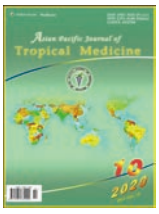

Case Report

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Haemophagocytic lymphohistiocytosis secondary to *Plasmodium falciparum* malaria: Case report and review of the literature

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ABSTRACT

Rationale: Haemophagocytic lymphohistiocytosis is a rare complication of malaria, which is often misdiagnosed.

Patient concerns: A 30-year-old male was admitted to our department for persistent fever, which began after returning from a stay in Guinea-Conakry. The laboratory investigations revealed a pancytopenia and an elevated C-reactive protein. Peripheral smear examination showed *Plasmodium falciparum*, therefore confirming the diagnosis of malaria. The laboratory tests showed a worsening pancytopenia. Bone marrow aspiration and biopsy revealed images of hemophagocytosis.

Diagnosis: The diagnosis of haemophagocytic lymphohistiocytosis complicating malaria infection was established.

Interventions: The patient was treated with artemether-lumefantrine. No immunosuppressant treatment was delivered to the patient. He received antipyretic and antimalarial treatment only.

Outcomes and lessons: We report a case of haemophagocytic lymphohistiocytosis trigged by malaria infection and we review all reported cases secondary to *Plasmodium falciparum* malaria by searching PubMed publications till October 2019. Haemophagocytic lymphohistiocytos secondary to malaria should be suspected even in non-severe cases of malaria.

KEYWORDS: Diagnosis; Haemophagocytic lymphohistiocytosis; Malaria; *Plasmodium falciparum*

1. Introduction

Malaria, a public health problem, is still endemic in the tropical and subtropical areas, most notably Southeast Asia, the Amazon and Africa[1]. Despite preventive measures, mortality rate related to malaria globally ranges from 0.3% to 2.2% and reaches 11% to 30% in cases of severe forms of malaria in regions with tropical climate[2]. Since 1979, malaria have been eliminated from our country and since then, only imported cases were reported[3]. Fever, in a patient returning from a tropical area, accompanied by malaise and musculoskeletal pain are the symptoms of uncomplicated malaria[4]. However, serious complications may occur such as cerebral malaria, bleeding, severe anemia, liver dysfunction and renal failure[5]. Another rare complication is haemophagocytic lymphohistiocytosis (HLH), which is a systemic disorder caused by an excessive immune reaction[5]. We distinguish primary (familial) HLH, occurring in children with known genetic defects, and secondary (acquired) HLH caused by infection, malignancy or rheumatologic disorders and occurring in patients typically older[6,7].

The diagnosis, often delayed, remains a significant concern due to the complexity of diagnostic criteria and similarity to other inflammatory disorders[7]. We report herein a case of HLH trigged by malaria infection in a 30-year-old immunocompetent male and we review all reported cases of HLH secondary to *Plasmodium (P.) falciparum* malaria by searching PubMed publications till October

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2019. We excluded from the search cases of non *P. falciparum* malaria or non documented species of malaria. Written consent to publish the case report has been obtained from the patient.

2. Case report

A 30-year-old male with no significant medical history was presented to our department for persistent fever which have been evolving since 8 days, associated with polyarthralgia and myalgia. His symptoms began 5 days after returning from a stay in Guinea-Conakry, which lasted 2 years and a half. On admission, he had a body temperature of 40 ℃, his heart rate was 106 beats/min and his blood pressure was 102/60 mmHg. Physical examination showed a conjunctival pallor and a splenomegaly, but with no icterus, nor lymphadenopathy. His laboratory investigations revealed an elevated C-reactive protein (177 mg/L) and a pancytopenia. Blood tests showed low white blood cells count (2 400/mm^3) with a neutrophil rate at 1 010/mm^3, thrombocytopenia (44 000/mm^3) and anemia (8.1 g/dL). He had normal liver and renal functions. Peripheral smear examination showed *P. falciparum*, therefore confirming the diagnosis of malaria. The patient was treated with artemether-lumefantrine at a dose of 4 tablets twice-daily for 3 days. Although his fever resolved after initiation of the treatment, pancytopenia continued to worsen. Ferritin level was elevated at 891 μg/L and triglyceride rate was high at 2.7 mmol/L. Blood tests also showed a fibrinogen level of 1.16 g/L and a serum lactate dehydrogenase (LDH) level at 236 UI/L.

Bone marrow aspiration and biopsy revealed images of hemophagocytosis (Figures 1 and 2). Satisfying six out of eight criteria including fever, splenomegaly, pancytopenia, hypofibrinogenemia, hyperferritinemia and images of hemophagocytosis, the diagnosis of HLH complicating malaria infection was confirmed. No immunosuppressant treatment was delivered to our patient. He received antipyretic and antimalarial treatment only.

The disease evolution was favourable. His general condition improved. There were no more episodes of fever. His blood tests showed an improvement. The white blood cells count was 4 000/mm^3 with a neutrophil rate at 2 330/mm^3, platelets rate was 148 000/mm^3 and hemoglobin level was 10.9 g/dL after 5 days of treatment. Control peripheral smear examination at day 3 and day 7 were both negative. The patient was discharged after one week. His follow-up visit a week later showed normal blood tests.

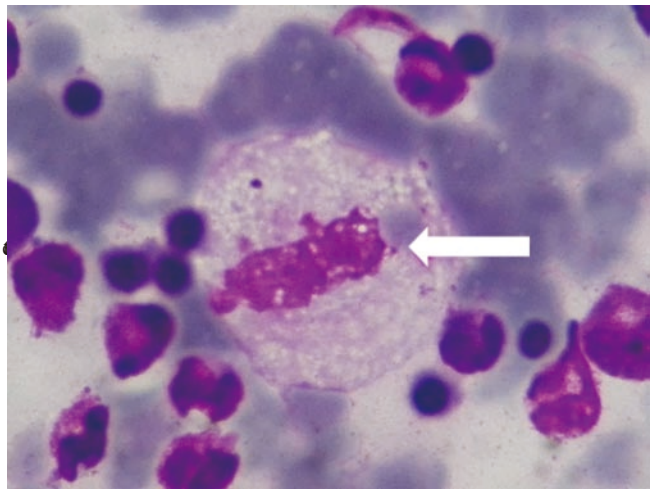

Figure 1. Bone marrow biopsy of a 30-year-old male with persistent fever showing macrophage (arrow) phagocyting platelets (Wright-Giemsa stain × 100).

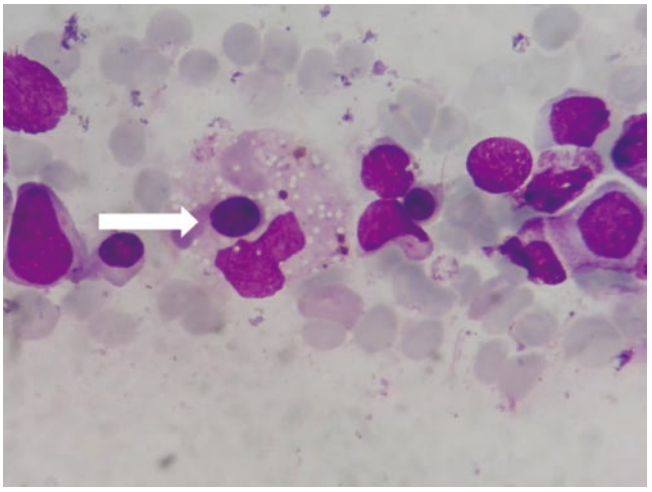

Figure 2. Bone marrow biopsy of a 30-year-old male with persistent fever showing macrophage (arrow) phagocyting erythroblasts and platelets (Wright-Giemsa stain ×100).

3. Discussion

HLH trigged by malaria was a rare disease. The literature search yielded 22 cases with HLH secondary to *P. falciparum* malaria, including our case[6,8–26] (Table 1). The majority of the cases reported in the literature were trigged by severe malaria and the diagnosis of HLH was mostly considered after the deterioration of the clinical condition of the patient. Our patient had no signs of severe malaria. The diagnosis of HLH was suspected and confirmed in front of a worsening cytopenia during the resolution phase of malaria. The majority of the described cases had 5 of the 8 criteria used for HLH[7]. Neither the evaluation of the interleukin-2 (IL-2) receptor, nor the natural killer cell activity were performed, except for one case of a 5-year-old boy who had an elevated IL-2

Table 1. Clinical characteristics and management of malaria-related haemophagocytic lymphohistiocytosis reported in the literature.

References	Age (years)	Sex	Country (recent travel)	Fever	SMG	Pancy-topenia	TG >265 mg/dL	Fg< 1.5 g/dL	Ferritin >500/ mg/dL	Hemo-phagocytosis in BMA	Malaria diagnosis (parasite index)	Anti-malarial therapy
Muthu (2017)[6]	34	M	India	+	+	+	+	-	+	+	RDT Smear	Artesunate, doxycycline
Muthu (2017)[6]	43	F	India	+	NL	+	+	-	+	+	RDT	Artesunate, doxycycline
Harioly (2017)[8]	32	F	Madagascar	+	+	+	NL	+	+	+	RDT Smear (15%)	Artemisinin-based combination therapy
Niang (2008)[9]	37	F	Senegal	+	NL	bicyt	NL	-	+	+	Smear	Quinine
Ohnishi (2007) [10]	30	F	Japan (Guinea)	+	NL	+	NL	NL	NL	+	Smear (25%)	Quinine, astesunate relayed by mefloquine
Ladeb (2018)[11]	27	M	Tunisia	+	NL	+	NL	NL	+	+	Smear (20%)	Quinine
Selvarajan (2017) [12]	24	M	India	+	+	+	+	NL	+	+	Smear (5%)	Artesunate relayed by atovaquone/ proguanil
Weeratunga (2016)[13]	55	M	Sri Lanka (South Africa)	+	+	+	+	+	+	+	Smear (6%)	Artesunate
Bhagat (2015)[14]	5	F	Mumbai	+	+	+	+	-	+	-	Smear	Artesunate primaquine relayed by quinine
Trifi (2014)[15]	16	F	Tunisia (Ivory Coast)	+	+	+	+	NL	+	+	RDT Smear (3%)	Quinine relayed by artemether-lumefantrine
Santos (2015)[16]	5	M	Portugal (Mozambique)	+	+	+	+	+	+	NL	Smear (<1%)	Quinine
Vinoth (2011)[17]	11*	M	India	+	+	+	+	+	+	+	Smear BMA	Artesunate
Dass (2010)[18]	16	M	India	+	+	bicyt	+	+	+	+	Smear (8.4%)	Quinine relayed by artesunate
Sermet (2000)[19]	2	M	Gabon	+	+	+	-	+	NL	Unsuccessful	Smear	Quinine
Zvulunov (2002) [20]	11	F	Israel (Cameroon)	+	+	+	NL	NL	NL	+	Smear	Mefloquine, primaquine
Sanklecha (2012) [21]	12	F	Mumbai	+	+	bicyt	+	NL	+	+	Smear	Artesunate halofantrine relayed by mefloquine
Abdelkefi (2004) [22]	25	M	Tunisia	+	+	+	NL	NL	NL	+	Smear (23%) BMA	Quinine
Rehman (2012) [23]	22	M	Kingdom of Saudi Arabia	+	NL	+	+	NL	+	+	Peripheral film (6.1%)	Quinine
Retornaz (2000) [24]	73	M	Marseille (Madagascar)	+	+	bicyt	-	NL	+	+	Smear (5%) BMA	Quinine
Anwar (1995)[25]	NL	M	Germany (Pakistan)	+	+	+	NL	NL	NL	+	Smear BMA	Chlomquine relayed by fansidar
Ohno (1996)[26]	24	M	Japan (Tropical areas)	+	+	bicyt	NL	NL	+	+	Smear	NL
Our case (2019)	30	M	Tunisia (Guinea-Conakry)	+	+	bicyt	-	+	+	+	Smear	Artemether-lumefantrine

M: male, F: female, SMG: splenomegaly, TG: triglyceride, Fg: fibrinogen, BMA: bone marrow aspiration, Bicyt: bicytopenia, NL: not listed, RDT: rapid diagnostic test, *: months.

receptor at 4 352 U/mL[16]. All patients recovered. No death due to malaria-associated HLH was reported[6, 8–26]. All patients received antimalarial therapy. Eleven patients received specific treatment for HLH represented by corticosteroids in 7 cases[9–12,14,18,19] and intravenous immunoglobulin in 4 cases[6,15,24].

The real incidence of HLH complicating malaria infection might be underestimated in front of the low index of suspicion. For example, cytopenia and splenomegaly which can be seen during HLH, can be associated to malaria. However, for our patient, a worsening cytopenia during the resolution phase of malaria, and the association with hyperferritinemia, hypertriglyceridemia and hypofibrinogenemia, were alarming signs which indicated the bone marrow biopsy.

Malaria remains responsible for significant mortality in endemic areas[8]. Previous studies showed that more than half of the world's population are at risk of contracting malaria, although a decline in the incidence of malaria in endemic areas over the last decade was reported[27]. As soon as the diagnosis is established, antimalarial treatment is indicated. The treatment choice is based on the patient characteristics and his concomitant medication, the geographic region of infection, the clinical features of malaria, the causative *Plasmodium* species and the use of chemoprophylaxis and/or previous curative treatment for malaria[27].

HLH may lead to death if not promptly diagnosed and treated. It is a rare, but a life-threatening syndrome associated with excessive immune activation. Familial HLH is mostly recognized in childhood, whereas the acquired form can occur at any age and is secondary to infections (viral, bacterial, fungal or parasitic infections), autoimmune or neoplastic conditions[6,28].

The secondary HLH treatment strategy includes supportive care, treatment of the underlying etiology and the use of immunosuppressants (steroids, intravenous immunoglobulin and other immunosuppressive drugs such as dexamethasone or etoposide) in unresponsive cases in order to target the hyperinflammatory state [6,28]. However, for HLH associated to infections, patients usually recover with the treatment of the causative infection[5], like the case of our patient. The prognosis of HLH depends mainly on its early diagnosis and the underlying etiology. The 5-year survival rate was 83% in patients with HLH associated to infections[29].

HLH secondary to *P. falciparum* malaria was a rare disease, probably underrecognized and misdiagnosed. Malaria should always be considered in front of an unexplained fever after returning from an endemic country. The diagnosis of HLH secondary to malaria must be bearded in mind even in non-severe cases of malaria. A prompt diagnosis and treatment of malaria associated to HLH may prevent serious complications and improve the prognosis.

Conflict of interest statement

We declare that we have no conflict of interest.

Authors' contributions

FH, MK and MBJ developed the theoretical formalism. MC, RC, AZ collected the exact data from the patient, and other para-clinical findings. FH and MK wrote the manuscript. FH, MK, KR, FS and MBJ contributed in data analysis and critical revision of the manuscript. All authors approved the manuscript for publication.

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