Herpes simplex virus associated sepsis in an immunocompetent adult: the value of next-generation sequencing

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To the Editor: A previously healthy 33-year-old Chinese man initially presented to local hospital with fever, upper abdominal pain, vomiting, and diarrhea over a period of 5 days. Laboratory findings of local medical center revealed liver and kidney function impairments. The patient was treated for suspected bacterial infection and anuria. On illness day 8, the patient became confused and disoriented. He was transferred to our emergency room. Initial investigations showed severe elevations of transaminases and moderate coagulopathy [Table 1]. Viral serologies for hepatitis A, B, C, and E were negative. Chest X-ray was normal. Computed tomography of brain and abdomen showed hepatomegaly and a small amount of ascites. On illness day 10, he developed status epilepticus and was intubated for airway protection. The relatives denied history of alcohol abuse, illicit drug use, and orolabial lesions. The patient was admitted to intensive care unit for further management on illness day 10.

On admission, the patient's Glasgow coma scale was E1V1M1. Pulse rate was 105 beats per min. Other vital signs were normal. There were no orolabial lesions. The physical examination was unremarkable. Serological tests for Herpes simplex viruses (HSV)-IgM, Coxsackievirus A16-IgM, Toxoplasma-IgM, Rubella virus-IgM, Cytomegalovirus-IgM, Parvovirus B19-IgM, and Cytomegalovirus-DNA were negative. Blood and urine cultures were negative. Epstein-Barr virus (EBV)-DNA in peripheral blood was 5400 copies/mL. Anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, antibodies for primary biliary cholangitis and autoimmune hepatitis were negative. Twenty-eight hours after admission, the patient's clinical condition deteriorated with severe hypotension. Pulmonary artery catheter revealed cardiac output of 10.2 L/min and systemic vascular resistance of 384 dynes.s·cm^{-5} with blood pressure of 74/53 mmHg. The patient died in refractory hypotension in spite of aggressive support on illness day 12. The family disagreed to an autopsy. On the next day after his death, next-generation sequencing (NGS) of the patient's blood revealed 14,054 reads of HSV-1 DNA. The coverage rate of HSV-1 genome was 87.03% [Supplementary Figure 1, http://links.lww.com/CM9/A265]. HSV-1 infection was confirmed by positive HSV-1 polymerase chain reaction (PCR) of stored sera obtained antemortem. On the contrary, both IgG and IgM for HSV-1 and HIV-2 were negative. Detailed information was shown in Table 1.

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Early administering antibiotic has been shown to decrease mortality. However, rapid and specific pathogen identification is more important than broad antibiotics for atypical infection with rare etiology, such as the case we reported. For HSV-sepsis, the high mortality is largely due to the non-specific clinical presentation, lack of awareness, delay in diagnosis and therapy.[2] Our report suggested that NGS might be helpful in identification of certain microbial pathogens in sepsis as etiologic agents and subsequently beneficially impact patient care.[3]

Fulminant HSV hepatitis with liver failure should be considered in this patient for international normalized ratio 2.01 and status epilepticus. The diagnostic gold standard of HSV hepatitis is the liver biopsy. We did not perform liver biopsy because of high bleeding risk. We acknowledge this as a limitation of our case. However, for either HSV hepatitis or sepsis, earlier initiation of systemic acyclovir would be the key role of managements. This highlighted the advantage of NGS for rapid universal pathogen detection, especially for critically ill patients.

The presence of EBV DNA and absence of HSV IgM might suggest EBV-associated hemophagocytic syndrome. However, the copy number of our patient was similar to patients with no EBV disease as described by Kanakry *et al*.[4] Meanwhile, a positive PCR without serology of HSV would be highly likely to represent acute infection course.[5]

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Table 1: Laboratory findings and management of the patient.

Items	Day 7 Local hospital	Day 8 Local hospital	Day 9 22:00 ER arrival	Day 10 05:00	Day 10 10:00 ICU admission	Day 10 16:00	Day 11 05:00	Day 11 21:00	Day 12 01:00
Laboratory findings									
WBC ($\times10^9$/L)	3.3	1.14	5.79	7.62	6.55	5.53	4.36	5.33	4.32
Lymphocytes ($\times10^9$/L)		0.49	0.84	2.20	1.24	1.59	1.24	0.99	0.31
Hemoglobin (g/L)		150	137	141	129	127	115	56	70
Platelets ($\times10^9$/L)	118	97	81	117	86	74	64	40	36
Albumin (g/L)			31		30		35	27	
T/DBil (μmol/L)		15.8/13.9	52.9/47.9	48.0/44.0	53.2/49.0		74.6/63.1	61.7/50.9	
ALT/AST (U/L)		2487/5405	7799/–	4575/15,284	3723/–		4701/18,105	3521/–	
PT (s)			22.6	23.7	24.5	23.5	17.5	22.1	20.7
aPTT (s)			80.8	92.8	73.1	71.5	60.9	67.2	63.8
TT (s)			>150.0	>150.0	137.1	113.8	75.7	59.0	41.0
INR			2.01	2.11	2.21	2.09	1.53	1.96	1.83
Fibrinogen (g/L)			1.83	1.57	1.51	1.48	1.71	0.97	1.28
D-Dimer (mg/L)			23.21	22.11	21.80	21.82	16.68	8.23	6.30
Lactate (mmol/L)			1.7		1.8	1.9	2.5	8.0	12.8
Creatinine (μmol/L)		228	365	419	516		372	341	
BUN (mmol/L)		18.1	15.99	19.6	22.83		17.30	14.56	
Management									
FFP Transfusion (mL)				800		1000	1000	1600	
RBC transfusion (U)								7.5	
NE (μg/kg per min)							0	1.50	1.67

ER: Emergency room; WBC: White blood cells; T/DBil: Total/direct bilirubin; ALT/AST: Alanine transaminase/aspartate transaminase; PT: Prothrombin Time; aPTT: Activated partial thromboplastin time; TT: Thrombin time; INR: International normalized ratio; BUN: Blood urea nitrogen; FFP: Fresh frozen plasma; RBC: Red blood cell; NE: Norepinephrine; –: No data.

In conclusion, NGS might be a promising single, universal pathogen detection method for sepsis with rare etiology.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the article. The patient understands that his name and initials will not be published and due efforts will be made to conceal the identity of the patient, although anonymity cannot be guaranteed.

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Conflicts of interest

None.

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