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LETTER TO THE EDITOR

Hemophagocytic lymphohistiocytosis secondary to Falciparum malaria in a 5 year-old boy

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Dear Editor,

A previously healthy 5-year-old Portuguese boy presented to our Emergency Department (ED) with a history of 4 days of high fever and painful abdomen. He had been living in Mozambique (Matola) for the last year and didn't held malaria prophylaxis. At the time of admission, he was febrile and jaundiced, and a splenomegaly was noticed on physical examination. Initial laboratory data showed leucopenia, thrombocytopenia, high liver enzymes, direct hyperbilirubinemia, and elevated C-reactive protein. The diagnosis of malaria was confirmed by the presence of *Plasmodium falciparum* trophozoites in thin and thick blood films and by positive *Plasmodium* antigenemia. Despite a parasitemia of <1 %, he was admitted and treated with IV quinine and clindamycin with diagnosis of severe malaria according to WHO criteria (Table 1). On the following days, his clinical condition deteriorated, presenting with high fever, hypotension, mucosal bleeding, pleural effusion, and ascites. Laboratory workout revealed disseminated intravascular coagulation, pancytopenia, cholestatic hepatitis, hypoalbuminemia, as well as elevated ferritin (5,890 ng/mL) and soluble CD25 (sIL2R =4,352 U/mL). Other co-infections were excluded (Table 1).

Despite the diagnosis of Falciparum malaria-associated hemophagocytic lymphohistiocytosis (HLH), he did not receive HLH-directed therapy and was treated with antimalaric drugs and supportive measures: packed red cells, platelets, fresh frozen plasma, cryoprecipitate, purified concentrate of fibrinogen, as well as inotropic support with dopamine (day 2 - 4). His clinical and laboratory condition slowly improved (Table 1). He was discharged home 12 days after being hospitalized.

A hereditary cause for HLH was not investigated due the prompt improvement without HLH-targeted therapy.

HLH is a potentially fatal hyperinflammatory condition caused by a highly stimulated but ineffective immune response [1]. It has been described as a familial disorder (due to defects in Nk citotoxicity) and as a sporadic one [2]. The latter has been associated with infections, malignancies, or rheumatologic disorders [3].

Infection-associated HLH can be triggered by virus, bacteria, fungi, or protozoa [1–4], but *P. falciparum* has rarely been reported as a cause of HLH [5–7], especially in children [10].

A deranged immune response is the cause of HLH, and the associated cytokine storm is responsible for the majority of the clinical and laboratory abnormalities [1–4]. The clinical diagnosis is established fulfilling five of the eight HLH-2004 criteria [1]. Noteworthy are the facts that hemophagocytosis is not required for establishing the diagnosis, that ferritin levels above 10,000 ng/mL are highly specific for HLH and that very high levels of sIL2Rα are almost never seen outside HLH [3].

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Table 1 Laboratory data performed on admission day (day 1), during hospitalization (between days 2 and 3), and at discharge (day 12)

Laboratory evaluation	Day 1	Day 2–3	Day 12
Hemoglobin (g/dL)	13.6	**8.9**	11.7
WBC ($\times 10^9$/L)	**3.8**	**3.8**	9.6
ANC ($\times 10^9$/L)	1.99	**0.94**	4.22
Platelet count ($\times 10^9$/L)	**21**	**9**	502
PT (s)/INR/APTT (s)	11.1/0.97/37	**16.6/1.45/53.3**	10.8/0.95/30.8
Fibrinogen (g/L)	–	**0.6**	**1.5**
D-dimer (μg/mL)	–	**13.288**	**2.382**
CRP (mg/L)	**73.9**	**81.3**	2.9
AST/ALT/LDH (U/L)	**147/84/1063**	**139/76/1411**	53/**53/510**
GGT/ ALP (U/L)	**281/605**	**190/626**	**141/622**
T-Bil/D-Bil (mg/dL)	**10.53/6.09**	**10.91/6.71**	**2.33/0.87**
Triglycerides (mg/dL)	91	**306**	**197**
Albumin (g/L)	–	**21**	36
BUN/creatinine (mg/dL)	34/**0.46**	**51/0.62**	12/0.20
Na (mEq/L)	**129**	**135**	139
Ferritin (ng/mL)	–	**5890**	**734**
sCD25 (U/mL)	–	**4352**	–
Plasmodium falciparum	Positive antigenemia Trophozoites on peripheral blood smear Parasite density 0 %	Positive antigenemia Trophozoites on peripheral blood smear	Negative antigenemia
EBV, CMV and PVB19 serology, blood cultures, O&P test	Negative		

Normal range—hemoglobin, 11.5–13.5 g/dL; WBC, 5–15×10^9/L; ANC, 1.5–8×10^9/L; platelet count, 200–450×10^9/L; PT, 10.1–12.1 s; INR, 0.91–1.11; APTT, 26–36 s; fibrinogen, 1.57–4 g/L; D-dimer, <0.23 μg/mL; CRP, <5 mg/L; AST 15–60 U/L; ALT, <39 U/L; LDH, 110–295 U/L; GGT, <22 U/L; ALP, 86–362 U/L; *T-Bil,* 0.3–1.2 mg/dL; *D-Bil,* 0–0.2 mg/dL; triglycerides, <150 mg/dL; albumin, 35–52 g/L; BUN, 10.8–38.4 mg/dL; creatinine, 0.16–0.39 mg/dL; Na, 136–145 mEq/L; ferritin, 24–336 ng/mL; sCD25, <1,000 U/mL. Bold numbers - abnormal values

WBC white blood cell, *ANC* absolute neutrophil count, *PT* prothrombin time, *INR* international normalized ratio, *APTT* activated partial thromboplastin time, *CRP* C-reactive protein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, GGT gamma-glutamyl transferase, *ALP* alkaline phosphatase, *T-Bil* total bilirubin, *D-Bil* direct bilirubin, *BUN* blood urea nitrogen, *Na* sodium, *sCD25* soluble CD25, *EBV* Epstein–Barr virus, *CMV Cytomegalovirus, PVB19* human parvovirus B19, *O&P* ova and parasite (stool) test

The authors believe that despite being rarely described, HLH-associated malaria should be suspected in patients with severe malaria and unexpected multiorgan failure. Experimental studies have demonstrated that several soluble exoantigens of *P. falciparum* induce inappropriate macrophage activation and a Th1-stimulated hypercytokinemia with excessive production of the TNF-α and INF-γ [8], which are some of the major cytokines responsible for HLH. This has also been well described with other infectious agents, such as EBV [9].

Most cases of malaria-induced HLH reported in literature have responded completely to antimalarial therapy alone [5–7], as observed in our case. Nevertheless, like in EBV-associated HLH [10], in the rare cases where there is progression of HLH despite appropriate antimalarial therapy, a stepwise approach can probably be applied, in order to allow disease control without jeopardizing the infection control.

Conflict of Interest The authors declare that they have no conflict of interest.

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