJ was primary consultant in case 3. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Fulminant Epstein Barr Virus (EBV), also known as (herpes simplex virus-4(HSV-4) induced multiple organ failure is rarely reported and should be considered a potential diagnosis in patients with multiple organ failure. From a clinical perspective, it should be remembered that fulminant herpes simplex Virus (HSV) infection may masquerade as "routine" bacterial severe sepsis/septic shock. This potentially fatal condition should be diagnosed early and treated. Here we describe three cases who were admitted with multi organ dysfunction and two of them finally deceasing in a septic shock with multi organ failure. No bacterial or fungal infection could be detected in one of these cases and were adequately treated in other two cases. The presence of EBV (HSV-4) was detected in plasma confirming EBV viremia. The presentation, clinical course and management are discussed.

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Keywords: Epstein barr virus; human herpes virus-4 (HHV-4); multi organ failure; sepsis; immunocompetent.

1. INTRODUCTION

There are 9 herpes virus types known to infect humans: herpes simplex viruses 1 and 2, HSV-1 and HSV-2, (also known as HHV1 and HHV2), varicella-zoster virus (VZV,also known as HHV-3), Epstein–Barr virus (EBV or HHV-4), human cytomegalovirus (HCMV or HHV-5), human herpes virus 6A and 6B (HHV6A and HHV-6B), human herpes virus 7 (HHV-7), and Kaposi's sarcoma-associated herpes virus (KSHV, also known as HHV-8). In total, there are more than 130 herpes viruses [1]. EBV share with other herpes viruses the feature of initial infection of young hosts, establishment of latency, and "reactivation" later in life, with variable consequences. Thus, it generally affects immunocompromised individuals as a result of de novo infection or reactivation of the latent infection. In immunocompromised patients such as post transplant, cancer chemotherapy, autoimmune disease, malnutrition, burns or human immunodeficiency virus infection, reactivation of these viruses may have serious outcomes. The pathogenesis of these infections is not completely understood, but certainly multifaceted [2].

Here, we report three cases of EBV associated hepatitis, pneumonitis and Multiorgan failure in immunocompetent patients. EBV must be considered in all patients presenting with liver & respiratory failure of unknown cause or persistent multi organ dysfunction despite adequate management of associated co-pathogens. If suspected, prompt treatment with anti viral drugs should be initiated.

2. CASE REPORT

2.1 Case 1

Ms SG, 42 year, known case of hypertension, was admitted on 06.08.2017 through triage in medical intensive care unit (MICU) with a history of shortness of breath (orthopnea), pain abdomen in right upper quadrant, occasional loose stools and vomiting of 4-5 days duration. She had three admissions at tertiary centers in past two months for similar symptoms with fever off and on and was diagnosed to have right lung pneumonitis, pulmonary edema, moderate pulmonary hypertension, mild bilateral pleural effusion, erosive gastritis, and sepsis with multi organ dysfunction. Her blood and other body fluid cultures done outside were persistently sterile in last two months. On examination she was febrile, pulse 98/minute, BP 108/62 mm Hg, oxygen saturation 90-91% on room air, mild tachypnea with respiratory rate 24/minute. She had pan systolic grade 3/6 murmur, bibasal fine crepitations and non tender hepatomegaly. Her investigations are shown in Table 1. She was diagnosed to have multi-organ dysfunction with sepsis. She had metabolic acidosis with high lactate, transaminitis, coagulopathy, pneumonitis (Fig. 1) with hypoxemia, polyserositis, azotemia, leucocytosis, raised inflammatory markers, high leukocyte counts, and later raised procalcitonin .She also had moderate pulmonary hypertension with features of right heart failure. Her serology for anti nuclear antibody (ANA), hepatitis A, B, C and E, anti neutrophil cytoplasmic antibody (ANCA), leptospira and human immunodeficiency virus were negative. Her nasopharyngeal swab for Influenza A (H1N1-2009) and all cultures were also negative. She was managed with antibiotics (initially cefoperazone+sulbactum, moxifloxacin, later meropenem, aztreonem, and colisitn), diuretics, antihypertensives, methylprednisolone, blood and blood products and other supportive management. However she progressively deteriorated, developed hypotension, was intubated and mechanically ventilated on 11.08.2017. Hemodialysis was also done .Syndromic evaluation system (SES) panel was done on blood on 11.08.2017 which detects DNA of 6 gram positive bacteria, 11 gram negative bacteria, 3 fungi (*Candida*, *Aspergillus* and *Cryptococcus neoformans*), 8 viruses and 1 parasite (*Toxoplasma gondii*). However, she developed resistant hypotension, severe metabolic acidosis and succumbed to her illness on 12.08.17. Later her SES panel report received on 12.08.2017 was positive for human herpes virus-6(HHV-6) and epstein barr virus (EBV) in blood sample. Autopsy was declined by the family.

2.2 Case 2

Mr.SK,17 years, attended triage on 19.09.2017 with the complaints of diffuse body-aches, sore throat, swelling in left thigh, breathlessness, occasional loose stools and fever off and on for last 4-5 days. He had primary dengue fever

(Dengue NS1 detected) on 07.09.2017 and was admitted outside where he received antibiotics and symptomatic treatment. On examination he was febrile 101^0F, pulse 130/minute, BP 114/60 mm Hg ,oxygen saturation 93% on room air, respiratory rate 39/minute, few oropharyngeal ulcers, bibasal coarse crepitations, mild (just palpable) hepatosplenomegaly, tender swelling over left thigh and gluteal area, and few ulcers on both lateral upper third of thighs. He was admitted in MICU and further evaluated. His abdomen ultrasound showed mild hepato-splenomegaly, bilateral mild pleural effusion and minimal ascites (evidence of plasma leakage), enlarged right iliac and inguinal lymph nodes. Ultrasound of left thigh showed edema in subcutaneous tissue and myofascial planes. With plasma leakage and persistent symptoms he was evaluated to rule out associated other tropical diseases. His investigations are tabulated in Table 1. He was diagnosed to have expanded dengue fever with myocarditis, myositis, panniculitis, and multiorgan dysfunction. He had mild transaminitis, bilateral pneumonitis (Fig. 2), developed ulcers on gluteal and leg areas (Fig. 3), mediastinal and peripheral lymphadenopathy. He had persistent fever and raised inflammatory markers. His venous doppler for lower limbs, serology for HIV, HBsAg, Hepatitis C virus, leptospira antibody, nasopharyngeal swab for influenza A(H1N1-2009), *Salmonella typhii* IgM, chikungunya virus IgM antibody, Scrub typhus IgM antibody, and malaria parasite antigen were negative. ANA by IFA was moderately positive (1:320,++ grade) with homogeneous pattern. All his cultures (blood, urine, and swab from ulcer bed) were sterile. With a possibility of vasculitic ulcer, he was given 250 mg of methylprednisolone for 3 days. However, ANCA(c and p) and extractable nuclear antigens (ENA) were not detected. With persistence of fever, lymphadenopathy, panniculitis, and myositis with marked aches his blood was sent for SES panel which detected DNA for *staphylococcus aureus* and EBV. He was treated with supportive treatment, clindamycin, piperacillin+tazobactum, and azithromycin, which were later changed to colistin, teicoplanin and meropenem. After SES panel report antibiotics were changed to intravenous vancomycin and acyclovir. With antiviral treatment he became afebrile and was discharged on 02.10.2017. His cutaneous ulcers healed. Presence of EBV DNA in blood and positive EBV IgG serology suggests that he had virus reactivation secondary to underlying infection leading to EBV viremia.

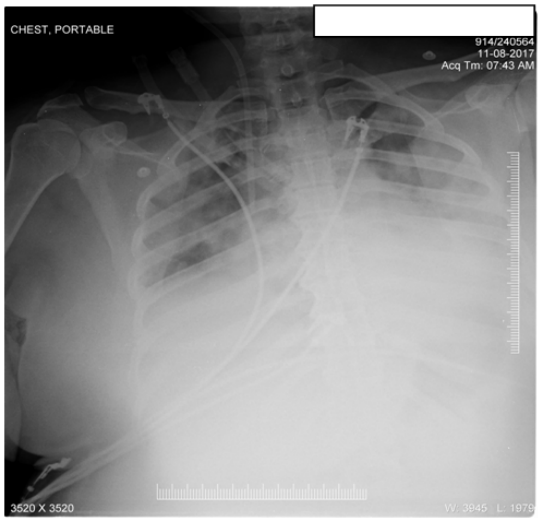

Fig. 1. X-ray chest 11.08.2017 (case 1) showing bilateral pneumonitis with? pleural effusion

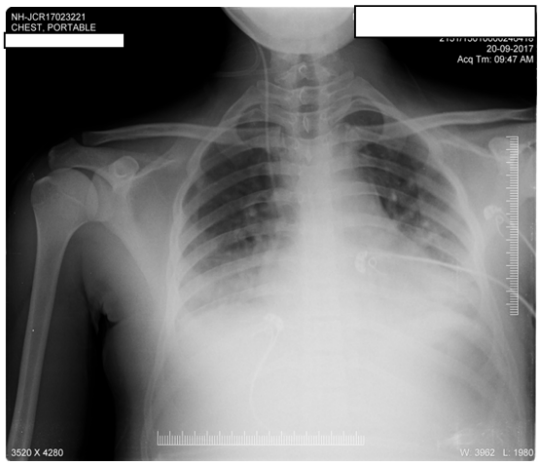

Fig. 2. X ray chest dated 20.09.2017 (case 2) showing bibasal pneumonitis with bilateral mild pleural effusion

2.3 Case 3

Mr. SJ, 48 years, known case of alcoholism, chronic liver disease, portal hypertension, chronic kidney disease-renal failure, on maintenance hemodialysis, was admitted on 18.09.2017 with the complaints of fever, cough and weakness of four days duration. On examination he was febrile 99.4°F, pulse 114/minute, BP 90/60 mm Hg, oxygen saturation 94% on room air, respiratory rate 37/minute, bilateral coarse crepitations, mild splenomegaly, free fluid in abdomen, and mild pedal edema. Rest of the systemic examination was

unremarkable. His investigations are mentioned in Table 1. USG showed evidence of chronic liver disease, splenomegaly, portal hypertension, moderate to gross ascites, bilateral bright small kidneys with loss of corticomedullary differentiation, and right renal calculus with few concretions-ray chest showed bilateral pneumonitis (Fig. 4). He was managed as suspected infective endocarditis with sepsis and multi organ dysfunction syndrome with meropenem, clarithromycin, vasopressors, supportive treatment and maintenance hemodialysis. However, his fever persisted and he had to be intubated and mechanically ventilated on 29.09.2017.Later SES panel test reported on 27.09.2017 on blood detected DNA of *pseudomonas aeruginosa* and EBV. His serology for IgM and IgG EBV antibodies was negative confirming it to be a acute primary (newly acquired) EBV viremia. Colisitin was added in modified renal doses. Acyclovir, however was not added in view of deteriorating renal status. He succumbed to his illness on 29.09.2017. Autopsy was refused by his family.

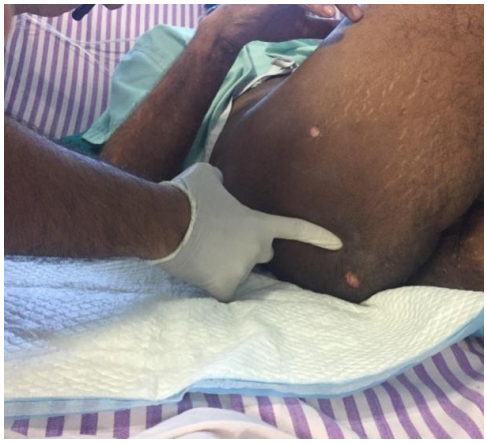

Fig. 3. Punched out superficial ulcers on right gluteal and upper lateral thigh in case 2

3. DISCUSSION

The Epstein–Barr virus (EBV) was discovered 51 years ago by electron microscopy of cells cultured from Burkitt's lymphoma tissue by Epstein, Achong, and Barr [1]. It is a ubiquitous virus that infects at least 95% of the population. Most persons are infected during infancy and early childhood and are asymptomatic or have nonspecific symptoms [3]. It can be reactivated without causing symptoms of illness, but reactivation has potential to create chaos in the immune system.

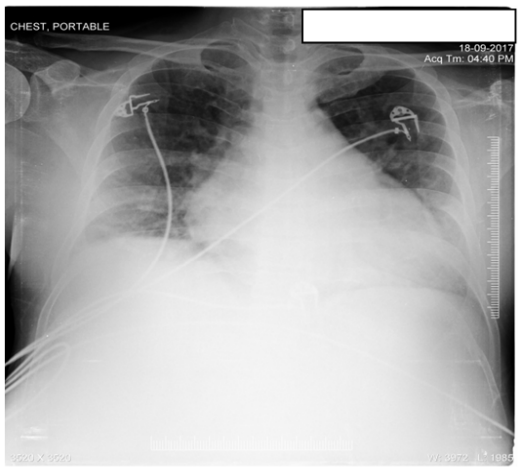

Fig. 4. X ray chest dated 18.09.2017 (case 3) showing cardiomegaly with bibasal pneumonitis

In developed countries the incidence of viral sepsis is believed to be less than 1% of septic episodes of patients admitted to intensive care [2]. Though rare, nevertheless, they could be the cause for sepsis and should be thought of. We have presented three immune competent cases with EBV viremia who presented as severe sepsis along with underlying other co-infection in two of them. Case 1 had multi organ dysfunction related to EBV viremia along with HHV6 virus infection. She succumbed to her illness. Case 2 had recent dengue infection, presented with Multiorgan dysfunction and had EBV viremia along with staphylococcal aureus infection. He responded to acyclovir, corticosteroids and anti staphylococcal antibiotics. He was successfully discharged. Case 3 had co-infection with *Pseudomonas aeruginosa* along with EBV viremia. He was treated with anti pseudomonas drugs but antiviral were not given in view of deteriorating renal status. He also succumbed to his illness.

EBV DNA was detected in EDTA (ethylenediaminetetraacetic acid) plasma samples in all these three cases indicating florid systemic infection. Viremia and dissemination to viscera in adults are rare and can predominantly be seen in immunocompromised individuals like patients with hemato-oncologic malignancies, transplant recipients, or due to immunosuppressive medication. However, none of these three adult cases were immunocompromised.

Table 1. Multi organ failure associated with EBV among the cases investigated

Test	Normal value	Case 1	Case 2	Case 3
Lowest hemoglobin	12-15 gm/dl	7.8	8.7	7.6
Highest TLC	4-10x10^3/cmm	24.65	29.3	27.07
Lowest platelet counts	150-400x10^3/ul	50	36	31
ESR	0-10 mm 1st hour	25	110	
CRP	<=3 mg/L	116	31.2	
S. Procalcitonin	< 0.5 ng/ml	< 0.5 on 06.08.17 >10.0 on 11.08.17	>2<10 on 22.09.17	>2<10 on 25.09.17
S.Ferritin	10-232 ng/ml	446	1190	
BUN	7-18 mg/dl	89.27	31.25	69.99
Serum creatinine	0.6-1 mg/dl	4.76	2.28	9.73
S.Total Proteins	6.4-8.2 gm/dl	5.57	5.09	6.49
S. Albumin	3.5-5.0 gm/dl	2.62	1.74	2.95
S. Total bilirubin	0-1.3 mg/dl	5.87	1.84	1.50
S.Direct bilirubin	0-0.3 mg/dl	3.38	1.02	0.72
AST	15-37 U/L	4750	113.2	30.1
ALT	30-65 U/L	4164	40.4	28.6
S.ALP	50-136U/L	95.2	134	100.6
PT-INR	0.9-1.1	4.76	1.69	2.09
D-Dimer	0-0.5 ug/ml	10.03		
Creatine Kinase	< 235 U/L		1226	
Weil felix Test		OX2 1:80 OX19 NR OXK NR		
Cultures	Sterile	Blood/urine/ET: sterile	Blood/urine/pus swabs: sterile	Blood/urine/ascitic fluid/ET: sterile
SES Panel	Not detected	HHV 6 DNA detected EBV DNA detected	*Staphylococcus Aureus* DNA detected EBV DNA detected	*Pseudomonas Aeruginosa* DNA detected EBV DNA detected
EBV serology	IgM <8 U/ml IgG <8 U/ml	Not done	IgM:2.50 IgG:59.68	IgM:3.47 IgG:7.03
ABG		pH7.370,pCO2 12.9 mm Hg, pO2 96.2 mm Hg, HCO3 7.3 mmol/L, BE(ecf) (-) 18,sO2 96.6%, Lactate 11.38 mmol/L	pH7.424,pCO2 25.4 mm Hg, pO2 61.7 mm Hg,HCO3 19.2 mmol/L, BE(ecf) (-) 8.1, sO2 92.7%, Lactate 3.3 mmol/L	pH7.408,pCO2 38.1 mm Hg, pO2 64.3 mm Hg,HCO3 23.5 mmol/L, BE(ecf) (-) 1.2, sO2 92.8%.
Cardiac markers CK-MB BNP TNI	0-4.3 ng/ml 0-100 pg/ml 0-0.02ng/ml	<1.0 910 <0.01	6.8 1560 <0.01	
ECHO		RA, RV dilated, 5 mm small perimembranous VSD, mild to	Mild TR, mild pulmonary Hypertension RVSP 44 mm	Suspicion of mobile vegetation on thickened aortic valve, mild MR,

	moderate TR, moderate pulmonary hypertension. RVSP 60 mm Hg.	Hg.LVEF 50%	moderate TR, moderate pulmonary hypertension, RVSP 51 mm Hg, Grade 1 LV DRA, mild pericardial effusion.
NCCT abdomen	Mild free fluid seen in perihepatic, subhepatic, right paracolic gutter and pelvis. Mild hepatomegaly. Small b/l renal concretions.		
NCCT/CECT Chest with CTPA	Mild cardiomegaly. Prominent Pulmonary arteries. No e/o PTE. Focal Ground glass attenuation changes in Right upper and middle lobe. Pleural Thickening, reticular opacities, atelactatic Changes in b/l lower lobes. Minimal Right pleural effusion.	Symmetric multifocal areas of parenchyma consolidation and ground glass attenuation changes. Multiple mediastinal lymph nodes < 12mm,bilateral minimal pleural effusion, mild cardiomegaly with mildly dilated pulmonary arteries.	

SES: Syndrome evaluation system; BNP: B type natriuretic peptide; TNI: Troponin I; HHV: Human herpes virus; RVSP: Right ventricular systolic pressure; LVEF: Left ventricular ejection fraction; DRA: Diastolic relaxation abnormality

Whether primary or reactivation, they can be an important cause of morbidity and mortality. Primary EBV infection is often asymptomatic, especially in children. In young adults, the infection causes EBV associated Infectious Mononucleosis (IM), a febrile pharyngitis with prominent cervical lymphadenopathy and significant fatigue and malaise. Usually, recovery is complete within a few weeks, although cases lasting several months have been reported in literature. Complications may be due to tissue-invasive viral disease or to immune-mediated damage. The following complications, listed alphabetically, have been described for less than 1% of patients: conjunctivitis, hemolytic anemia, hemophagocytic syndrome, hepatitis, and interstitial nephritis, and myocarditis, neurologic diseases other than meningoencephalitis, pancreatitis, parotitis, pericarditis, pneumonitis, psychological disorders, and splenic rupture. [4,5,6,7,8] these complications are uncommon, but point to the diversity of clinical manifestations of acute EBV infection.

The pathogenesis of these infections is not completely understood. EBV is immunopathogenic, involving an activated and distorted immune system. EBV infected B cells are transformed and tend to proliferate spontaneously and if uncontrolled it can result in serious and fatal disease. This infection does not cause illness by causing lyses of tissues as seen in cytomegalovirus (CMV) infection, but by causing immune suppression of these proliferating B cells [4]. Acute EBV can also cause a hemophagocytic syndrome, a sepsis-like syndrome caused by EBV triggering widespread macrophage activation and histiocytosis leading to a cytokine storm with multiple organ failure [4,5,9,10]. None of the three cases fulfilled criteria for secondary hemophagocytic lymphohistiocytosis syndrome (sHLHS). EBV can

also result in a broad spectrum of neoplasm's and lymphoproliferative states including Burkitt's lymphoma, Hodgkin's lymphoma, post transplant lymphoproliferative disorder, X-linked lymphoproliferative disorder, primary CNS lymphoma, nasopharyngeal carcinomas of Southeast Asia, T cell and NK cell lymphomas, and leiomyosarcomas [4].

These viral infections need to be recognized early in their course so that antiviral intervention or other therapies can be affected promptly. The demonstration of the appropriate serologic findings, viral antigens, and DNA confirm the diagnosis. In all three cases detection of EBV DNA in blood confirmed acute viremia. Serology could not be done in case 1 as we did not suspected it to be the underlying cause and the report of DNA PCR was received after the patient succumbed to her disease. In case 2 serology suggested it to be a reactivation viremia and in case 3 it appeared to be a de-novo acquired infection.

One of the mimics of EBV is HHV6 disease [11]. HHV6 and EBV DNA were isolated from the blood of case 1. HHV-6 comprises 2 forms, A and B and HHV-6A and HHV-6B are officially considered distinct species rather than a variant of 1 species .Sub typing was not done in this case as it wasn't available. Acute HHV-6 infection is rare in immunocompetent adults but may manifest as a mononucleosis like illness characterized by fever, lymphadenopathy, and hepatitis or encephalitis. This patient had thrombocytopenia, azotemia, fulminant hepatitis, coagulopathy, and pneumonitis. EBV and HHV6 PCR assay were positive in her blood and she had no evidence of any other co-infection. How much symptoms were contributed by either of the two viruses cannot be commented but it does show that primary infection with two different herpes viruses may occur simultaneously or in close succession, adversely affecting the course of the disease.

Case 2 had oral and cutaneous ulcers as described earlier. A variety of cutaneous, mucosal and even genital ulcerations have been described in infectious mononucleosis [12,13]. Though we did not do any biopsy of the lesion and since tests for vasculitis were negative (ANA, ANCA), these cutaneous lesions could be attributed to herpes virus infection.

As regards management, the mainstay of treatment for patients with EBV associated infectious mononucleosis and other manifestations of primary EBV disease is supportive care. Studies focusing on steroid therapy alone have been imperfect but do suggest that these agents induce a modest improvement with diminishment of lymphoid and mucosal swelling [14]. A trial of corticosteroids is warranted in individuals with impending airway and should be considered in those suffering from severe overwhelming life-threatening infection (e.g., liver failure) or other severe complications such as aplastic anemia. Acyclovir is a nucleoside analogue that inhibits permissive EBV infection through inhibition of EBV DNA polymerase but has no effect on latent infection. We could not treat case 1 with these therapies as diagnosis was made posthoumously. Case 2 was managed with acyclovir and corticosteroids and responded to treatment. His ulcers healed and lymphadenopathy subsided. Case 3 expired within 48 hours of diagnosis of EBV viremia. He was not considered for acyclovir due to chronic kidney disease stage 5 with severe azotemia.

Is EBV virus the primary cause of sepsis and multi-organ failure, or does detectable EBV in the blood stream represent viral reactivation in an individual whose immune system is impaired by ongoing sepsis syndrome by another causative organism or other underlying disease needs further clinical research. All these three cases were immunocompetent. Nevertheless, our case series highlights that in a patient with unexplained fever, multi organ dysfunction, sepsis with no evidence of any other co-infection or even if present and adequately treated, clinician should take into consideration of viral sepsis as a possibility and do every effort to salvage the patient. We would also emphasize that in addition to supportive intensive care in these patients, a delay in diagnosis and initiation of specific antiviral therapy and immunosuppressive treatment (if there is evidence of sHLHS) could contribute to the poor clinical outcome.

4. CONCLUSION

1. Primary infection with two different herpes viruses may occur simultaneously or in close succession, and may adversely affect the course of the disease.
2. Viral infections, though reported to be the causative agent in 1% of sepsis and multi organ dysfunction cases, should be considered if there is no usual causative agent in cultures or even if present, it has been adequately treated.

3. Early virological diagnosis and timely initiation of specific antiviral therapy is advisable to decrease morbidity and mortality. These viruses must be considered in all patients presenting with liver and respiratory failure of unknown cause.
4. EBV and other HHV may cause severe disease even in immunocompetent persons.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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