

# World Journal of *Clinical Cases*

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## REVIEW

- 3932 Liver replacement therapy with extracorporeal blood purification techniques current knowledge and future directions

*Papamichalis P, Oikonomou KG, Valsamaki A, Xanthoudaki M, Katsiafylloudis P, Papapostolou E, Skoura AL, Papamichalis M, Karvouniaris M, Koutras A, Vaitis E, Sarchosi S, Papadogoulas A, Papadopoulos D*

## MINIREVIEWS

- 3949 Prediction models for recurrence in patients with small bowel bleeding  
*Kim JH, Nam SJ*
- 3958 Investigation of possible relationship between atopic dermatitis and salivary biomarkers, stress, and sleep disorders  
*Estefan J, Ferreira DC, Cavalcante FS, dos Santos KRN, Ribeiro M*
- 3967 Value of clinical applications of differential pressure and relative pressure imaging in the left ventricle  
*Zheng AS, Yu HX*
- 3976 Low-dose immunotherapy as a potentiator to increase the response with neo-adjuvant chemotherapy in oral cancers  
*Rathinasamy N, Muthu S, Krishnan A*
- 3980 Kidney disease in patients with chronic liver disease: Does sex matter?  
*Cooper KM, Colletta A, Moulton K, Ralto KM, Devuni D*

## ORIGINAL ARTICLE

## Case Control Study

- 3993 Elabela is a reliable biomarker for predicting early onset preeclampsia: A comparative study  
*Amer Ali E, Nori W, Salman AF, Al-Rawi TSS, Hameed BH, Al-Ani RM*

## Retrospective Cohort Study

- 4003 Acute-on-chronic liver failure is independently associated with higher mortality for cirrhotic patients with acute esophageal variceal hemorrhage: Retrospective cohort study  
*Terres AZ, Balbinot RS, Muscope ALF, Longen ML, Schena B, Cini BT, Rost Jr GL, Balensiefer JIL, Eberhardt LZ, Balbinot RA, Balbinot SS, Soldara J*

## Retrospective Study

- 4019 Elastic fiber degradation in the development of pediatric granuloma annulare: Report of 39 cases  
*Zhang DY, Zhang L, Yang QY, Xie YC, Jiang HC, Li JZ, Shu H*

- 4026** Anti-bacterial mechanism of baicalin-tobramycin combination on carbapenem-resistant *Pseudomonas aeruginosa*  
Jin LM, Shen H, Che XY, Jin Y, Yuan CM, Zhang NH

### SYSTEMATIC REVIEWS

- 4035** Acknowledging the use of botanicals to treat diabetic foot ulcer during the 21<sup>st</sup> century: A systematic review  
Narzary I, Swarnakar A, Kalita M, Middha SK, Usha T, Babu D, Mochahary B, Brahma S, Basumatary J, Goyal AK

### CASE REPORT

- 4060** Pregabalin induced balance disorder, asthenia, edema, and constipation in an elderly adult: A case report  
Ma LP, Wen C, Zhao TX, Jiang XM, Gu J
- 4065** Emergency internal iliac artery temporary occlusion after massive hemorrhage during surgery of cesarean scar pregnancy: A case report  
Xie JP, Chen LL, Lv W, Li W, Fang H, Zhu G
- 4072** Hemophagocytic lymphohistiocytosis after autologous stem cell transplantation in angioimmunoblastic T-cell lymphoma: A case report  
Zhang ZR, Dou AX, Liu Y, Zhu HB, Jia HP, Kong QH, Sun LK, Qin AQ
- 4079** Successful reconstruction of an ankle defect with free tissue transfer in a hemophilia A patient with repetitive hemoarthrosis: A case report  
Lee DY, Lim S, Eo S, Yoon JS
- 4084** Primary pelvic *Echinococcus granulosus* infection: A case report  
Abulaiti Y, Kadi A, Tayier B, Tuerkan T, Shalayiadang P, Abulizi A, Ahan A
- 4090** Epstein-Barr virus-induced infection-associated hemophagocytic lymphohistiocytosis with acute liver injury: A case report  
Sun FY, Ouyang BQ, Li XX, Zhang T, Feng WT, Han YG
- 4098** Cardiac arrest secondary to pulmonary embolism treated with extracorporeal cardiopulmonary resuscitation: Six case reports  
Qiu MS, Deng YJ, Yang X, Shao HQ
- 4105** Flared inflammatory episode transforms advanced myelodysplastic syndrome into aplastic pancytopenia: A case report and literature review  
Ju B, Xiu NN, Xu J, Yang XD, Sun XY, Zhao XC
- 4117** Frontal penetrating arrow injury: A case report  
Rodríguez-Ramos A, Zapata-Castilleja CA, Treviño-González JL, Palacios-Saucedo GC, Sánchez-Cortés RG, Hinojosa-Amaya LG, Nieto-Sanjuanero A, de la O-Cavazos M
- 4123** Chest wall osteochondroma resection with biologic acellular bovine dermal mesh reconstruction in pediatric hereditary multiple exostoses: A case report and review of literature  
Alshehri A

- 4133** Massive pulmonary embolism in Klippel-Trenaunay syndrome after leg raising: A case report  
*Lo CY, Chen KB, Chen LK, Chiou CS*
- 4142** Improved super-elastic Ti-Ni alloy wire intrusion arch for skeletal class II malocclusion combined with deep overbite: A case report  
*Yang CY, Lin CC, Wang LJ, Chen YH, Yu JH*
- 4152** Glucocorticoid pulse therapy in an elderly patient with post-COVID-19 organizing pneumonia: A case report  
*Park S, Jang Y, Koo SM, Nam BD, Yoon HY*
- 4159** Endoscopic and surgical treatment of jejunal gallstone ileus caused by cholecystoduodenal fistula: A case report  
*Fan WJ, Liu M, Feng XX*
- 4168** Application of advanced platelet-rich fibrin for through-and-through bony defect during endodontic surgery: Three case reports and review of the literature  
*Algahtani FN, Almohareb R, Aljamie M, Alkhunaini N, ALHarthi SS, Barakat R*
- 4179** Facial Merkel cell carcinoma in a patient with diabetes and hepatitis B: A case report  
*Ren MY, Shi YJ, Lu W, Fan SS, Tao XH, Ding Y*
- 4187** Pregnancy and lactation-associated osteoporosis with pyogenic spondylitis: A case report  
*Zhai K, Wang L, Wu AF, Qian Y, Huang WM*
- 4194** Hourglass-like constriction of the anterior interosseous nerve in the left forearm: A case report  
*He R, Yu JL, Jin HL, Ng L, Wang JC, Li X, Gai TT, Zhou Y, Li DP*
- 4202** Crohn's disease in human immunodeficiency virus-infected patient: A case report  
*Vinikaite A, Kurlinkus B, Jasinskaite D, Strainiene S, Buineviciute A, Sadauskaite G, Kiudelis V, Kazenaite E*

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## Epstein-Barr virus-induced infection-associated hemophagocytic lymphohistiocytosis with acute liver injury: A case report

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### Abstract

#### BACKGROUND

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory reaction, which is rare and life-threatening. According to the pathogen, HLH is divided into genetic and acquired. The most common form of acquired HLH is infection-associated HLH, of which Herpes viruses, particularly Epstein-Barr virus (EBV), are the leading infectious triggers. However, it is difficult to distinguish between simple infection with EBV and EBV-induced infection-associated HLH since both can destroy the whole-body system, particularly the liver, thereby increasing the difficulty of diagnosis and treatment.

#### CASE SUMMARY

This paper elaborates a case about EBV-induced infection-associated HLH and acute liver injury, aiming to propose clinical guides for the early detection and treatment of patients with EBV-induced infection-associated HLH. The patient was categorized as acquired hemophagocytic syndrome in adults. After the ganciclovir antiviral treatment combined with meropenem antibacterial therapy and methylprednisolone inhibition to inflammatory response, gamma globulin enhanced immunotherapy, the patient recovered.

#### CONCLUSION

From the diagnosis and treatment of this patient, attention should be paid to routine EBV detection and a further comprehensive understanding of the disease as well as early recognition and early initiation are keys to patients' survival.

**Key Words:** Epstein-Barr virus; Hemophagocytic lymphohistiocytosis; Computed tomography; Case report

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**Core Tip:** Most Epstein-Barr virus (EBV) infection resolves spontaneous complications. We report a unique case of hemophagocytic lymphohistiocytosis (HLH) complicating EBV infection and acute liver injury. EBV-associated acute liver injury is rare, occurs in children and young adults usually, and has conservative management. It is equivocal in distinguishing simple infection with EBV and EBV-induced infection-associated HLH. The doctor only cares about the symptoms of his/her personal clinical experience and ignores the detection of the EBV, thus, the optimal treatment miss. It is appropriate to comprehend the nature of the malady, searching for the primary cause of the disease in treatment.

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## INTRODUCTION

According to the guidelines of Chinese medical doctor association, hemophagocytic lymphohistiocytosis (HLH) can be divided into familial and acquired. Primary HLH mainly appears during childhood and adult HLH is rarely considered primary HLH[1]. The patient was diagnosed as Epstein-Barr virus (EBV)-induced infection-associated HLH. EBV, are the leading infectious triggers particularly, which can result in the acute liver injury. It is inevitable that EBV destroy the whole functional organs in a quick speed, so that it is too late to protect the other preserved body parts. In this case, the successful treatment of the patient can be because of the early diagnosis and timely standardized treatment in the early stage of the disease. In a word, the tips of preventing the diseases are early detection and normative treatment as soon as possible.

## CASE PRESENTATION

### Chief complaints

A 66-year-old woman with a 2-d history of weakness and poor appetite without a known etiology and a 1-d history of headache, dizziness, and fever presented to Seventh People's Hospital of Shanghai on May 28, 2021. At home, her body temperature was 40 °C, with no other associated symptoms. However, her symptoms were not alleviated despite rest (Figure 1).

### History of present illness

Upon presenting to the emergency department, she was unconscious, sagging, hyperthermic (40 °C), had poor appetite, and was weak. Instant routine blood tests revealed the following results: White blood cell,  $0.50 \times 10^9/L$ ; granulocyte%, 4.0%; lymphocyte%, 94.0%; C-reactive protein, 198.61 mg/L; and procalcitonin (PCT), 15.51 ng/mL. Pereion computed tomography (CT) revealed scattered fibrosis in both lung lobes, with consolidation on left lobe base. Abdominal CT revealed a fatty liver and a thickened appendix with coprolith. The patient was admitted and diagnosed with agranulocytosis after a discussion with the intensive care unit doctor. The patient was unconscious, lethargic, sagging, and weak had poor appetite, and was hyperthermic. Moreover, the amount of urine was within the normal range; however, stool unresolved since she had been admitted to the hospital.

### History of past illness

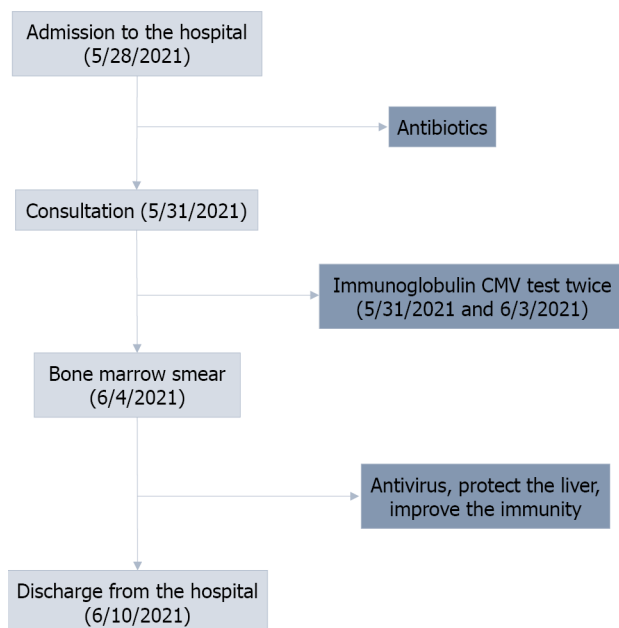
The patient was previously well and was not using any specific drugs.

### Personal and family history

The patient had no history of associated diseases and had no drinking or smoking habits.

### Physical examination

On physical examination, the patient was drowsy; sagging; with yellowish sclerae; and had left inguinal lymphoglandular swelling, with a hard texture, no tenderness, and no adhesion with neighboring tissues. The abdomen was soft, with no distention, no gastrointestinal movement or peristalsis, no varicosity, no tenderness, no rebound tenderness, no hypochondriac tenderness of the liver and spleen, no tenderness on both kidneys, no ureteral pain, had an accommodation reflex of three times/min, negative pathologic reflex, and positive physiologic reflex.



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Figure 1 The process of treatment and diagnosis. CMV: Cytomegalovirus.

### Laboratory examinations

Test results revealed the following findings on admission: PCT, 16.47 ng/mL; complete blood cell indicated agranulocytosis; the liver function test revealed liver injury; and ultrasonography revealed left inguinal lymphoglandular swelling. Completing the hepatitis-related virus test and assaying the indicators of rheumatism as well as immunization, tumor, autoantibodies, and bone metabolism, the results were negative. However, further virus examination showed that the patient may be infected with a virus and bacteria; therefore, meropenem was initially used following consultation with our hospital antimicrobial management committee. We subsequently invited the professor of Huashan Hospital, Fudan University Infection Department for a consultation. The professor suggested including the detection of cytomegalovirus (CMV), immunoglobulin G (IgG), IgM, CMV DNA, and EB DNA (Table 1) and performing bone marrow aspiration (Figure 2). Peripheral blood smear was performed to determine whether or not a cytophagocytosis phenomenon existed. The abovementioned detections were completed, clearly suggesting an EBV infection (EB DNA,  $2.83 \times 10^4$  IU/mL; CMV < 500 IU/mL which is below the lower limit). Following obtaining consent from the patient's dependents, bone marrow aspiration was performed on June 4, 2021; the result was suggestive of an infection-associated hemophagocytic syndrome (HPS). Therefore, this case was an example of EBV-induced infection-associated HLH with acute liver injury (Tables 1 and 2).

### Imaging examinations

Ultrasonography was performed immediately after admission in the patients. Ultrasonic testing revealed the following findings: 1-2 hypoechoic groups subcutaneously in both inguinal areas, measuring approximately 11 mm × 6 mm on the left, regular morphology, clear boundary, clear cutaneous medullary demarcation, clear lymph node portal structure, and a small amount of blood flow signal. Abdominal contrast-enhanced computed tomography: (1) The local wall at the end of the ileum is thickened and the surrounding fat space is blurred with multiple small lymph nodes, suggestion: Inflammation may exist (Figure 3A); and (2) presence of appendiceal fecal stones (Figure 3B).

## FINAL DIAGNOSIS

EBV-induced infection-associated HLH with acute liver injury.

## TREATMENT

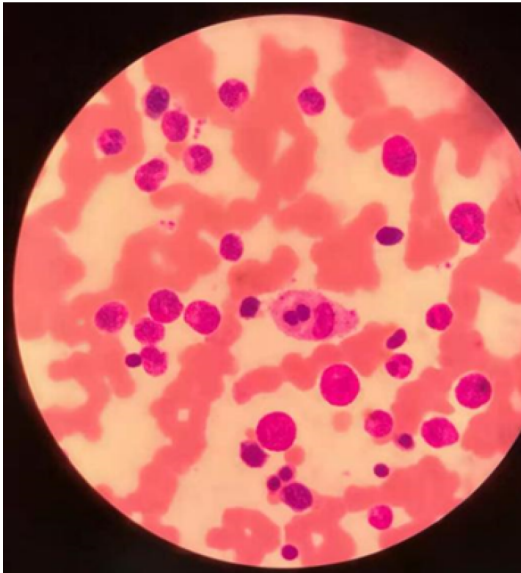
Owing to agranulocytosis, we injected immunoglobulin intramuscularly 0.4 g/kg for 3 d, thereby enhancing immunizing power and lowering infection risk. We adjusted the medication regimen using



**Table 1 Virology assay**

| Item                | May 31 | Jun 3                                  |
|---------------------|--------|--|
| CMV-IgM (AU/mL)     | 0.081  | CMV DNA: < 500 IU/mL                   |
| CMV-IgG (AU/mL)     | > 1000 |  |
| EBV-VCA-IgG (AU/mL) | 30.900 | EB virus DNA: $2.83 \times 10^4$ IU/mL |
| EBV-NA-IgG (AU/mL)  | 6.790  |  |
| EBV-EA-IgG (AU/mL)  | 0.520  |  |
| EBV-EA-IgA (AU/mL)  | 0.070  |  |
| EBV-EA-IgG (AU/mL)  | 0.520  |  |
| EBV-VCA-IgM (AU/mL) | 0.970  |  |
| EBV-VCA-IgA (AU/mL) | 1.960  |  |

CMV: Cytomegalovirus; EBV: Epstein-Barr virus.



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**Figure 2 Bone marrow smear.** 2021.6.4: Visible phagocytes, phagocytic red blood cells, and platelets; granular hyperplasia is significantly active with left shift and dramatic changes.

acyclovir to fight the virus infection; recombinant human granulocyte colony-stimulating factor and 2-(2-ethoxy-2-oxo-1-phenylethyl)-1,3-thiazolidine-4-carboxylic acid (Leucoson) to improve leukocyte formation; and  $\gamma$ -globulin to boost the immunity.

## OUTCOME AND FOLLOW-UP

After a 5-d treatment of fighting infection, enhancing immunity, protecting the liver, and symptomatic supportive care, the WBC count increased to  $12.58 \times 10^9/L$ , and liver and coagulation function returned to the normal range. No discomforts were noted and her relevant indicators were within the normal range.

## DISCUSSION

HPS is also known as HLH, with fever and splenomegaly as the main clinical manifestations. Laboratory determination of macrophages, methemoglobinemia, hypertriglyceridaemia, hypofibrinogenemia, spleen, lymph nodes, and bone marrow detected hemophylic cells[1]. Owing to the low rate of

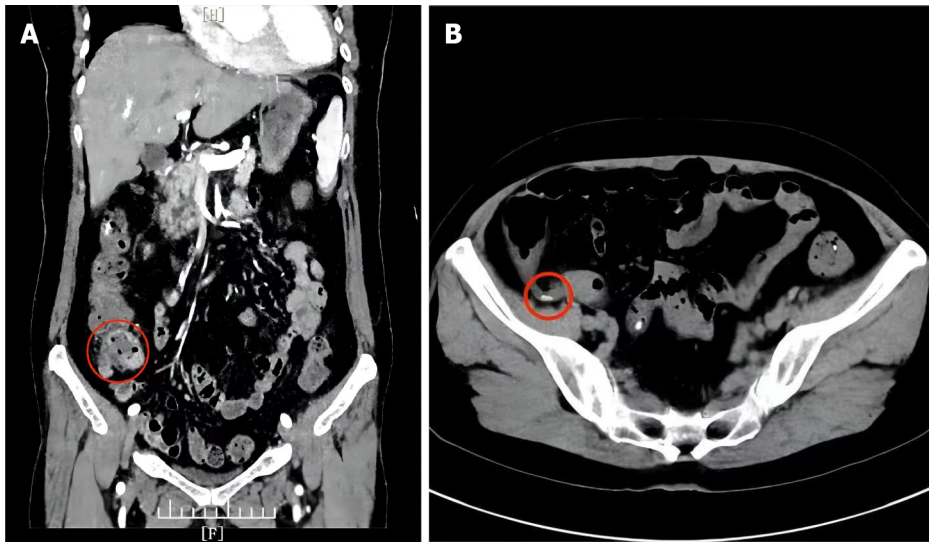
Table 2 Ancillary investigations

| Item                                      | May 28  | June 1 | June 3 | June 10 |
|---|---------|--------|--------|---------|
| White blood cell ( $\times 10^9/L$ )      | 0.25    | 0.51   | 12.58  | 8.76    |
| Neutrophil (%)                            | 8.00    | 4.00   | 60.50  | 73.70   |
| Lymphocyte (%)                            | 88.00   | 62.70  | 25.10  | 20.00   |
| Red blood cell ( $\times 10^{12}/L$ )     | 4.48    | 3.93   | 4.23   | 4.14    |
| Hemoglobin (g/L)                          | 126.00  | 109.00 | 117.00 | 117.00  |
| Platelet ( $\times 10^9/L$ )              | 121.00  | 163.00 | 195.00 | 173.00  |
| C-reactive protein (mg/L)                 | 164.96  | 69.17  | 46.26  | 1.55    |
| Procalcitonin (ng/mL)                     | 16.47   | 1.94   | 0.86   | -       |
| IL-6 (pg/mL)                              | 14.18   | -      | 9.57   | -       |
| IL-8 (pg/mL)                              | 90.13   | -      | 43.15  | -       |
| Alanine aminotransferase (U/L)            | 44.50   | 337.20 | 154.00 | -       |
| Aspartate aminotransferase (U/L)          | -       | 37.70  | 42.80  | -       |
| $\gamma$ -GT (U/L)                        | -       | 221.00 | -      | -       |
| Erythrocyte sedimentation rate (mm/h)     | 50.00   | 102.00 | 63.00  | 51.00   |
| Albumin (g/L)                             | 39.80   | 30.80  | 28.00  | 19.10   |
| Total bilirubin ( $\mu\text{mol/L}$ )     | 90.50   | 37.50  | -      | 12.10   |
| Direct bilirubin ( $\mu\text{mol/L}$ )    | -       | 15.10  | -      | -       |
| Lactate dehydrogenase (U/L)               | 137.90  | -      | 934.30 | -       |
| Ferritin (ng/mL)                          | 1759.00 | > 2000 | -      | -       |
| Triglyceride (mmol/L)                     | 5.08    | -      | 4.89   | -       |
| Prothrombin time (s)                      | 18.90   | 13.40  | 14.10  | 12.70   |
| Activated partial thromboplastin time (s) | 42.60   | 30.90  | 24.80  | 24.50   |
| Fibrinogen (g/L)                          | 7.95    | 9.81   | 7.26   | 4.47    |
| D-Dimers (mg/L)                           | 1.69    | 1.83   | 2.07   | -       |
| International normalized ratio            | 1.51    | 1.10   | 1.15   | -       |
| Total lymphocyte (M/L)                    | -       | 320.00 | -      | -       |
| Total-T-lymphocyte (%)                    | -       | 62.77  | -      | -       |
| Helper T cell CD4 (%)                     | -       | 44.62  | -      | -       |
| Cytotoxic T cell CD8 (%)                  | -       | 9.23   | -      | -       |
| CD4/CD8 ratio                             | -       | 4.83   | -      | -       |
| Total lymphocyte B CD19 (%)               | -       | 28.70  | -      | -       |
| Natural killer cell (CD56 + CD16) (%)     | -       | 18.00  | -      | -       |

IL: Interleukin;  $\gamma$ -GT: Gamma-glutamyltransferase.

correct diagnosis and high mortality rate of HPS in the general population, clinicians lack understanding of the disease.

The first cases of HPS were reported in 1939[2]. According to the etiology, HPS can be divided into familial and acquired. Primary HPS mainly appears during childhood and adult HPS is rarely considered primary HPS. The patient in this report has no known genetic disease or family history; therefore, she was categorized as acquired HPS. In adults, the incidence of acquired HPS is approximately 1 in 800000 individuals[3]. The triggers of HPS in normal adults mainly include infection, tumor, and autoimmune disease[4]. Viral infections, including Herpes virus, particularly EBV and CMV infection, are the most common triggers[4-6]. This is followed by bacteria (mainly *Mycobacterium tuberculosis*), protozoa (mainly *Leishmania*), and fungi (*Histoplasma*)[7]. The most commonly associated



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**Figure 3** Abdominal contrast-enhanced computed tomography. A: The local wall at the end of the ileum is thickened and the surrounding fat space is blurred with multiple small lymph nodes, suggestion: Inflammation may exist; B: Presence of appendiceal fecal stones.

malignancy with HPS development is lymphoma and HPS-associated autoimmune disorders include systemic lupus erythematosus and adult Still's disease[8].

The clinical manifestations of EBV-isolated infection and HPS caused by EBV infection are similar; however, we can differentiate them from their duration and severity. A simple EBV infection is mostly manifested as mild clinical symptoms, short disease course, and spontaneous recovery. In contrast, HPS caused by EBV infection tends to have progressive exacerbations, has multiple-organ involvement, and can lead to death. Liver injury has been reported as an independent risk factor for mortality[9].

The patient mainly presented with fever and agranulocytosis with a decline in neutrophil proportion and increasing lymphocytes, suggesting viral infection. The PCT level increased and the erythrocyte sedimentation rate was within the normal range, suggesting bacterial infection. Therefore, we performed further assaying on the virus, bacteria, and fungal-related infection indicators. Nevertheless, the patient's condition rapidly deteriorated, with a progressive decline in liver function, persistently low blood cell levels, and continuously decreasing albumin levels. We did not rule out HPS because the bone marrow smear showed easily noticeable phagocytes. As this patient met 5 of 8 criteria, according to the HLH diagnostic criteria formulated by the International Organization Cytology Association in 2004, a clear diagnosis of HPS was made.

On physical examination, the patient had lymphadenopathy; however, both excluded tumor lesions from lung and abdominal CTs. Therefore, a tumor-related disease was not considered. The results of the patient's immune-related tests were negative; therefore, immune disorders can be excluded. Moreover, the patient was diagnosed with EBV infection, which improved following antiviral therapy, and the transaminase levels decreased with anti-infective therapy. Therefore, EBV infection-related HPS could be diagnosed. The patient had agranulocytosis and liver injury. According to the relevant medical history, symptoms, and auxiliary examinations, the possibility of liver injury caused by viral hepatitis, alcoholic liver injury, drug-induced liver injury, and autoimmune diseases was little. Therefore, we initially considered liver injury caused by EBV infection.

HPS treatment is divided into the following two aspects: First, induction and remission therapy, which is to primarily control excessive inflammatory symptoms; second, etiological treatment, which focuses on correcting underlying immune deficiencies and controlling the primary disorder[10]. In this case, following ganciclovir antiviral treatment combined with meropenem antibacterial therapy and methylprednisolone inhibition to inflammatory response, gamma globulin enhanced immunotherapy, granulocyte levels increased, transaminase levels decreased, and the symptoms were relieved. According to the medical history, the patient was vaccinated before getting sick, which may have caused post-vaccination immune abnormalities, resulting in the potential EBV virus turning into an infectious state. Through early standardized treatment, the body's immunity returned to a balanced state.

## CONCLUSION

From the diagnosis and treatment of this patient, attention should be paid to routine EBV detection. Furthermore, HPS-related indicators should be monitored timely to avoid misdiagnosis and missed

diagnosis of EBV infection-associated HPS for patients with fever, unexplained agranulocytosis, and liver injury. In this case, the successful treatment of the patient can be because of the early diagnosis and timely standardized treatment in the early stage of the disease. Therefore, a further comprehensive understanding of the disease as well as early recognition and early initiation are keys to patients' survival.

## FOOTNOTES

**Author contributions:** Sun FY and OuYang BQ contributed equally to this work; Sun FY, OuYang BQ, Li XX, Zhang T and Feng WT designed the research study; Li XX, Zhang T, Feng WT, and Han YG performed the research; Li XX, Zhang T contributed new reagents and analytic tools; Sun FY and OuYang BQ analyzed the data and wrote the manuscript; and all authors have read and approved the final manuscript.

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