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Malaria-associated secondary haemophagocytic lymphohistiocytosis: Report of two cases & a review of literature

Sir,

Haemophagocytic lymphohistiocytosis (HLH), a systemic disorder caused by immune dysregulation, occurs in primary (genetic) and secondary (acquired) forms. Secondary HLH refers to cases triggered by infections, malignancy (predominantly haematologic) and autoimmune diseases[1]. Primary HLH is mostly recognized in childhood whereas the secondary form can occur at any age[2]. HLH secondary to infections can occur with viral, bacterial, fungal or parasitic infections; viral infections, [especially Epstein–Barr virus (EBV)], being the most common[1,3]. While the treatment of familial or primary HLH has been systematically studied and reported, the optimum treatment of secondary HLH remains speculative[4]. Literature on malaria-associated HLH is sparse. We describe here two cases of malaria-associated secondary HLH successfully managed with intravenous immunoglobulin (IVIG). The literature on secondary HLH associated with malaria, has also been reviewed.

The first case was a 43 yr old male presented to the Pulmonary Medicine Outpatient Department (OPD), Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, in August 2013 with fever, dry cough and breathlessness of four days' duration. Examination revealed pallor, icterus and tachypnoea. Investigations showed the presence of anaemia, thrombocytopenia and conjugated hyperbilirubinaemia (Table I). Rapid diagnostic test [based on species-specific lactate dehydrogenase (LDH)] was positive for *Plasmodium vivax* as well as *P. falciparum*. The peripheral blood smear revealed *P. vivax* ring forms. Chest radiograph was suggestive of acute respiratory distress syndrome (ARDS). During the hospital stay, the patient developed worsening respiratory distress and hypotension. He was intubated and started on mechanical ventilation; vasopressors were administered. He was treated with intravenous (i.v.) ceftriaxone, i.v. artesunate and oral doxycycline. Following a transient clinical improvement, the patient's clinical status worsened. Investigations on day seven of hospitalization revealed pancytopenia. Clinical possibilities of sepsis-associated bone marrow suppression, drug-induced bone marrow suppression and HLH, were considered. Further investigations showed raised liver transaminases, raised serum LDH, hypertriglyceridaemia, raised serum ferritin and splenomegaly on abdominal ultrasonography. EBV and *cytomegalovirus* (CMV) serologies (IgM) were negative. Bone marrow aspiration showed the presence of haemophagocytosis (Figure A). A diagnosis of secondary HLH was made. IVIG (2 g/kg given in divided doses over five days) was administered for the management of secondary HLH. The patient's condition improved gradually and laboratory parameters including leucocyte and platelet counts, liver transaminases, serum LDH and triglycerides normalized. The patient was extubated on day 13 of hospitalization and discharged two days later. The patient was doing well after six months and his blood counts were all within normal limits.

The second case was a 34 yr old female who was admitted in December 2013 with high-grade fever and progressive breathlessness for 10 days. She had tachypnoea and pallor but no icterus or lymphadenopathy. On admission, she had normal liver and renal functions. Rapid diagnostic test (species-specific LDH-based immunochromatographic test) was positive for *P. falciparum*. However, the peripheral smear for malarial parasite was negative on four occasions. Chest radiograph and arterial blood gas analysis suggested ARDS. She was intubated and mechanically ventilated for respiratory failure. The patient was treated with i.v. ceftriaxone, i.v. artesunate

Table I. Laboratory parameters of the two cases

Parameters	Case 1		Case 2	
	In hospital*	At discharge	In hospital*	At discharge
Haemoglobin (g/dl)	7.8	9.2	6.8	9
Total leucocyte count (×10⁹/l)	3.1	11.2	0.8	8.3
Absolute neutrophil count (×10⁹/l)	1.9	7.9	0.48	5.3
Platelet count (×10⁹/l)	27	402	35	140
Serum ferritin (µg/l)	2110		7400	
Urea (mg/dl)	88	17	71	44
Creatinine (mg/dl)	0.7	0.51	0.44	0.46
AST/ALT (U/l)	89/54	24/27	184/80	34/36
Alkaline phosphatase (IU/l)	133	112	375	200
Total/conjugated bilirubin (mg/dl)	6.3/4	1.8/0.6	1.2/0.5	1.3/0.6
Protein/albumin (g/dl)	6.02/2.3	7/3.4	4.0/1.9	6/3.2
Lactate dehydrogenase (U/l)	1592	245	1233	210
Triglycerides (mg/dl)	546	210	328	180
Fibrinogen (g/l)	4.5	4	2.13	3

*Values present at the time of diagnosis of HLH (and not at the initial presentation) during hospital stay.
AST, aspartate transaminase; ALT, alanine transaminase; HLH, haemophagocytic lymphohistiocytosis

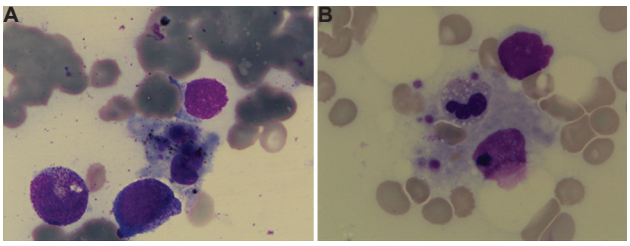

Figure (A) Hamophagocytosis seen on the bone marrow aspiration smear of case 1. **(B)** Bone marrow aspiration smear of case 2 showing haemophagocytosis with leucocytes, erythrocytes and platelets inside a macrophage.

and oral doxycycline along with best supportive care. She remained clinically stable for two days, following which high-grade fever reappeared. Shock and hypoxaemia resolved, but pancytopenia worsened. Drug-induced bone marrow suppression, sepsis-associated bone marrow suppression and HLH were considered in the differential diagnosis. Secondary HLH was suspected in view of pancytopenia, raised liver transaminases, raised LDH, hypertriglyceridaemia, raised serum ferritin and hypofibrinogenaemia (Table I). Bone marrow aspiration and biopsy revealed haemophagocytosis (Figure B). IgM antibodies against CMV and EBV were absent. IVIG was administered over two days (total dose of 2 g/kg). Following this therapy, the laboratory parameters improved. She was extubated after 12 days of admission and discharged on day 21 of hospitalization after resolution of the nosocomial infection. No recurrence of fever or cytopenia was noted on follow up at six months.

The two cases described here exemplify the classic course of HLH secondary to tropical infections. HLH is suspected in patients presenting with high-grade fever and multisystem involvement[1,5]. Cytopenia and splenomegaly often draw the clinician's attention to the possibility of this rare syndrome. The findings of raised ferritin and triglyceride and/or a low fibrinogen further increase the probability of HLH. Confirmation often arrives from the demonstration of haemophagocytosis in the bone marrow biopsy[6]. It is noteworthy that the criteria used for diagnosing secondary HLH are an extrapolation from what is used for primary HLH and have not been validated systematically for secondary HLH[4].

Malaria as a cause of secondary HLH is rare. The literature search yielded 17 studies (18 patients) reporting on patients with HLH secondary to malaria (Table II)[7-23]. A majority of the described cases have reported only six of the eight criteria used for HLH, and investigations to look for natural killer cell activity and soluble CD25 antigen levels were not available in most cases except one[11]. Only three of the 18 previously reported cases of malaria associated HLH had shown malarial parasites in bone

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

References	Age (yr)	Sex	Comorbidity	Country (recent travel)	Species	Diagnosis (parasite index)	Management	Additional therapy
Ohno *et al*[7]	24	Male	None	Japan (tropics travel)	*Plasmodium falciparum*	Smear	Antimalarials (further details NA)	
Anwar *et al*[8]	Young adult	Male	None	Germany (Pakistan)	*P. falciparum*	Smear	Chloroquine (failed) Sulphadoxine pyrimethamine	
Retornaz *et al*[9]	73	Male	None	France (Madagascar)	*P. falciparum*	Smear (>5%)	Quinine 1.2 g/day for five days	IVIG 20 g/day for three days
Park *et al*[10]	23	Male	None	South Korea	*P. vivax*	Smear	Hydroxy-chloroquine and primaquine	
Ohnishi *et al*[11]	30	Female	None	Japan (Papua new guinea)	*P. falciparum*	Smear (25%)	Quinine (420 mg) i.v., artesunate (200 mg) suppository Mefloquine p.o.	Methyl-prednisolone pulse followed by oral prednisolone – partial improvement Prolonged course of oral prednisolone for persisting marrow haemo-phagocytosis
Aouba *et al*[12]	41	Female	None	France (Costa Rica)	*P. vivax*	Marrow	Chloroquine 500 mg/day p.o. five days	
Bae *et al*[13]	22	Male	None	South Korea	*P. vivax*	Smear (PCR confirmed, marrow parasites present)	Hydroxy-chloroquine, primaquine 14 days	
Sung *et al*[14]	64	Female	None	South Korea	*P. vivax*	Smear (confirmed by PCR also)	Hydroxy-chloroquine three days (25 mg/kg) primaquine 14 days (15 mg/day)	
Rehman *et al*[15]	22	Male	Sickle cell trait	Saudi Arabia	*P. falciparum*	Smear (6.1%)	Quinine i.v.	
Abdelkefi *et al*[16]	25	Male	CMML post-PBSCT	Tunisia	*P. falciparum*	Smear (23%)	Quinine i.v. 10 mg/kg three days	

Contd...

References	Age (yr)	Sex	Comorbidity	Country (recent travel)	Species	Diagnosis (parasite index)	Management	Additional therapy
Dass *et al*[17]	16	Male	none	India	*P. falciparum*	Smear (8.4%)	Quinine i.v., artesunate i.v. and exchange transfusion	Pulse methyl-prednisolone 1 g/day for three days followed by 60 mg oral prednisolone 14 days
Nair *et al*[18]	28	Male	-	India	*P. falciparum* and *P. vivax*	Smear and RDT	Artesunate combination therapy (artesunate and doxycycline)	IVIG 400 mg/kg/day for five days
Nair *et al*[18]	58	Female	-	India	*P. falciparum*	Smear and RDT	Artesunate combination therapy (doxycycline and artesunate)	IVIG 400 mg/kg/day for five days
Sanklecha *et al*[19]	12	Female	None	India	*P. falciparum*	Smear	Artesunate i.v. followed by artemether i.m. with halofantrine three days and mefloquine	
Tanwar *et al*[20]	Child	Female	None	India	*P. vivax*	Smear, RDT (confirmed by PCR)	Artesunate i.v. two days Oral artemether, lumefantrine three days Primaquine 14 days	
Zvulunov *et al*[21]	11	Female	None	Cameroon	*P. falciparum* and *P. vivax*	Smear	Mefloquine followed by primaquine 14 days	
Vinoth *et al*[22]	11 months	Male	None	India	*P. falciparum*	Bone marrow	Artesunate i.v.	
Sermet-Gaudelus *et al*[23]	2	Male	None	Gabon	*P. falciparum*	Smear	Quinine i.v. 25 mg/kg/day	Prednisolone 1.5 mg/kg/day

CMML, chronic myelomonocytic leukaemia; i.m., intramuscular; i.v., intravenous; PBSCT, peripheral blood stem cell transplant; PCR, polymerase chain reaction; p.o., per oral; RDT, rapid diagnostic test; NA, not available; IVIG, intravenous immunoglobulin

marrow[12,13,22]. Although malarial parasite/pigment was not demonstrated in the bone marrow of the remaining patients (including the index patients), malaria seems to be the most likely cause of secondary HLH in these cases due to the temporal relationship to the illness.

Of the 20 cases (including present two cases), three patients had dual infection with *P. vivax* and *P. falciparum*. All patients were either native of countries in Asia or Africa or had travelled to these places. The diagnosis of malaria was based on peripheral blood smear and/or rapid diagnostic tests for malarial antigens, supported by molecular methods in a few instances[13,14,20]. Malaria-associated HLH was observed in previously healthy individuals except

for two patients: an adult with sickle cell trait and the other with chronic myelomonocytic leukaemia following peripheral blood stem cell transplant[15,16]. Twelve patients improved with antimalarial therapy alone and eight patients (40%) required additional immunosuppression. Of these eight patients, IVIG was used in five and corticosteroids in three. All patients recovered. No death due to malaria-associated HLH has been reported.

The treatment strategy for secondary HLH includes supportive care, treatment of inciting factor and the use of immunosuppressants (steroids, IVIG and other immunosuppressive drugs) in unresponsive cases[1]. Polyclonal IVIG, a preparation of IgG antibodies derived from pooled serum of thousands of donors, is used primarily as replacement therapy for patients with immunodeficiencies. IVIG has also been found to be used in the treatment of autoimmune conditions and even in sepsis where its primary mechanism of action is by immunomodulation[24]. The exact mode of its action in HLH needs further elucidation. The use of IVIG as the sole immunological treatment in infection-associated HLH, in particular malaria-associated HLH, warrants further investigation.

In conclusion, HLH in malaria is rare, although underrecognition and underreporting may contribute to the apparent rarity. Prospective and systematic data collection is essential to assess the incidence and the natural history of secondary HLH in the tropics. IVIG as an additional treatment option for this form of HLH needs further research.

***Conflicts of Interest*:** None.

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