INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome of pathological immune activation caused by activated macrophages and cytotoxic T cells. The manifestation of HLH is comprised of recurrent fever, cytopenia, splenomegaly, and a sepsis-like syndrome which may cause multiple organ failure even sudden death. Familial (primary) HLH, a major HLH subtype in children, is caused by genetic mutations. Secondary (acquired) HLH is always triggered by infections or malignancies, autoimmune disorders. Many malignancies are associated with HLH in adults, including T-cell or natural killer (NK) cell lymphomas (35%), B-cell lymphomas (32%), leukemias (6%), Hodgkin lymphoma (6%), and other hematologic tumors (14%), solid tumors (3%), and other nonspecified neoplasms (3%). 1,2 The treatment protocols HLH-94 and HLH-2004 have been established.
and based on the patients younger than 18 years old. However, adults may differ from children regarding pathogenesis, diagnosis, and treatment. Moreover, diagnosis of HLH is difficult because of its rarity and complexity and historically was often delayed. In this article, we reported that a male was diagnosed with secondary HLH, triggered by peripheral T-cell lymphoma, got temporary remission for nearly 2 months.

2 CASE PRESENTATION

A 65-year-old male patient was admitted to the hospital because of persistent high-grade fever (>38.5°C), chills, fatigue, dry cough, and abdominal distension. The patient had been in his usual state of good health until 1 month before admission. On admission, the physical examination revealed a body temperature of 39.1°C, pulse of 98 beats per minute, and respiratory rate of 20 breaths per minute. Jaundice can be seen all over the body, especially scleral icterus (Figure 1A). Multiple enlarged lymph nodes can be palpable in the cervical region, axilla, and inguinal region. The liver and spleen cannot be palpable.

Computed tomography (CT) showed multiple lymph nodes enlargement in the mediastinum, abdomen, pelvic cavity, and bilateral inguinal region (Figure 1B). Based on the pathological results of cervical lymph nodes, the peripheral T-cell lymphoma was diagnosed (Figure 2A). Laboratory results reflected neutropenia, thrombopenia, and elevated levels of serum ferritin and triglyceride. In addition, the level of interlukin 2 receptor (IL-2R) was elevated to 7500 U/ml. The patient’s liver function worsened on admission with extremely abnormal aminotransferase and bilirubin. Hepatitis B virus screening was positive, though the copies of virus DNA cannot be detected. Moreover, hemophagocytic histiocytes were identified in his bone marrow.

Since the patient met six of the eight HLH-2004 diagnostic criteria, the diagnosis of HLH was confirmed. On Day 2 of admission, the patient was treated with systemic chemotherapy biweekly, including liposome doxorubicin with 35 mg/m², etoposide with 75 mg/m², and methylprednisolone (2 mg/kg for 3 days, 0.75 mg/kg for 4 days, 0.25 mg/kg for 3 days and 0.1 mg/kg for 3 days). Meanwhile, the patient received fluid replacement, platelet and plasma transfusion and nutrients supply. Glycyrrhizin compound and ademetionine were added to improve his liver function. In addition, he took entecavir orally to prevent virus replication. On Day 6 of hospitalization, the patient’s temperature dropped down to normal range and lymph nodes shrunk. The hematopoietic function of bone marrow apparently recovered. However, the aminotransferase declined slowly and bilirubin got worse. Then, on Day 7 and 8 of hospitalization, the patient received plasmapheresis two times consecutively. After that, the aminotransferase declined to normal and bilirubin decreased significantly (Figure 2B). Since the patient could not tolerate the gastrointestinal toxicity and myelosuppression, so the COPE regimen (cyclophosphamide, epirubicin, etoposide, and prednisolone) with orally chidamide was conducted. This patient got temporary remission for nearly 2 months and finally died because of disease progression.

3 DISCUSSION

Hemophagocytic lymphohistiocytosis is an abnormal hyperinflammatory immune response syndrome that is driven by T cells and always associated with a potentially fatal cytokine storm. The cause of primary HLH is familial inheritance or an identifiable genetic mutation in the pediatric age group. Secondary HLH (sHLH) is the more prevalent in adults with a mean age of 49 years old and 63% are males. sHLH comprises two main groups:
malignancy-HLH and non-malignancy-associated HLH such as infection or autoimmune diseases. The incidence of malignancy-HLH varies from 1% in patients with hematological malignancies (0.36/100,000 individuals per year)\(^8\) to 2.8% in patients with malignant lymphoma.\(^9\) Patients with HLH include persistent fever, pancytopenia, splenomegaly, hypertriglyceridemia, hypofibrinogenemia, multiple cytokines release, and even end organ failure. In this case, the male patient presented extremely typical features of HLH, which was triggered by peripheral T-cell lymphoma. As soon as the diagnosis of HLH identified, the chemotherapy had been conducted. The treatment protocols HLH-94 and HLH-2004 have been commonly used for diagnosis and treatment of HLH patients younger than 18 years old.\(^3\)-\(^5\)

The HLH-94 protocol is composed of corticosteroids, etoposide, cyclosporine A, and intrathecal therapy, in which etoposide and corticosteroids can delete activated T cells and suppress inflammatory cytokine secretion.\(^10\)

However, elderly patients may suffer from comorbidities and more vulnerable to cytokine storm caused by HLH or chemotherapy. In our case, this 65-year-old male patient had a poor performance status on admission and severe pancytopenia. Therefore, we modified the chemotherapy into combination of liposome doxorubicin, etoposide, and methylprednisolone biweekly. Also, the treatment of organ function improvement, nutrients supply, and fluid replacement was also crucial. Fortunately, the patient's symptoms and blood cells became much better. But the patient's liver function, especially bilirubin, worsened even with liver-protecting and entecavir therapy. sHLH is associated with multiple end organs failure, and acute liver failure caused by HLH has a high mortality.\(^11\) The mechanism for HLH-mediated liver damage still remains unknown, which might be the infiltration of activated hemophagocytic histiocytes or overproduction of cytokines.\(^12\) Alternatively, liver abnormality can result from underlying diseases such as hepatitis B. Recent study demonstrated that the average time from earliest diagnosis of liver failure to a definitive diagnosis of HLH was 17.27 days and suggested that HLH occurred late in liver failure, specifically within 5 weeks after diagnosis of liver failure.\(^13\)

Plasmapheresis or cytokine adsorption columns may provide a therapy in rescuing patients from the cytokine storm.\(^14\) For this patient, it may be the overwhelming cytokines production that resulted in liver damage; therefore, plasmapheresis should be an optimal therapy. Plasmapheresis was conducted two times and then his liver function apparently improved. The patient got temporary remission and good quality of life for nearly 2 months but died because of disease progression.

In conclusion, as malignant-HLH is associated with multiorgan failure, high rates of morbidity and mortality, there are three principles to be mentioned. First, it is critical that HLH should be screened as early as possible. Second, plasmapheresis might be a useful method to eliminate excess cytokines production and improve liver function. Third, organ support and nutrient supply are also necessary and important.

**AUTHOR CONTRIBUTIONS**

X.S., X.D., and Y.C. supervised the case report. Y.C. drafted the manuscript. L.X., X.Z., X.Q., and J.S. interpretated the results and revised the article.

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**CONFLICT OF INTEREST**

The authors declare no potential conflict of interest.

**DATA AVAILABILITY STATEMENT**

None.
CONSENT
Written informed consent was obtained from the patient’s daughter to publish this report in accordance with the journal’s patient consent policy.

ORCID
Yuxuan Che © https://orcid.org/0000-0002-0714-6411

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