A Case Report of Malaria-associated Secondary Hemophagocytic Lymphohistiocytosis and a Review of the Literature

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Case report

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Abstract

Background: Malaria-associated secondary hemophagocytic lymphohistiocytosis (HLH) is rare. Moreover, the literature on malaria-associated HLH is sparse, and there are no similar cases reported in China.

Case presentation: We report a case of a 29-year-old young woman with unexplained intermittent fever who was admitted to our hospital due to an unclear diagnosis. The patient concealed her history of travel to Nigeria and Dubai before onset. We made a diagnosis of malaria-associated secondary HLH. The treatment strategy for the patient included treatment of the inciting factor (artemether for 9 days followed by artemisinin for 5 days), the use of immunosuppressants (steroids, intravenous immunoglobulin) and supportive care. The patient was discharged in normal physical condition after 25 days of intensive care. No relapses were documented on follow-up at six months and 1 year.

Conclusion: Early diagnosis of the primary disease along with timely intervention and a multidisciplinary approach can help patients achieve a satisfactory outcome.

Background

HLH is a systemic disorder caused by immune dysregulation that occurs in primary and secondary forms. Secondary HLH refers to cases caused by infections, malignancy and autoimmune diseases. HLH secondary to infections can occur with viral, bacterial, fungal or parasitic infections[1]. Malaria is rarely reported to cause HLH. We report a case of a 29-year-old young woman with fever, hepatosplenomegaly, pancytopenia, high serum ferritin, hypertriglyceridemia, hypofibrinogenemia and bone marrow hemophagocytosis, consistent with hemophagocytic syndrome. Plasmodium falciparum (P. falciparum) was identified on a peripheral blood smear. Rapid recovery was observed after treatment with antimalarial medications, immunomodulatory therapy and supportive care.

Case presentation

A 29-year-old young woman was admitted to the hospital due to intermittent fever for 12 days. The patient had an unexplained fever (Tmax 41°C), chills and anorexia after a trip to Nigeria and Dubai in September 2018. However, the patient concealed her travel history while visiting the local hospital. She was diagnosed with pneumonia and received antibiotic treatment. With poor response to antibacterial treatment, the patient developed nausea, vomiting, upper abdominal pain, respiratory distress and oliguria. Further investigations showed negativity for Epstein–Barr virus (EBV) DNA but positivity for EBV-IgM. Bone marrow biopsy revealed hemophagocytosis. The patient was diagnosed suspiciously with EBV-related HLH, and she was transferred to our hospital for emergency treatment.

We obtained a detailed medical history from the patient and learned about her history of travel. Physical examination revealed a blood pressure of 105/64 mmHg, wet rales in the lower lung and upper abdominal tenderness. Blood tests showed cytopenias, increased liver transaminases, increased bilirubin, hypertriglyceridemia, increased serum ferritin and splenomegaly on abdominal ultrasonography and CT

(computed tomography) (Figure 1). Tests for EBV and cytomegalovirus DNA were negative. There was no evidence of a tumor. A peripheral blood smear showed P. falciparum (Figure 2a), which was determined to have a 3D7 genotype. Bone marrow aspiration showed the presence of hemophagocytosis (Figure 3), with a soluble CD25 (sCD25) level of 21,574 pg/ml and negative results for natural killer cell (NK cell) activity. A final diagnosis of malaria-associated secondary HLH was made.

The treatment regimen for malaria included artemether at 80 mg q12h for 4 days and then 80 mg qd for 5 days, which was changed to dihydroartemisinin and piperaquine phosphate 2 tablets qd for 5 days. At the same time, the patient received treatment with methylprednisolone 80 mg qd for 4 days. Since we considered the HLH to be secondary to malaria, we treated the primary disease and used intravenous immunoglobulin (IVIG) for 5 days (total dose of 2 g/kg). After 7 days of treatment, no P. falciparum was found in the peripheral blood smear (Figure 2b), and tests for malarial antigens were negative. The patient's condition improved gradually, and her clinical and laboratory manifestations were normalized (Table 1).

Subsequently, the patient manifested multiorgan dysfunction. She exhibited acute kidney injury (creatine 569 μmol/l with oliguria), acute liver injury, acute respiratory distress syndrome (P/F 100 mmHg) and coagulopathy and was treated with continuous renal replacement therapy, high-flow nasal cannula oxygen therapy (HFNC), blood transfusion and nutritional support in the critical care unit. After 7 days of organ support treatment, the patient's respiratory and renal function recovered to normal, and her liver-enzyme and bilirubin levels decreased. She was discharged in normal physical condition after 25 days. No relapses were documented at her six-month and 1-year follow-ups.

Discussion

Malaria is a mosquito-borne infectious disease that is caused by a parasitic protozoan of the genus Plasmodium and has diverse clinical manifestations[2]. The epidemiological history is important for diagnosis. Therefore, we should solicit a thorough and detailed medical history. The diagnosis of malaria was based on a peripheral blood smear and/or rapid diagnostic tests for malarial antigens. Artemisinin is mainly used in the treatment of malaria. Our patient was treated with artemether first because the effect of artemether is 6 times more potent that of artemisinin. Then, she subsequently took oral dihydroartemisinin and piperaquine phosphate. There are also reports of oral doxycycline treatment in the literature.

HLH, a life-threatening disease associated with excessive stimulation of tissue macrophages[3], occurs in primary and secondary forms. Primary HLH is mostly recognized in childhood, whereas the secondary form can occur at any age. Secondary HLH refers to cases caused by infections, malignancy and autoimmune diseases. HLH secondary to infections can occur with viral, bacterial, fungal or parasitic infections; viral infections, especially those caused by EBV, are the most common[4]. The clinical and laboratory manifestations of HLH include fever, splenomegaly, neurologic dysfunction, coagulopathy,

liver dysfunction, cytopenias, hypertriglyceridemia, hyperferritinemia, hemophagocytosis, and diminished NK-cell activity. In fact, the clinical manifestations of HLH lack specificity. The severity is related to the levels of immune cell activation and cytokines. Currently, we make the diagnosis based on HLH-2004 criteria[5] (Table 2). Hemophagocytosis cannot be used as a necessary condition to exclude or diagnose HLH. The sensitivity of hemophagocytosis in the diagnosis of HLH is approximately 60%. HLH cannot be excluded in the absence of hemophagocytosis. The sensitivity of ferritin > 500 μg/L in the diagnosis of HLH is 84%. Serum ferritin < 500 μg/L has a negative evaluative significance for the diagnosis of HLH. NK-cell activity is a landmark diagnostic indicator that is irreversible in primary HLH but can be recovered in secondary HLH. The reference range varies depending on the detection method. sCD25 is the most useful marker of inflammation, which reflects the excessive immune activation status of patients. The literature reports that elevated sCD25 in children has a sensitivity of 76.2% and a specificity of 98.2% for the diagnosis of HLH[6]. The treatment strategy for secondary HLH includes supportive care, treatment of inciting factors and the use of immunosuppressants (steroids, IVIG and other immunosuppressive drugs).

Malaria as a cause of secondary HLH is rare. We reviewed the related literature, and fewer than 20 cases have been reported[7]–[21]. There are no similar cases reported in China. The reason is that on the one hand, China is not a malaria-endemic area, and on the other hand, some cases have not been recognized and diagnosed. The types of malarial parasites that cause secondary HLH are P. falciparum and P. vivax[8][13], with P. falciparum accounting for most of these cases. The pathogenesis is not yet clear but may be related to immune dysfunction caused by falciparum malaria. Whether the pathogenic mechanisms of the different types of Plasmodium are different still needs further study.

In this case, the patient had fever and gastrointestinal symptoms, such as fatigue, anorexia, nausea, and vomiting, but no enlarged lymph nodes, rash, bleeding or neurologic dysfunction. Although NK-cell activity was negative, the diagnosis of HLH clearly met seven out of the eight HLH-2004 criteria. However, in most cases reported in the literature, NK-cell activity and soluble CD25 antigen levels were not available. Thanks to the new diagnostic markers, we made the diagnosis in time. Meanwhile, intensive care unit intervention played a valuable role in the patient's recovery during the course. No death due to malaria-associated HLH has been reported. Our patient also had a good prognosis.

Conclusion

In conclusion, malaria-associated secondary HLH is rare. If the patient has fever, splenomegaly and an elevated ferritin level, HLH should be highly suspected, and relevant examinations should be conducted. Early diagnosis of the primary disease along with timely intervention and a multidisciplinary approach can help patients achieve a satisfactory outcome.

Abbreviations

HLH
hemophagocytic lymphohistiocytosis

P.falciparum
Plasmodium falciparum
EBV
Epstein–Barr virus
CT
computer tomography
sCD25
Soluble CD25
NK cell
natural killer cell
IVIG
intravenous immunoglobulin
HFNC
high-flow nasal cannula oxygen therapy
P. vivax
Plasmodium vivax

Declarations

- Ethics approval and consent to participate

This study was approved by the Hospital Ethics Committee, No. 2018-P2-190-01. This study obtained consent for publication from the patient. The participant consent was written.

(Picture seen in the appendix)

- Consent for publication

All of the authors have consented to the publication of this study.

- Availability of data and material

Not applicable.

- Competing interests

The authors declare that they have no competing interests.

- Funding

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- Authors' contributions

MLD developed the treatment strategies for the patient. XZ administered the treatments and read the literature. XZ was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

- Acknowledgments

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Tables

Table 1 The change in clinical and laboratory manifestations before and after treatment

	Reference range	Before treatment	7 days after treatment	14 days after treatment
Tempreture (℃)	36-37	Tmax39.8	No fever	No fever
White blood cells($x10^9$/L)	3.50-9.50	2.88	3.78	4.33
Neutrophils($x10^9$/L)	1.8-6.3	1.31	2.15	2.00
Hemoglobin(g/L)	115-150	49	108	93
Platelet count($x10^9$/L)	125-350	50	112	151
Reticulocytes($x10^{12}$/L)	0.0140-0.0900	0.1443	0.2269	0.0902
IB(umol/L)	0.00-12.00	15.44	16.09	8.59
TG(mmol/L)	0.57-1.70	2.45	2.42	2.23
Ferritin(ng/ml)	11.00-306.00	1989.00	1730	1516
Fbg(ng/ml)	1.70-4.00	1.41	1.31	1.63
NK-cell activity		negative		-
sCD25(pg/ml)		21574		4775
Speen ultrasonography	length 8.5±1.0cm	14.2		-
	thickness 2.8±0.5cm	3.8		3.4

Table 2 Diagnosis of HLH-2004 criteria

The diagnosis HLH can be established if either condition 1 or condition 2 below is fulfilled.
(1) A molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
(A) Initial diagnostic criteria (to be evaluated in all patients with HLH)
Fever
Splenomegaly
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):
Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L)
Platelets $<100 \times 10^9$/L
Neutrophils $<1.0 \times 10^9$/L
Hypertriglyceridemia and/or hypofibrinogenemia:
Fasting triglycerides ≥3.0 mmol/L (i.e., ≥265 mg/dl)
Fibrinogen ≤1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
(B) New diagnostic criteria
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin ≥500 μg/L
Soluble CD25 (i.e., soluble IL-2 receptor) ≥2,400 U/ml

Figures

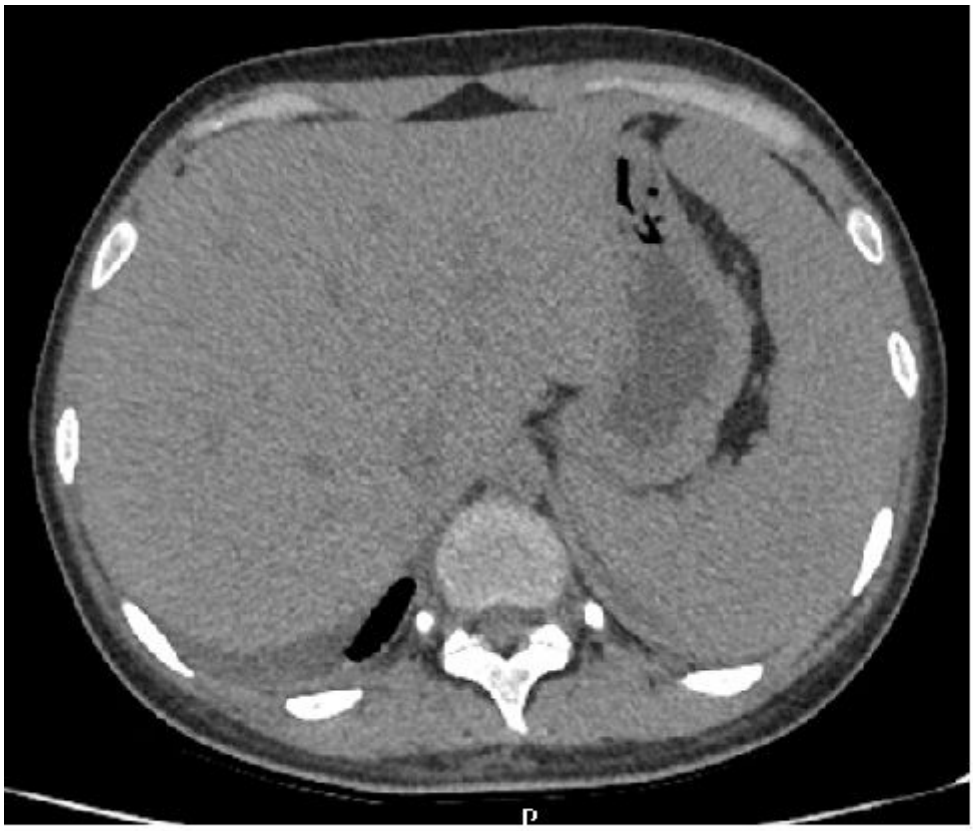

Figure 1 Abdominal CT showed hepatosplenomegaly.

Figure 1

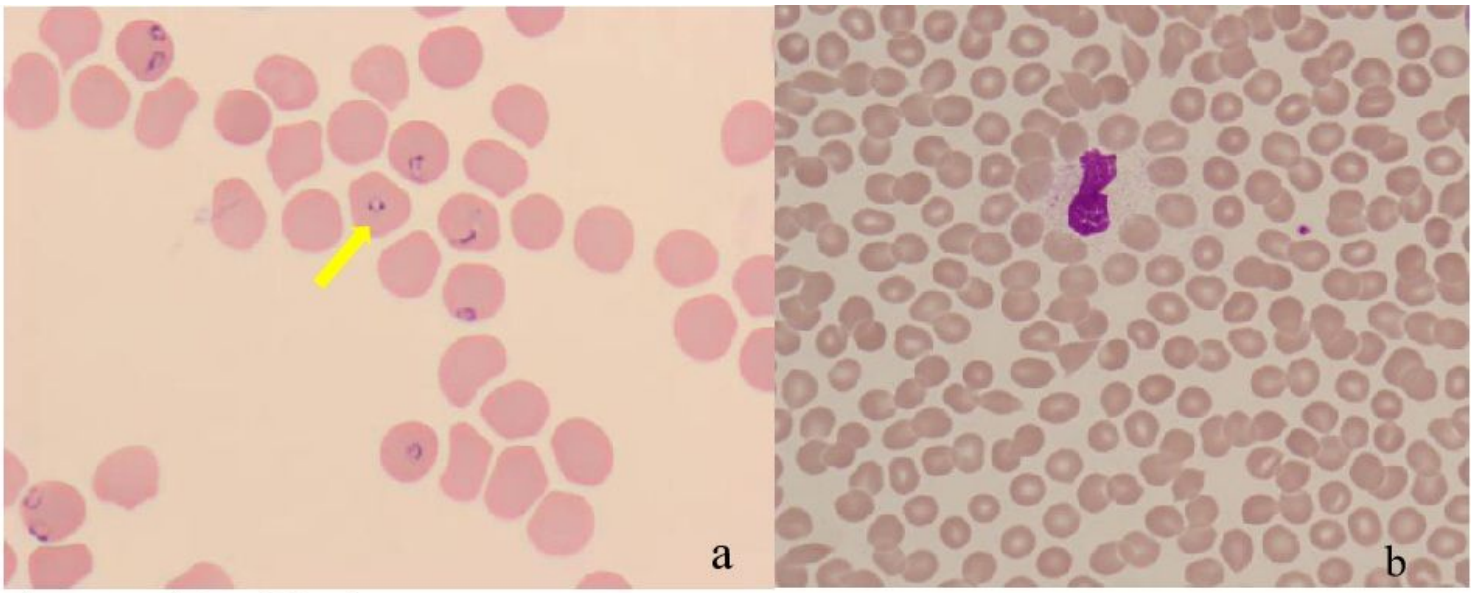

Figure 2 Peripheral blood smear.
Figure 2a (left) showed hemophagocytes with malarial gametocytes(yellow arrow).
Figure 2b (right) showed that no Plasmodium was found..

Figure 2

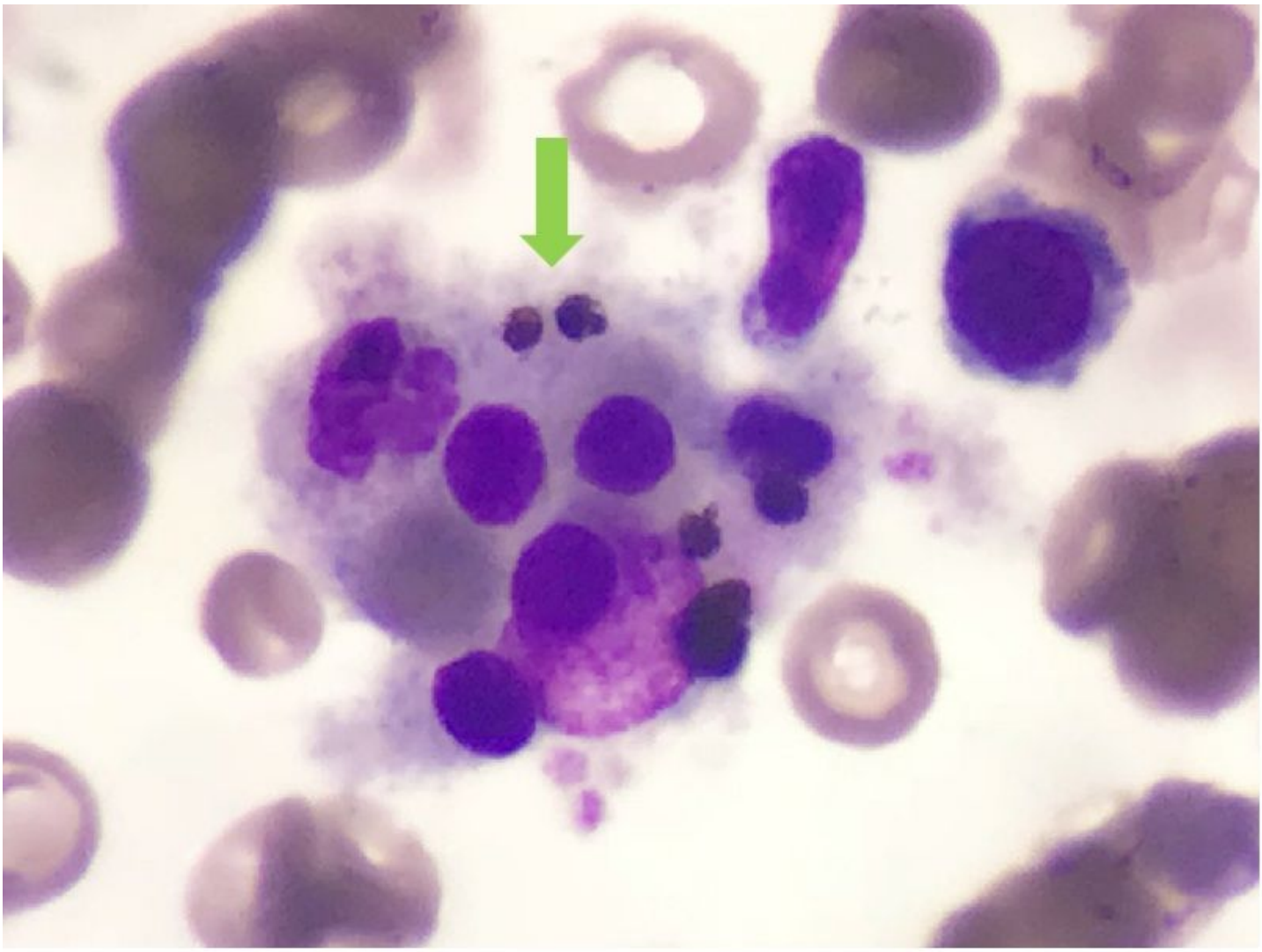

Figure 3 Bone marrow aspiration showed the presence of hemophagocytosis (green arrow).

Figure 3

Supplementary Files

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- supplement9.jpg
- supplement10.jpg