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Case Report

HaemophagocyticLymphohistiocytosis Secondary to Severe Falciparum Malaria: A Case Series from a UK Tertiary Centre.

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Abstract

Background: Haemophagocytic lymphohistiocytosis (HLH) is a rare but often fatal hyperinflammatory syndrome that can be triggered by infections, including *Plasmodium falciparum*. Although HLH secondary to malaria is documented, it remains under-recognised in clinical practice. We describe two cases of HLH complicating severe falciparum malaria, aiming to highlight diagnostic challenges and therapeutic considerations.
Methodology: This is a retrospective case series of two adult female patients admitted to a tertiary intensive care unit (ICU) in London, UK. Clinical data were extracted from the electronic health record (Epic Hyperspace). HLH was diagnosed using HLH-2004 criteria and the HScore (calculated with MDCalc). Both patients were treated with anti-malarials and HLH-directed immunomodulation, including corticosteroids, IVIG, and anakinra.
Results: Both patients fulfilled ≥5 of the HLH-2004 criteria and had elevated ferritin (>21,000 and 48,000 µg/L, respectively) with HScore probabilities of 98–99%. One case was confirmed by bone marrow haemophagocytosis. Both required renal replacement therapy and invasive ventilation. Ferritin and organ function improved following combined immunosuppressive therapy, with complete clinical recovery and discharge by days 31 and 32 of illness.
Conclusion: Malaria-associated HLH, though rare, should be suspected in adults with severe P. falciparum infection and extreme hyperferritinaemia. Early recognition and immunomodulatory therapy guided by HScore and HLH-2004 criteria can be lifesaving. Clinicians in endemic regions and among returning travellers should maintain vigilance for HLH in cases of severe malaria unresponsive to standard treatment.

Keywords: HLH, malaria, hyperinflammation, critical care, anakinra, immunosuppression, intravenous immunoglobulin, HScore, continuous renal replacement therapy (CRRT).

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Introduction

Haemophagocyticlymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome characterised by fever, cytopenias, hepatosplenomegaly, hyperferritinaemia, and multiorgan failure [1]. It results from uncontrolled activation of cytotoxic lymphocytes and macrophages, leading to excessive cytokine release and tissue damage [2]. HLH may be primary (familial) or secondary, most often triggered by infections, malignancies, or autoimmune diseases [3].

In adults, infection-associated secondary HLH is more frequent but remains under-recognised due to its nonspecific presentation and clinical overlap with other critical illnesses, including severe malaria [4,5]. Plasmodium falciparum malaria, the most severe form, is highly prevalent in sub-Saharan Africa and frequently presents with fever, cytopenias, acidosis, renal failure, and hepatic dysfunction [6,7]. Although malaria has been identified as a potential trigger for HLH, reports in immunocompetent adults remain rare, particularly in African and diaspora populations where diagnostic resources are limited [8,9].

The overlap between HLH and severe malaria can delay diagnosis and targeted therapy, especially in settings where ferritin testing and specialist awareness are limited. Tools such as the HLH-2004 criteria [10] and the HScore [11] can assist diagnosis, but clinical suspicion remains crucial. Without prompt recognition and treatment, HLH carries high mortality even in previously healthy individuals [12].

We describe two adult cases of HLH secondary to P. falciparum malaria, both requiring intensive care management and immunomodulatory therapy. These cases illustrate the diagnostic challenges and underscore the need for increased awareness of HLH in malaria-endemic regions and among returning travellers.

Subjects, Materials and Methods

We conducted a retrospective case series describing two adult female patients admitted to the intensive care unit (ICU) at a tertiary academic hospital in London, United Kingdom, between January 2019 and January 2025. Both patients were diagnosed with severe *Plasmodium falciparum* malaria and developed clinical and biochemical features consistent with haemophagocyticlymphohistiocytosis (HLH) [1,2].

Inclusion criteria were:

A. Confirmed P. falciparum infection on microscopy,
B. Fulfilment of at least five of eight HLH-2004 diagnostic criteria or an HScore ≥169 (probable HLH), and
C. Admission to the ICU with multiorgan dysfunction.

Patients with incomplete laboratory data or alternative explanations for hyperinflammation were excluded.

Clinical data were extracted from the hospital's electronic health record system (Epic Hyperspace™), including laboratory values, imaging reports, bone marrow findings, and clinical observations. HLH was diagnosed using the HLH-2004 criteria [10,15] and the validated HScore [11]. Ferritin, triglyceride, fibrinogen, liver transaminase levels, and full blood count were assessed in accordance with established diagnostic thresholds [5]. Ferritin > 500 µg/L (diagnostic criterion); values > 10,000 µg/L (13 - 150 µg/L) considered highly suggestive of HLH.

Triglycerides ≥3.0 mmol/L (< 1.7 mmol/L) were diagnostic of hyperinflammatory activity.

Imaging included abdominal ultrasound, echocardiography, and cross-sectional neuroimaging where indicated. Bone marrow aspirate was performed in one case to confirm haemophagocytosis [13]. Both patients received anti-malarial therapy with intravenous artesunate followed by artemether-lumefantrine,

and immunomodulatory therapy for HLH, including corticosteroids, intravenous immunoglobulin (IVIG), and anakinra [3,10].

The timeline of illness was reconstructed from initial symptom onset to HLH diagnosis and recovery milestones. In Case 1, HLH was suspected on day 11 of illness and confirmed on day 13 following transfer to a tertiary ICU. In Case 2, HLH was suspected on day 7, and therapy was initiated the following day. Key events, including initiation of renal replacement therapy, immunomodulation, and discharge, occurred between days 13–32 and 8–31 of illness, respectively.

Ethical Considerations

This study adhered to institutional governance for retrospective anonymised case reviews. Formal ethical approval was waived by the University College London Hospitals Research Governance Committee because the study involved no direct patient contact or identifiable data.

Results/Case Presentations

Case 1:

A 65-year-old Black African woman presented with severe Plasmodium falciparum malaria (parasitaemia >18%) and multiorgan failure. She developed acute kidney injury requiring continuous renal replacement therapy, circulatory shock, and respiratory failure necessitating intubation. HLH was suspected due to persistent fever, cytopenias, transaminitis, and ferritin of 21,570 µg/L (HScore 255). Bone marrow aspirate confirmed haemophagocytosis.

She was treated with intravenous artesunate, corticosteroids (methylprednisolone 1 g daily ×3 days), IVIG (1 g/kg ×2 days), and anakinra (200 mg twice daily). EBV reactivation and critical illness neuropathy complicated her course, but she recovered after 32 days of hospitalisation. Ferritin decreased to 1,845 µg/L by day 31, and renal function normalised before discharge (Figure1).

Figure Legend

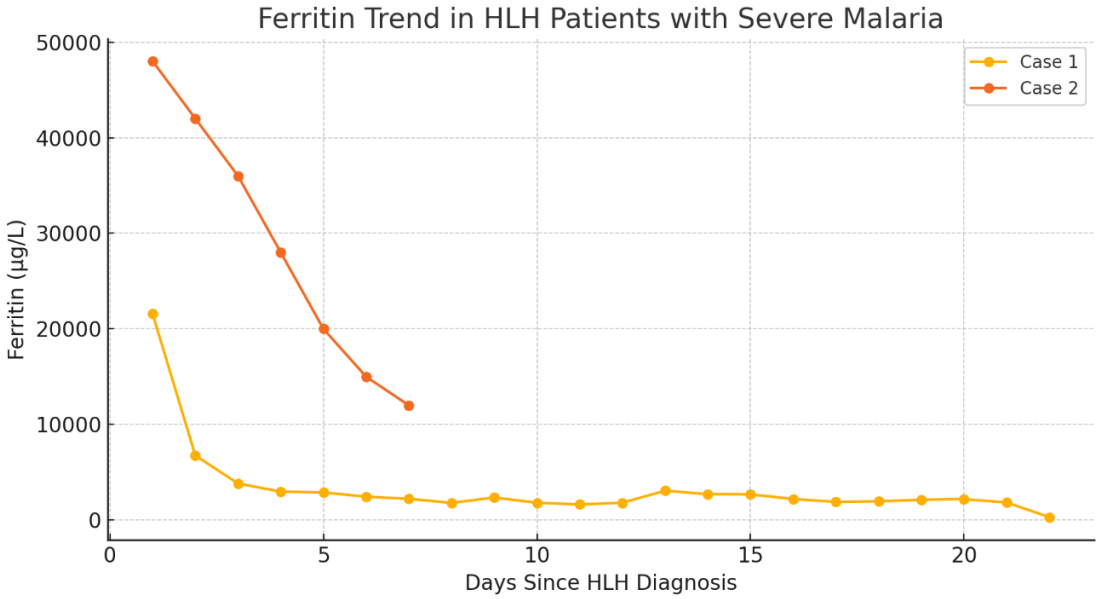

Figure 1. Ferritin Trend in both cases

Case 2:

A 34-year-old woman of mixed background returned from Nigeria without malaria prophylaxis and presented with fever, diarrhoea, and confusion. P. falciparum parasitaemia was 21.5%. She developed cerebral malaria and acute kidney injury requiring renal replacement therapy. HLH was suspected based on fever, cytopenias, hepatosplenomegaly, hyperferritinaemia (48,000 µg/L), and hypertriglyceridaemia (4.8 mmol/L). Bone marrow biopsy was not performed (HScore 229).

She received intravenous artesunate, pulsed methylprednisolone followed by dexamethasone taper, IVIG, and anakinra (100 mg twice daily). She was extubated on ICU Day 6, weaned from filtration on day 13, and discharged on a tapering steroid course.

Discussion

Severe *Plasmodium falciparum* malaria remains a major cause of critical illness and mortality across sub-Saharan Africa[6,7]. Although haemophagocyticlymphohistiocytosis (HLH) has been recognised as a complication of malaria—particularly in paediatric or immunocompromised populations [9], its occurrence in immunocompetent adults remains underreported, especially in African and diaspora contexts [2,8].This case series highlights the diagnostic challenge and potential reversibility of HLH when triggered by falciparum malaria.

Both patients presented with classic features of HLH, including persistent fever, cytopenias, elevated transaminases, hyperferritinaemia, and multiorgan dysfunction [1,4]. Ferritin levels in both cases exceeded 10,000 µg/L, a value considered an early red flag for HLH and a critical clue for differentiation from uncomplicated malaria. Trends in ferritin levels for both patients are illustrated (Figure 1), and the corresponding diagnostic criteria and HScore values are summarised (Table 2). Many of these features overlap with severe malaria, making HLH easy to overlook without a high index of suspicion. In our cases, use of the HScore [11,15] provided a quantitative estimate of diagnostic probability and supported early initiation of immunomodulatory therapy (Table I).

Table 1: Illustrating clinical comparison of both cases

Parameter	**Case 1**	**Case 2**
Age***(years)***	65	34
Sex	Female	Female
Ethnicity	Black African	Mixed background
Travel to endemic area	Yes (Nigeria)	Yes (Nigeria)
Parasitaemia***(%)***	>18	21.5
Thin Film	P. Falciparum	P. Falciparum
Ferritin Peak**(µg/L)**	21,570	48,000
Organ support required	Mechanical ventilation, CRRT, Vasopressors	Mechanical ventilation, CRRT, Vasopressors
Immunotherapy	Steroids, IVIG, Anakinra	Steroids, IVIG, Anakinra

HScore	210	225
Outcome	Complete clinical recovery following immunomodulatory therapy	Complete clinical recovery following immunomodulatory therapy

*Abbreviations: * CRRT - continuous renal replacement therapy, IVIG – intravenous immunoglobulin G

Table 2: HLH Criteria and HScore Table comparing Case 1 and 2

HScore Parameter	**Case 1**	**Case 2**	**Normal Range**
Known underlying immunosuppression	No	No	_
Temperature **(°C)**	38.5	≥39*	_
Organomegaly	None	Splenomegaly	_
Number of cytopenias	2	2	
Ferritin **(µg/L)**	21,570	48,000	13 - 150
Triglycerides **(mmol/L)**	4.5	4.8	<1.7
Fibrinogen **(g/L)**	2.5	4.2	2.0 – 4.0
Serum AST **(U/L)**	135	124	<40
Hemophagocytosis on the BM aspirate	Yes	Not done†	Absent
Leukocyte count **(×10⁹/L)**	3.0	3.95	4.0 – 11.0
HScore**(Total)**	255	229	_
HLH Probability **(%)**	>99%	93–96%	_

*Peak documented temperature prior to ICU transfer, †Bone marrow aspiration not performed due to critical condition, ** Abbreviation: ** BM - Bone Marrow

Bone marrow aspiration confirmed haemophagocytosis in one patient, while treatment in the other was initiated empirically based on clinical and biochemical criteria, in keeping with current guidance supporting prompt therapy when biopsy is delayed or impractical [10].

The combination of corticosteroids, intravenous immunoglobulin (IVIG), and anakinra (a recombinant interleukin-1 receptor antagonist) was used successfully in both cases, with good tolerance and complete clinical recovery. This approach contrasts with traditional etoposide-based regimens, which may be more toxic in infection-associated HLH, and offers a safer alternative in the critically ill [3,14]. Interleukin-6 inhibitors such as tocilizumab have shown promise in cytokine storm syndromes, but evidence in malaria-associated HLH remains limited.

Recognition of HLH in malaria-endemic regions is particularly important given the high background burden of infection and diagnostic overlap [7]. In West Africa, where P. falciparum transmission is intense, and ferritin testing or bone marrow access is often limited, the consequences of missed HLH can

be catastrophic. Strengthening clinician awareness and developing simplified diagnostic algorithms may improve outcomes even in resource-constrained environments.

This series also underscores the importance of advanced critical care support in HLH management. Both patients required renal replacement therapy, invasive ventilation, and broad-spectrum antimicrobials, but recovered following targeted immunosuppression. Early multidisciplinary involvement:combining infectious diseases, rheumatology, and intensive carewas pivotal to survival.

The limitations of this work include its small sample size, retrospective design, and potential selection bias. Nonetheless, it contributes to the limited adult data on malaria-associated HLH, demonstrating that timely diagnosis guided by the HScore and HLH-2004 criteria, together with prompt immunomodulatory therapy, can lead to full clinical recovery.

Conclusion

HLH is a rare but severe complication of Plasmodium falciparum malaria that can mimic or overlap with severe malaria manifestations. Early recognition using structured diagnostic tools such as the HLH-2004 criteria and HScore, coupled with prompt initiation of immunomodulatory therapy, can improve outcomes. In endemic regions and among returning travellers,there should be a high index of suspicion for HLH in patients with severe malaria and unexplained systemic inflammation.
Prospective studies are needed to determine the true incidence and outcomes of malaria-associated HLH in African populations.

References

1. Bauchmüller K, Singh D, Morgan S, Price S. HLH in critical care: a life-threatening syndrome. *Crit Care*. 2019;23(1):39.
2. Hutchinson M, Jones A, Peters N, Chua M, Lamming A, Shaw C. HLH – An underrecognised hyperinflammatory syndrome. *Lancet Haematol*. 2020;7(10):e776–e785.
3. Wohlfarth P, Agis H, Gualdoni GA, Weber J, Staudinger T, Schellongowski P. Interleukin-1 antagonist, IVIG, and corticosteroids in the management of HLH. *Hematology*. 2018;23(5):275–283.
4. West J, Wood H, Batchelor J, Morris D, Ashton M, Leonard S, et al. Incidence and survival of haemophagocyticlymphohistiocytosis: a population-based study. *Lancet Reg Health Eur*. 2021;5:100093.
5. Machowicz R, Janka G, Wiktor-Jedrzejczak W. Similar but not the same: differential diagnosis of HLH. *J Clin Med*. 2021;10(9):1964.
6. World Health Organization. Severe malaria. *Trop Med Int Health*. 2014;19 Suppl 1:7–131.
7. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. *Lancet*. 2014;383(9918):723–735.
8. Day NPJ, Phu NH, Mai NT, Chau TT, Loc PP, Chuong LV, et al. The pathophysiology of falciparum malaria. *Curr Mol Med*. 2001;1(2):209–218.
9. Lelliott PM, Coban C, Yamamoto M, Burgio G, Heath WR, Beeson JG, et al. Immunopathogenesis of cerebral malaria and potential for adjunctive therapy. *Clin Microbiol Rev*. 2021;34(3):e00217-20.

10. La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of HLH in adults. *Blood*. 2019;133(23):2465–2477.

11. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore for reactive HLH. *Arthritis Rheumatol*. 2014;66(9):2613–2620.

12. Ravelli A, Minoia F, Davi S, Horne A, Bovis F, Pistorio A, et al. Macrophage activation syndrome. *Nat Rev Rheumatol*. 2012;8(3):165–172.

13. Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *Am J Clin Pathol*. 2013;139(6):713–727.

14. Grom AA, Horne A, De Benedetti F. HLH and cytokine storm syndromes: a review. *Rheum Dis Clin North Am*. 2021;47(4):703–720.

15. Henter JI, Horne A, Aricò M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH: clinical and pathologic features and diagnostic guidelines. *Pediatr Blood Cancer*. 2007;48(2):124–131.