CASE REPORT

Haemophagocytic lymphohistiocytosis (HLH): a rare but potentially fatal association with *Plasmodium vivax* malaria

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SUMMARY

Haemophagocytic lymphohistiocytosis (HLH) is a potentially fatal syndrome that is caused by an abnormal activation of the immune system. It can present as the primary syndrome or occur secondary to a variety of conditions such as malignancy, autoimmune diseases and infections. We present a case of a man who developed HLH secondary to *Plasmodium vivax* infection. He presented with symptoms of fever, chills and myalgias. Physical examination revealed significant hepatosplenomegaly. The presence of pancytopenia, elevated ferritin levels and haemophagocytosis on bone marrow biopsy confirmed the diagnosis of HLH (based on HLH-2004 criteria). There was a significant improvement after the initiation of intravenous antimalarials. No relapses were documented on follow-up. It is imperative that physicians should promptly recognise and treat this rare condition, as a timely intervention can be lifesaving.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) was first reported by Scott and Robb-Smith in 1939. The disease is characterised by inappropriate and uncontrolled activation of the immune system, which results in excessive inflammation and tissue damage.¹ Common manifestations include prolonged fever, rash, hepatosplenomegaly, various cytopenias, hyperferritinaemia, hypertriglyceridaemia and hypofibrinogenaemia.² It is a great mimic of common clinical diseases and remains a diagnostic challenge.

The underlying pathology is either a primary genetic abnormality or secondary to another condition such as an autoimmune or a metabolic disorder, infection or underlying malignancy.² Commonly associated infections are viral, but bacterial, fungal and parasitic infections are also associated with secondary HLH.² Primary HLH can be diagnosed by identification of HLH-associated gene mutations, while secondary HLH can be diagnosed by the criteria used in the HLH-2004 trial. Primary HLH treatment involves the use of different chemotherapeutic agents according to the HLH-94 treatment protocol. Secondary HLH treatment is centred on targeting the underlying condition responsible for HLH.

We present a case of HLH associated with *Plasmodium vivax* infection. The patient presented with an acute febrile illness, hepatosplenomegaly,

pancytopenia and hyperferritinaemia. Bone marrow biopsy demonstrated haemophagocytosis, which supported the diagnosis of HLH.

CASE PRESENTATION

A previously healthy 20-year-old man presented with a 2-week history of acute onset high-grade fever associated with rigors and chills. Review of systems was positive for headache and myalgias. He denied neck pain, sore throat, cough, urgency, frequency, dysuria or rash. His past medical and surgical history was unremarkable. Vitals signs included a temperature of 101°F, blood pressure of 110/80 mm Hg, heart rate of 96 bpm and a respiratory rate of 20 breaths/min. He looked pale and dehydrated, with mild scleral icterus. Abdominal examination revealed marked hepatomegaly and splenomegaly. The rest of the systemic examination was unremarkable. There was no lymphadenopathy.

INVESTIGATIONS

A complete blood count demonstrated pancytopenia with haemoglobin of 6.4 g/dL, white cell count of $2 \times 10^9/L$, platelet count of $58 \times 10^9/L$ and a corrected reticulocyte count of 0.42%. A peripheral smear revealed *P. vivax* trophozoites (figure 1). Total and direct bilirubin were 4.34 and 2.01 mg/dL, respectively. Other laboratory tests revealed elevated ferritin (817 mg/dL) and lactate dehydrogenase levels (1445 μ/L) with normal triglyceride at 96 mg/dL. Renal and liver functions were preserved. The liver was 19.2 cm and the spleen was 19.3 cm by both, ultrasound and CT scan. A bone marrow biopsy was performed, which revealed macrophage cells demonstrating haemophagocytosis (figure 2) and malarial pigments (figure 3).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis on presentation was broad and included bone marrow suppression secondary to infectious causes (viral, bacterial or parasitic) and non-infectious causes (lymphoma, leukaemia).

TREATMENT

The patient received supportive treatment with fluids and packed red blood cell transfusion. After establishing the diagnosis of HLH, intravenous artesunate was started, which resulted in significant improvement. The patient was discharged in a stable condition. No relapses were documented on follow-up.

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Figure 1 A haemophagocyte with malarial pigments (arrow) and an ingested platelet.

DISCUSSION

The worldwide incidence of HLH is not well reported. The estimated incidence ranges from 1/100 000 children in Texas to 1.2 children per million per year in Sweden.^{3 4} It is a potentially fatal condition that results from uncontrolled activation of macrophages by cytokines released by cytotoxic T cells, causing end-organ damage.

HLH can be familial (primary) or secondary to a variety of conditions such as infections, autoimmune diseases and malignancies. Familial HLH is usually diagnosed at an early age while the onset of secondary HLH is independent of age.¹ HLH secondary to infections most commonly occurs with viral infections such as *Cytomegalovirus*, *Epstein-Barr virus* and *Herpes simplex*. Although uncommon, the association with bacterial infections, parasitic infestations, and fungal and protozoal infections has been documented.^{5 6}

The association of HLH with *P. vivax* is rare but carries significant importance⁷ and, in endemic areas, may have direct implications on healthcare planning, as this entails a significant risk of HLH in endemic populations. The association of vivax malaria with HLH may be under-reported as most patients who suffer from vivax malaria never undergo a bone marrow biopsy and the opportunity to detect phagocytosis is missed. It is

Figure 2 Malarial pigments on bone marrow biopsy.

Figure 3 Peripheral smear of the patient, showing *Plasmodium vivax* trophozoites.

important to find the exact triggering factor for HLH, as it guides the therapeutic management and prognosis. It may be reasonable to expect that end-organ failure may reverse in these cases if the patient is supported and treated adequately, such as in our case with confirmed *P. vivax* on peripheral smear.

A structured literature search identified a total of 11 cases of *P. vivax*-related HLH, of which seven were described in detail with clinical features (table 1). Prolonged fever, splenomegaly, leukopaenia, thrombocytopaenia, hyperferritinaemia and haemophagocytosis on bone marrow examination were the most commonly reported findings.^{8–14} Three patients had severe normocytic anaemia with haemoglobin of <8 g/dL. These cases were restricted to malaria endemic regions with the exception of one report from France. Malaria-associated HLH should be considered in the right setting even in the developed world, especially if there is a history of travel to an endemic region. All except one patient recovered with antimalarial treatment, without complications. The majority of features in this case are consistent with the previous cases, with normal triglyceride levels being a unique feature.

According to the HLH-2004 trial, either a molecular diagnosis compatible with HLH should be made and/or five of the eight criteria given below in box 1 should be fulfilled.¹⁵ The cytopaenias should include at least two cell lines.

The diagnosis of our patient was established by presence of (1) fever, (2) anaemia and thrombocytopaenia, (3) splenomegaly, (4) haemophagocytosis revealed on bone marrow biopsy and (5) elevated ferritin levels.

The treatment of primary HLH is based on HLH-94 protocol, which includes combined chemotherapy and immunotherapy. In refractory and/or familial cases, this is followed by bone marrow transplantation.¹⁵ The treatment of secondary HLH follows a disease-specific approach and focuses on the underlying trigger. HLH-94 protocol is utilised only in refractory cases.

Treatment response is assessed by resolution of clinical signs/symptoms and laboratory findings such as serum ferritin levels, liver function tests and fibrinogen levels.¹⁶ In this patient, ferritin levels dropped significantly after treatment, along with clinical resolution of the disease.

Primary HLH has a poor prognosis with a 30-day mortality rate of 20–44% and an overall mortality rate ranging from 50% to 75%. Although the mortality rate for it is not well established, secondary HLH is fatal in the absence of treatment.¹⁷

Table 1 Reported case reports of HLH with *Plasmodium vivax*

Age/gender	41/F	23/M	22/M	64/F	19/M	8/F	Child/F	20/M
Country	France	Korea	Korea	Korea	Pakistan	India	India	Pakistan
Publication Journal/year	<i>Br J Haematol</i> /2000	<i>Am J Hematol</i> /2003	<i>Ann Hematol</i> /2011	<i>Chonnam Med J</i> /2011	<i>Case Rep Med</i> /2015	<i>J Vector Borne Dis</i> /2014	<i>J Vector Borne Dis</i> /2013	
Main symptom	Fever	Fever	Fever	Fever	Fever	Fever	Fever	Fever
Comorbidity	None	None	None	None	None	None	None	None
Hepatosplenomegaly	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
AST/ALT (U/L)	65/78	546/391	62/66	39/30	1283/37	Normal range	104/106	Normal range
Total bilirubin (mg/dL)	3.5	3.41	1.9	3.97	8.3	—	3.3	4.34
White cell counts (/mm ³)	2000	2590	2300	2380	3100	1400	2100	2000
Haemoglobin (g/dL)	9.4	15.4	12.5	11.7	7.8	4.2	5.2	6.4
Platelet (/mm ³)	64 000	53 000	38 000	36 000	62 000	11 000	16 000	58 000
Ferritin (µg/L)	1190	>1000	645.8	923	40 000	316	1070	817
Fibrinogen (mg/dL)	Normal	—	—	>500	135	90	102	Normal range
Triglyceride (mg/dL)	270	—	—	210	292	284	297	96
Bone marrow examination	Haemophagocytic histiocytosis	Haemophagocytic histiocytosis	Haemophagocytic histiocytosis	Haemophagocytic histiocytosis	Haemophagocytic histiocytosis	Haemophagocytic histiocytosis	Haemophagocytic histiocytosis	Haemophagocytic histiocytosis
Peripheral smear	Trophozoite and gametocyte	Trophozoite and gametocyte	Trophozoite and gametocyte	Trophozoite and gametocyte	Gametocytes and schizonts	Trophozoite and gametocyte	Gametocytes and schizonts	Trophozoites and gametocytes
Treatment	Oral chloroquine and primaquine	Oral chloroquine and primaquine	Oral chloroquine and primaquine	Oral chloroquine and primaquine	Intravenous artesunate	Intravenous artesunate, sulfadoxine and pyrimethamine	Intravenous artesunate, artemether, lumefantrine, primaquine (all per orally)	Intravenous artesunate
Outcome	Recovered	Recovered	Recovered	Recovered	Expired	Recovered	Recovered	Recovered
Reference	8	9	10	11	12	13	14	This case

ALT, alanine transaminase; AST, aspartate transaminase; F, female; HLH, haemophagocytic lymphohistiocytosis; M, male.

Box 1 Reproduced from Henter *et al*¹⁵

For diagnosis of haemophagocytic lymphohistiocytosis (HLH), either one or both of the following criteria should be met.

A. *Molecular diagnosis compatible with HLH*: pathological mutations of *STX11*, *PRF1*, *UNC13D*, *Rab27a*, *BIRC4*, *STX11*, *Munc18-2* or *SH2D1A*.

B. *Five of the following eight diagnostic criteria*

1. Fever
2. Splenomegaly
3. Cytopenias (at least 2 of the following lineages)
 - ▶ Haemoglobin <9 g/dL
 - ▶ Neutrophils <1×10³/mL
 - ▶ Platelets <100×10³/mL
4. Hypofibrinogenaemia (<150 mg/dL) and/or hypertriglyceridaemia (fasting, >265 mg/dL).
5. Haemophagocytosis found in bone marrow, lymph nodes, liver or spleen.
6. Ferritin levels >500 ng/mL.
7. Decreased or non-existent natural killer cell activity.
8. Increased levels of soluble CD25>2400 U/mL.

Learning points

- ▶ This case underscores the association of *Plasmodium vivax* with HLH.
- ▶ HLH can be primary or secondary to infections, malignant diseases, autoimmune and metabolic conditions, and the management of each type varies.
- ▶ The timely diagnosis of the inciting factor (*P. vivax* in this case) has significant prognostic implications.
- ▶ The association between HLH and vivax malaria cases in endemic area may have direct implications on healthcare planning, as this association entails a significant risk.

Contributors WU and MAS were in charge of writing the background and case presentation, and follow-up of the patient. SQ and HMAA were involved in writing the discussion and summary portions. All the authors were involved in the management of the patient and data collection for the report.

Competing interests None declared.

Patient consent Obtained.

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