CASE REPORT

A case of fulminant myocarditis complicated by hemophagocytic syndrome

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Received: February 2, 2023 **Accepted:** June 8, 2023 **Online Published:** July 6, 2023
DOI: 10.5430/dcc.v10n1p5 **URL:** https://doi.org/10.5430/dcc.v10n1p5

ABSTRACT

Background: Fulminant Myocarditis and Hemophagocytic Syndrome (HPS) are independent life-threatening diseases. HPS, however, is a rare complication of fulminant myocarditis. It is hard to diagnose HPS in patients with fulminant myocarditis early, but timely identification affects the clinical result. Here is the report of a female who has developed HPS complications after fulminant myocarditis.

Case presentation: A 15-year-old Chinese female was admitted to the emergency department with a 3-day history of progressively severe chest pain and then a 1-day history of worsening heart failure needing the veno-arterial extracorporeal membrane oxygenation (V-A ECMO). Interventions: V-A ECMO requiring continuous renal replacement therapy (CRRT) supported critically ill patients with heart failure. The vasoactive drug was used to improve cardiac function, maintain water, electrolyte, and acid-base balance, and nutritional supplements. High-dose methylprednisolone was administered for three days. Etoposide was given two times according to the treatment guideline, followed by cyclosporine. Diagnosis: The definitive diagnosis of the presented case was fulminant myocarditis complicated by hemophagocytic lymphohistiocytosis.

Conclusions: For fulminant myocarditis patients suspected of HPS, the functional examination must be considered for early diagnosis. The timely administration of adequate corticosteroids and standard chemotherapy is essential to reduce the risk of HPS mortality.

Key Words: Fulminant myocarditis, Hemophagocytic syndrome, Immune dysfunction, Case report

1. INTRODUCTION

Fulminant myocarditis and Hemophagocytic syndrome (HPS) are independent diseases and have high mortality risks. HPS is characterized by activating macrophages and histiocytes with prominent hemophagocytosis in the bone marrow and other reticuloendothelial systems.[1]

However, HPS is a rare complication of fulminant myocarditis. In patients with fulminant myocarditis, it is hard to figure out HPS, but diagnosis early and treatment timely affect clinical outcomes. Here is the report of a female who has developed HPS complications after fulminant myocarditis. This is the first report documenting the presentation of hemophagocytic syndrome during myocarditis recovery in Chinese children.

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2. Case presentation

A previously healthy 15-year-old Chinese female was admitted to the emergency department with a 3-day history of progressively severe chest pain and a 1-day history of worsening heart failure needing the veno-arterial extracorporeal membrane oxygenation (V-A ECMO) requiring continuous renal replacement therapy (CRRT). Laboratory data revealed elevated serum levels of cardiac markers (creatine kinase (CK) 12,358 U/L, CK-myoglobin (CK–MB) 416 U/L, Troponin I, 7.06 ng/ml, N-terminal pro-brain natriuretic peptide (Pro-BNP) 6,622.79 pg/ml), and impairment of liver (aspartate transaminase (AST) 6,310 U/L, alanine transaminase (ALT) 20,688 U/L) and kidney (urea (UA) 455 μmol/L, creatinine (Cr) 227 μmol/L). Then she presented with worsening heart failure and required ECMO. Subsequently, Influenza virus B was detected by oropharyngeal swab. Physical examination of the sedative patients with ECMO-associated CRRT showed cardiac sound low and arrhythmia. Chest X-ray suggested pulmonary exudation and no enlarged heart shadow (see Figure 1). Echocardiography showed ventricular tachycardia and measured the low ejection fraction (EF 17%) (see Figure 2). Electrocardiogram suggests borderline tachycardia (see Figure 3).

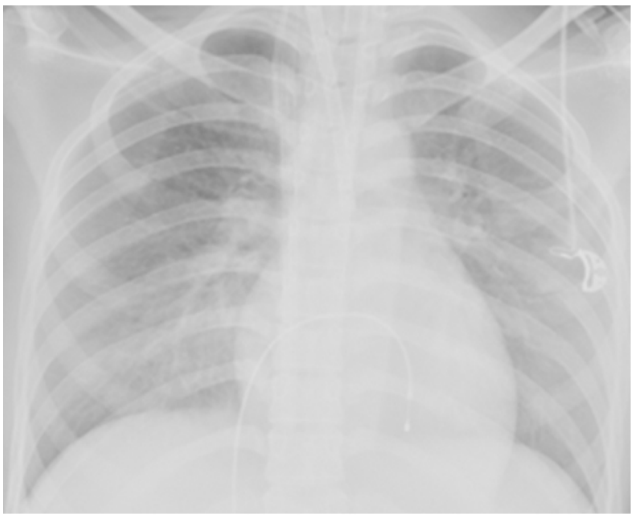

Figure 1. Pulmonary exudation and heart shadow on day 2 of the illness

Therefore, fulminant myocarditis was considered. She was treated with intravenous immunoglobulins (27.5 g per day), amiodarone, and methylprednisolone (120 mg daily). The laboratory findings returned to average values, and cardiac functions improved after treatment. But the spiking fever was presented, which was not cured even after advanced antibiotics were used after being recovered from fulminant myocarditis. Laboratory tests showed leukopenia (white blood cell (WBC) 2.7 $\times$ 10^9/L), lymphopenia (0.32 $\times$ 10^9/L), and blood platelet (PLT 222 $\times$ 10^9/L) were decreased. Besides, lactate dehydrogenase (LDH 467 U/L), NK cell (57.38 cell/μl), hemoglobin (83 g/L), triglyceride (TG 4.69 mol/L), and serum ferritin (SF 5,466.5 ng/dl) were increased. Fibrinogen was 1.62 g/L. Activated partial thromboplastin time (APTT) was elevated (47.6s). The International normalized ratio (INR) and prothrombin time (PT) were average. The bone marrow smear showed endocytosis (see Figure 4). The patient fulfilled seven HLH-2004[2] criteria for HPS, based on spiking fever, hepatosplenomegaly, anemia, coagulation disorders, high triglyceride, decreased NK cell activity, and endocytosis. The diagnosis of HPS was confirmed.

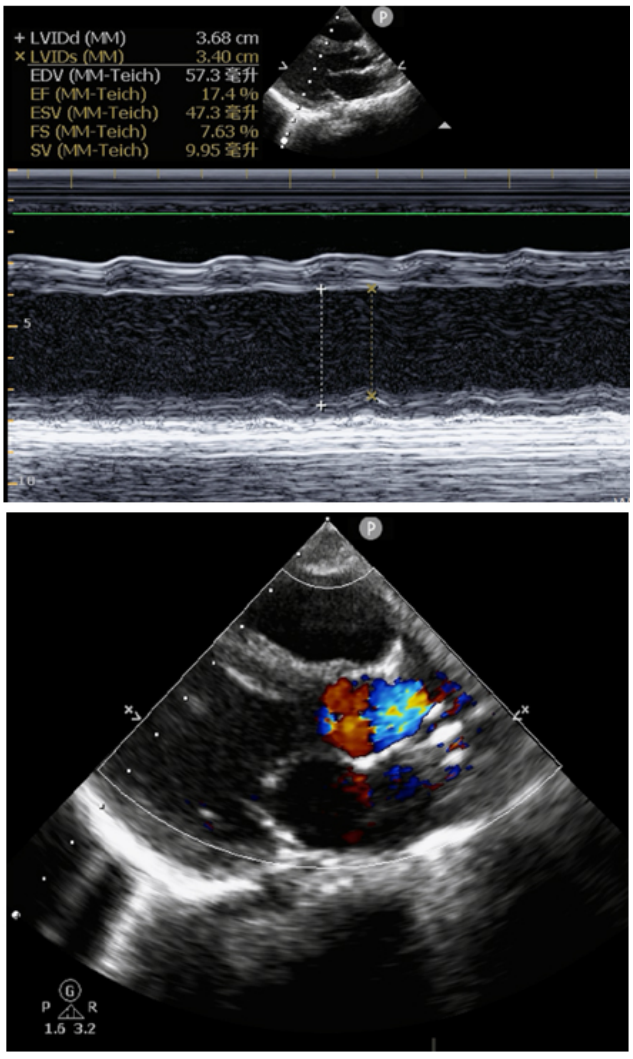

Figure 2. Low ejection fraction shows evidence of fulminant myocarditis

The patient's condition was not improved after giving high-dose intravenous methylprednisolone (5 mg/kg/d) for three days. Etoposide (VP-16) was given two times according to

the HLH-2004[2] treatment guideline, followed by VP-16 weekly to suppress immunity. At the same time, adequate dexamethasone administrations were not discontinued. The fever disappeared, and the laboratory findings reached the normal ranges.

The blood tests performed before discharge showed WBC (7.86 $\times$ 10^9/L), CRP (1.9 mg/L), hemoglobin (106 g/L), SF (764.4 ng/ml), TG (1.34 mol/L), ALT (23 U/L), AST (13 U/L), and LDH (151 U/L) were improved (see Figure 5). The patient was discharged with oral prednisolone and cyclosporine. The SF and TG reached normal ranges six months after discharge.

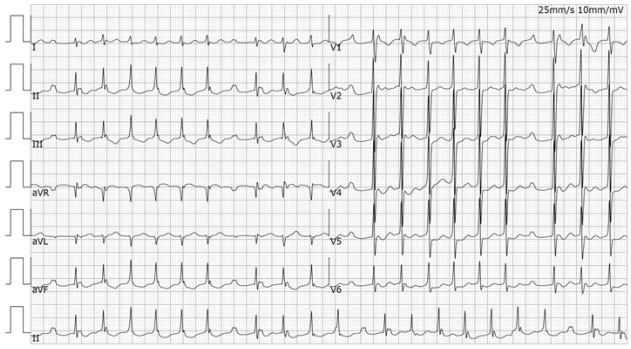

Figure 3. Electrocardiogram showing borderline tachycardia

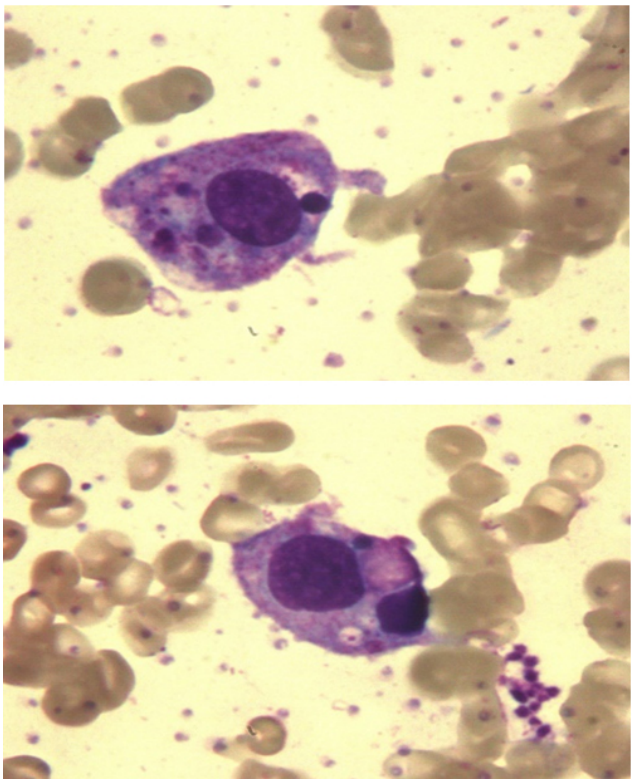

Figure 4. Bone marrow smear showing endocytosis

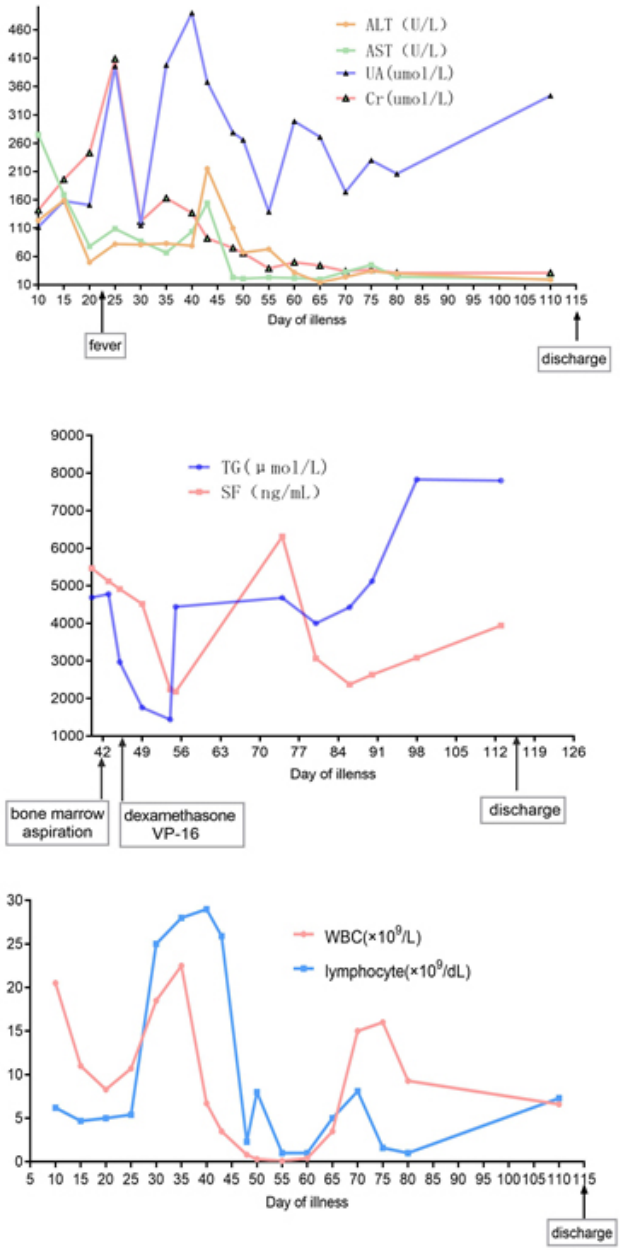

Figure 5. The clinical course of the patient and the function of liver and renal

ALT: Alanine Transaminase; AST: Aspartate Transaminase; UA: Urea; Cr: Creatinine; VP-16: Etoposide; SF: serum ferritin; TG:Triglyceride; WBC: white blood cells

3. Discussion

Hemophagocytic syndrome is a potentially life-threatening syndrome characterized by impaired function of cytotoxic T lymphocytes and natural killer cells. It is categorized as primary and secondary autoimmune conditions.[3,4] Research has confirmed multiple potential factors in almost one-third of secondary clinical practice.[5] The pathological process is excessive pro-inflammatory cytokines, including interleukin

IL-18, IL-1β, and TNF-α lead to a "cytokine storm."[6] The mechanism of HPS is not entirely clear, but some experts believe that autoimmune disorders are the key to pathogenesis. The TNF-α, IL-6, IL-8, IL-18, and serum ferritin levels suggest a highly activated immunity in fulminant myocarditis patients, and the continuous activation of immunity may lead to the relatively rare but dangerous HPS.

HPS is unusual in fulminant myocarditis as a complication. In this case, the patient is a previously healthy adolescent with good immune function. An essential feature of this case is the severity of renal damage. The need for CRRT continued intermittently after withdrawal from ECMO assistance. The high fever presented during the period of CRRT assistance. The clinical symptom was ultimately considered to be caused by HPS induced by immune disorder after fulminant myocarditis.

One of the relevant complications of extracorporeal life support (ECLS) is associated with an inflammatory response because of the release of cytokines and other biomarkers of inflammation, which have been related to multi-organ dysfunctions.[7] A rapid rise in pro-inflammatory cytokines following initiation of ECLS[8–10] is thought to be associated with systemic inflammatory response.[11] Because the blood exposes to the extracorporeal circuit during ECLS, an inflammatory response might be activated that mimics Systemic inflammatory response syndrome.[12] The potential inflammatory activation triggers intrinsic and extrinsic coagulation pathways, leading to inflammation and clot formation.[13] Other causes reported during ECLS may be bacterial translocation, gut barrier dysfunction, and endotoxin release. During ECMO, endotoxins can be released in response to the translocation of bacteria from ischemic gut mucosa into the bloodstream.[14, 15]

Familial hemophagocytic lymphohistiocytosis is a rare autosomal recessive immune disorder caused by mutations in 6 genes. However, genetic testing was not conducted because the child, in this case, is an adolescent with no family history and no previous hematological symptoms. But it was best to do a genetic test to rule out congenital disabilities.

Immunosuppressant, such as cyclosporine, is thought to be second-line drugs.[16] However, using steroid therapy is more important than using cyclosporine. In experience from this case, cyclosporine is an excellent choice to reduce the severe infection caused by bone marrow suppression.

The clinical conditions-associated inflammatory process is complicated to control. So bone marrow biopsies should be performed early to identify HPS. The case reported here was ultimately curable because of the early identification of HPS and the use of high-dose steroids and VP-16 timely to control the inflammatory response.

4. Conclusions

In conclusion, for patients with fulminant myocarditis who need ECMO assistance, systemic inflammation is easily activated, leading to immune dysfunction and HPS complications. For fulminant myocarditis patients during the recovery period, present symptom doubting HPS, bone marrow biopsies should be performed to search for pathological evidence. Additionally, for the patient with fulminant myocarditis whose liver and kidney functions are not improved significantly or deteriorate again after cardiac function improvement, and the clinical symptoms of fever are difficult to explain by infection, it would be considered if the patient's condition is worse for HPS.

Acknowledgements

We are grateful to the hematologist for cooperating in diagnosing and treating the patient.

Conflicts of Interest Disclosure

The authors declare they have no conflicts of interest.

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