Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.47

CASE REPORTS

A TROPICAL ADVENTURE IN THE IMMUNE SYSTEM

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ABSTRACT

Infection-associated secondary hemophagocytic lymphohistiocytosis (sHLH) is a potentially life-threatening hyperinflammatory condition, rarely associated with malaria. We present a case of sHLH triggered by P. falciparum, which was also complicated by acute kidney injury (AKI) and late onset pancreatitis, following intravenous artesunate.

Male adolescent with known sickle cell disease, who presented to the paediatric intensive care unit due to P. falciparum infection with low grade parasitemia (1%), shock and multisystem failure. Empirical treatment with ceftriaxone and clindamycin was started on admission, and intravenous artesunate was administered, with rapid clearance of malaria parasites. The severity of multisystem involvement led to investigation of sHLH, which was con?rmed (ferritin 136 791 ng/mL, CD25 16 000 pg/mL). Treatment with high dose dexamethasone led to a rapid improvement. On day 5, artesunate was stopped due to acute kidney injury with severe polyuria and mild elevation of pancreatic enzymes. The patient was transferred to the ward on day 10, and discharged home on day 20.

A severe clinical course of malaria with low parasitemia should raise the suspicion of sHLH. Prompt treatment of both the infectious trigger and the hyperin?ammation allowed for a good outcome. High dose dexamethasone alone may be sufficient in this setting. Our case also illustrates potential, although rare, toxicities of intravenous (IV) artesunate therapy, underscoring the need for continuous monitoring, as well as prompt antimalarial de-escalation to minimize iatrogenic effects.

ARTICLE HISTORY

Received : 6 September 2024

Accepted : 30 October 2024

KEYWORDS

secondary hemophagocytic lymphohistiocytosis, malaria, pediatric, acute pancreatitis, acute kidney injury.

Background

Hemophagocytic lymphohistiocytosis (HLH) is considered a rare immunological disorder marked by widespread activation of the inflammatory system, affecting the bone marrow and reticuloendothelial system.[1,2,3,4,5,6,7,8,9,10]

HLH can be primary (familial) or secondary (sHLH), as a result of an infection, malignancy, or autoimmune disorder.[9,10] Infectious triggers include viruses (cytomegalovirus, Epstein-Barr virus, human herpesvirus-8, human immunodeficiency virus), bacteria (Mycobacterium tuberculosis, Salmonella typhi), and parasites (Plasmodium falciparum and less frequently Plasmodium vivax). There are few cases reporting malaria as an sHLH trigger.[5] Malaria-related HLH can be fatal, with a 90% mortality rate if left untreated,[5] highlighting the need for an early diagnosis of the primary disease and timely intervention.

Artemisinin derivatives are the first line treatment for P. falciparum and have been used worldwide for a long period of time.[7,11] We also aim to report and raise awareness for possible severe side effects of intravenous artesunate.

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Case Report

A 15-year-old male with known sickle cell disease and a baseline haemoglobin (Hb) of 6.5-7.5 g/d was admitted to the paediatric intensive care unit (PICU) for suspected septic shock. He was on treatment with daily hydroxyurea and folic acid, and awaiting cholecystectomy for gallstones. The family medical history was irrelevant.

After a trip to Angola in the preceding 3 weeks, he developed fever and vomiting due to malaria with 1% *P. falciparum parasitemia*. On admission at the local hospital he received two saline boluses (10 ml/kg each) for hypotension (blood pressure 79-95/26-33 mmHg) and tachycardia, with warm extremities, palpable broad pulses, and no signs of cardiac compromise. Considering the hemodynamic instability, dopamine was started (max 12 mcg/kg/min) before PICU transfer. An echocardiogram showed good left ventricular function. Initial blood tests showed anemia (Hb 6.2 g/dL), severe hemolysis (LDH 1321, total bilirubin 16,2

Table 1. Maximum and minimum laboratory values during hospitalization in PICU.

	Day-1	Day-2	Day-3	Day-4	Day-5	Day-6	Day-7	Day-9
Leukocytes (uL)	15570	26000	24800	17300	14300	15500	12400	----------
Lymphocytes (uL)	880	900	3170	2730	1400	1740	2470	----------
Platelets (uL)	173000	97000	79000	47000	69000	75000	98000	124000
Hb (g/dL)	6,2	4,6	5,9	6,6	6,4	5,9	5,7	7,6
NTproBNP (pmol/L)	505	1715	2460	811	----------	----------	----------	----------
Troponin-T (ng/L)	8,3	16	19	--------	9	----------	----------	----------
PT (seconds)	56,7	53,6	32,2	25,2	19,6	17,1	17,4	20,2
INR	4,89	4,62	2,78	2,17	1,69	1,51	1,53	1,74
Fibrinogen (mg/dL)	176	170	214	164	163	121	----------	----------
PCT (ng/mL)	3,23	16,6	15,1	10,7	8,74	3,44	2,03	----------
CRP (mg/dL)	8,59	21,1	27,6	32,6	20,2	10,9	5,6	----------
Ferritin (ng/mL)	----------	----------	136791	----------	74297	3938	----------	----------
CD25 (pg/mL)	----------	----------	16000	----------	----------	----------	----------	----------
Creatinine (mg/dL)	0,72	1,02	1,53	1,29	1,11	0,68	0,58	0,41
Urea (mg/dL)	50	58	91	157	189	119	69	36
AST (U/L)	555	4277	4448	3899	2916	508	169	69
ALT (U/L)	246	1080	1128	1035	849	508	268	132
LDH (U/L)	1321	4475	8090	9882	6207	3938	2826	----------
GGT (U/L)	113	94	84	71	61	71	157	----------
D. Bilirubin (mg/dL)	7,91	----------	23,33	----------	25,96	16,12	----------	----------
ALP (U/L)	----------	----------	----------	350	568	516	----------	----------
Amylase (U/L)	----------	----------	----------	49	118	261	413	224
Lipase (U/L)	----------	----------	----------	---- --- ---	----------	----------	1088	----------
Triglyceride(mg/dL)	----------	----------	104	196	196	----------	----------	----------
Ammonia	56	----------	81	78	----------	----------	----------	----------

mg/dl, conjugated bilirubin 7,9 mg/dl, AST 555 U/L, ALT 246 U/L), elevated C-reactive protein (CRP) (12 mg/dl) and hyperlactacidaemia. A blood transfusion en route raised Hb to 7.2 g/dL.

On PICU admission, he was drowsy, with fever (38.5ºC) and low diastolic blood pressure. He had icteric sclera and hepatosplenomegaly. As he presented with distributive shock, with persistently low diastolic blood pressure, norepinephrine was started, up to a maximum dose of 0.4 mcg/kg/min, with concomitant down titration of dopamine. Vasoactive and inotropic drugs were suspended on Day-2, after a sustained hemodynamic response. Serial echocardiograms showed adequate ventricular function. Maximum values of NT-proBNP (2460 pg/mL) and Troponin T (19 ng/L) were seen on Day-2 of hospitalization, with maximum hyperlactacidaemia of 76 mg/dl. Two more blood transfusions were administered between Day-1 and 2, due to low hemoglobin levels (minimum 4.6 mg/dL). Coagulopathy (INR maximum 4.86, PT 56.7 sec, aPTT 47sec) and hypofibrinogenemia (176 mg/dL) were managed with fresh frozen plasma, vitamin K, and fibrinogen on Day-1. Thrombocytopenia was noted from admission (minimum 47,000/uL on Day 4), without active bleeding. Liver hepatocellular injury peaked on Day-3 (AST 4448 U/L, ALT 1128 U/L), with biliary dysfunction markers elevated from Days 1 to 5 (max GGT 120 U/L, direct bilirubin 25.96 mg/dL, ALP 568 U/L). (Table 1)

He was empirically started on clindamycin and ceftriaxone for septic shock, later switched to cefotaxime due to worsening cholestasis, for a total duration of seven days. Procalcitonin (PCT) and CRP values reached a maximum of 15.1 ng/mL and 32.6

mg/dl, on Day-3 and 4, respectively. Blood cultures became negatives. (Table 1)

Intravenous artesunate (2.4 mg/kg/dose) was started on Day-2 and was administered for five days (administered at 0h, 12h, 24h, 48h, 72h and 96h), with subsequent oral artemether-lumefantrine for three additional days.

Pancytopenia and severe multisystem involvement led to sHLH investigation, which was confirmed. High ferritin (136,791 ng/mL) and soluble CD25 (sCD25) (16,000 pg/mL) on Day-3 prompted high-dose dexamethasone initiation (10 mg/m²/day), resulting in clinical and analytical improvement, with sustained apyrexia from Day-7. Corticosteroids were tapered over two weeks due to rapid response.

Acute kidney injury (AKI) without oligoanuria was noted from Day-2 (Day-1 of artesunate), peaking on Day-3 (creatinine 1.53 mg/dL, GFR 44 mL/min/1.73m²) and normalizing after artesunate withdrawal. Hypernatremic dehydration due to marked polyuria (maximum 300-500mL/h) was seen from Day-3 (Day-2 artesunate), with peak sodium 156 mmol/L and urea 189 mg/dL on Day-5. Urinalysis showed normal urine density (Udens), adequate urinary sodium (uNa) and osmolarity (OsmU), as well as plasma osmolarity. He received IV fluids and free water, and a therapeutic trial with desmopressin was pursued, with an inconsistent response. Normal neurohypophysis on MRI and normal values of hypothalamic-pituitary axis related hormones on Day-20 made the diagnosis of central diabetes insipidus less likely.

Mild, late-onset acute pancreatitis was recognized on Day-7, with peak amylase 413 U/L and serum lipase 1088 U/L, about 24 hours after the last IV artesunate dose. Abdominal ultrasound showed no signs of relation to gallbladder lithiasis. He was managed conservatively, and pancreatitis markers were decreasing by Day-10, when transferred to the ward.

He remained neurologically stable, with no signs of nervous system infection. Electroencephalography (EEG) showed no signs of hepatic encephalopathy. He was transferred to the ward on Day-10.

The following table (Table 1) details the progression of laboratory blood tests, including critical (minimum and maximum) serum values, during his PICU stay.

Discussion

Malaria is an infectious disease caused by protozoan parasites of the genus Plasmodium, with a variety of clinical symptoms. Among the species, Plasmodium falciparum and Plasmodium vivax have been linked to sHLH so far, with P. falciparum being the predominant cause.[1] Most of sHLH cases associated with malaria worldwide have been reported in regions with high malaria prevalence, such as Sub-Saharan Africa and Southeast Asia.[1,2,3,4,5]

Although our patient came from a malaria-endemic area and had low blood parasitemia upon admission, it is crucial not to assume an asymptomatic carrier state. Immediate treatment is essential as delaying it can lead to adverse clinical outcomes.[1,2]

The exact mechanism of sHLH in the setting of malaria remains unclear, but it likely involves a combination of genetic predisposition and an excessive immune response triggered by the parasite.[1] The overlapping symptoms of malaria and HLH, such as fever, splenomegaly, anemia, thrombocytopenia, and elevated inflammatory markers, makes the diagnosis challenging. These symptoms in malaria probably result from parasite-induced cytotoxicity, microvascular issues, and organ sequestration. However, unusual findings like high ferritin, high triglycerides, and low fibrinogen levels may suggest superimposed HLH.[1,6] Persistent pancytopenia and severe multisystem failure, despite successful malaria treatment, should also prompt suspicion of sHLH.[5] Elevated sCD25 is a useful biomarker for diagnosing sHLH in children, with a sensitivity of 76.2% and specificity of 98.2%, indicating that this biomarker could be of clinical use.[9]

Intravenous artesunate is the preferred treatment for severe malaria due to its quick parasite clearance, safety, and effectiveness in reducing mortality.[11] When standard antimalarial treatments fail, leading to clinical deterioration or multiorgan failure, HLH-specific therapy, including immunosuppressants like steroids and intravenous immunoglobulin, may be necessary.[1,9] These drugs act by inhibiting the inappropriate macrophage activation [3]. Dexamethasone is favored for its ability to cross the blood-brain barrier and is typically tapered over eight weeks.[4] In our case, a high dose of 10 mg/m²/day was administered for one week and tapered over two weeks due to the patient's rapid and sustained response to treatment.

The exact pathophysiology of AKI in malaria is not well understood, but proposed mechanisms include blockage of renal microcirculation by infected erythrocytes, immune-mediated glomerular injury, and volume depletion.[12]

Our patient experienced worsening kidney function and polyuria starting on the second day after admission and the initiation of intravenous artesunate. AKI related to intravenous artesunate has also been documented.[11] The leading hypothesis is that artesunate-induced ‹pitting› of red blood cells shortens their lifespan to 7-21 days, causing severe hemolysis and free hemoglobin-mediated tubular damage. This delayed hemolysis typically occurs more than a week after treatment starts, indicated by a drop in hemoglobin and a rise in lactate dehydrogenase without recurring parasitemia.[11]

Harshil et al reported the case of a 12-year-old boy with severe malaria, who developed oliguria and edema 12 hours after starting artesunate, requiring dialysis.[12] Despite switching to oral Artemether and Lumefantrine on the sixth day, his serum creatinine peaked on the seventh day, to a maximum of 6.08 mg/dL. Dialysis continued, and by the tenth day, liver and kidney functions normalized. Additionally, a study to evaluate toxicity of artesunate in Plasmodium berghei-infected and uninfected rats, found that artesunate induced renal injury by the eighth day post-dosing, with histopathological evaluations revealing tubular necrosis in uninfected rats and in malaria-infected rats.[13] Although this mechanism could possibly contribute for AKI seen in our patient, with increased creatinine, a pre-renal component may also be implied, evidenced by a significant increase in urea levels.

Pancreatitis is an unusual cause of abdominal pain in malaria, likely due to the occlusion of pancreatic blood vessels by parasitized red blood cells.[14] This is usually associated with an acute process while the patient remains parasite-positive by microscopy. However, a case report of a 34-year-old male, who developed late-onset pancreatitis after starting intravenous artesunate suggests another possible mechanism. This pancreatitis occurred eight days post-admission, five days after the blood was parasite-negative, indicating that it might not be due to parasite sequestration. The patient was managed conservatively, and his serum amylase levels normalized with no abdominal pain after one month of follow-up.[15] Artesunate has been associated with hemolysis up to four weeks post-administration, even though the drug has long been excreted, potentially contributing to this late onset complication.[16]

The case we present is unique as it is the first documented case of late-onset acute pancreatitis probably associated with intravenous artesunate in a pediatric patient.

Conclusion

Secondary HLH associated with malaria is extremely rare, with limited literature available on this connection. The overlap between these conditions challenges the diagnosis of HLH superimposed on malaria. We emphasize that a severe case of malaria with low parasitemia should raise suspicion of sHLH. Early identification, close monitoring and treatment of both the infection and hyperinflammation can improve patient outcomes. High doses of dexamethasone for one week with a two-week tapering may be effective in this setting and diminishes the risk of corticosteroid-related side effects.

Our case also highlights two potential, though rare, toxicities of intravenous artesunate therapy – AKI and late-onset acute pancreatitis. To minimize iatrogenic effects, continuous monitoring and prompt de-escalation of antimalarial treatment should be reinforced.

Compliance with Ethical Standards

Funding None

Conflict of Interest None

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