International Journal of Infectious Diseases 171 (2026) 109036

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

Persistent non-viable *Plasmodium falciparum* parasitemia mimicking artesunate treatment failure and unmasking functional hyposplenism

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ARTICLE INFO

Article history:
Received 25 April 2026
Revised 22 July 2026
Accepted 4 August 2026

Keywords:
Plasmodium falciparum
Severe malaria
Artemisinin resistance
Hyposplenism
Parasite clearance

ABSTRACT

A 40-year-old woman was admitted with severe *Plasmodium falciparum* malaria. Although she improved clinically under intravenous artesunate, parasitemia unexpectedly increased. Reassessment identified previously unrecognized functional hyposplenism, leading to delayed clearance of non-viable parasites and falsely suggesting artemisinin resistance.

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Background

Malaria remains a major global health challenge, causing nearly 282 million cases and over 610,000 deaths in 2024 [1]. Despite intensive control efforts, several obstacles compromise progress, most notably the emergence of partial artemisinin resistance associated with P*fk*13 mutations and its geographical expansion [2-4]. This phenotype manifests as delayed parasite clearance, increased risk of resistance to partner drugs, and potential treatment failure. Nevertheless, complete artemisinin resistance has never been documented and parenteral artesunate remains the cornerstone of severe malaria management. Any clinical or biological sign of treatment failure, such as rising parasitemia during artemisinin-based therapy, must therefore be promptly recognized. Artesunate generates free radicals in infected erythrocytes, rapidly killing parasites. While partial artemisinin resistance is an increasing concern, persistent parasitemia after initiation of antimalarial therapy may result from other mechanisms, including inadequate antimalarial exposure or delayed clearance of non-viable parasites, particularly in patients with impaired splenic function. The spleen plays a key role in "pitting", the removal of dead parasites from infected red blood cells (RBCs) [5]. In hypo- or asplenic patients, pitting is ineffective and RBCs containing dead parasite remnants ("hearse RBCs") remain in circulation. Distinguishing viable parasites from the pyknotic remnants of dead trophozoites can be challenging, potentially leading to microscopy findings that mimic treatment failure [5,7]. Additionally, in case of asplenia or impaired splenic function, Roussel et al. described a potentially severe condition named APIH (Asplenia-related Post-antimalarial Inflammation

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https://doi.org/10.1016/j.ijid.2026.109036
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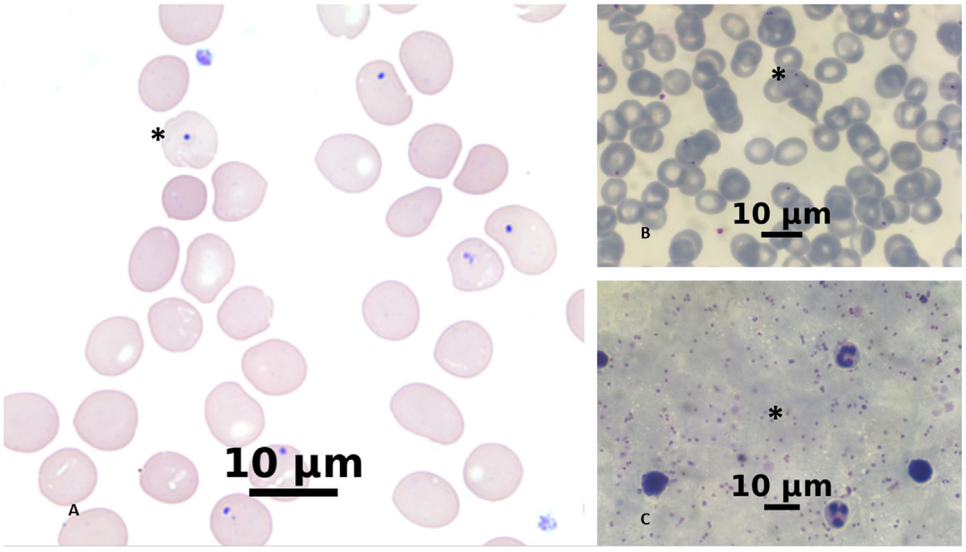


Figure 1. May–Grünwald–Giemsa–stained thin (A, B) and thick (C) blood smears showing pyknotic intraerythrocytic forms consistent with non-viable Plasmodium falciparum trophozoites (*). Original magnification (oil immersion): A × 1000; B–C × 500.

Table 1
Laboratory evolution during hospitalization.

	Day 1	Day 4	Day 7	Day 11	Day 18
Estimated parasitemia (%)	8.8	19	<0.02	0	0
Creatinine (µmol/L)	366	252	112	104	81
LDH (U/L)	–	1063	710	710	1558
Hemoglobin (g/L)	146	112	89	84	82
Platelets (× 10^9/L)	13	45	180	378	358
Total bilirubin (µmol/L)	130	73	27	25	26

and Hemolysis) characterized by persistent fever, delayed and often profound, hemolytic anemia with inflammation [5].

Case presentation

We report the case of a 40-year-old woman, born in Cameroon, raised and currently living in Switzerland, with no significant past medical history, who was admitted for severe malaria with severe prostration, jaundice, acute kidney failure and a parasitemia of 8.8%. She had returned 10 days earlier from a three-week trip to Ivory Coast undertaken without malaria chemoprophylaxis. Intravenous artesunate was initiated. Despite clinical and laboratory improvement, with resolution of organ dysfunction, parasitemia increased to 19% and fever persisted after 4 days of treatment (Table 1). After exclusion of concomitant bacterial infection, the delayed parasite clearance raised suspicion of artesunate-resistant malaria. The patient was then transferred to a tertiary care hospital where intravenous clindamycin was added. This discordance between the parasitological course and the otherwise improving clinical picture, despite persistent fever, prompted a reassessment of the parasitological findings. Initial discussions with parasitologists raised concerns regarding the reliability of the parasitemia measurement, as most circulating forms exhibited pyknotic features. Given the unexpected smear appearance, a second expert review was sought, who confirmed that the observed intraerythrocytic structures were non-viable and unlikely to represent active trophozoites (Figure 1).

Persistent parasitemia was attributed to impaired clearance rather than ongoing replication. Differential interference contrast (DIC) microscopy revealed 61% vacuolated erythrocytes (“pocked cells”), consistent with hyposplenism, and smears showed numerous erythrocytes containing pyknotic parasites. These findings suggested previously unrecognized functional hyposplenism, which may remain clinically silent for many years, explaining persistence of non-viable parasitized erythrocytes despite normal spleen size on ultrasonography [8]. Clinical evolution was favorable, with progressive improvement of the initial symptoms, including headache, dizziness, and asthenia, allowing transition to oral artemether–lumefantrine (Riamet) for 5 days, for a total treatment duration of 18 days. However, persistent fever and sustained hemolysis requiring blood transfusions continued until day 14, a clinical course more consistent with asplenia-related post-antimalarial inflammation and hemolysis (APIH) than with typical post-artesunate delayed hemolysis (PADH). No *Pf*K13 propeller domain mutations were detected. Splenic function was not reassessed during follow-up, as the patient declined further investigations after hospital discharge.

Discussion

This case illustrates three main points.

First, parasite morphology and clinical course must be integrated into parasitemia interpretation. In this case, rising parasitemia during artesunate therapy contrasted with overall clinical improvement. Smears showed predominantly pyknotic forms and pocked erythrocytes were observed using DIC microscopy, consistent with impaired splenic pitting and persistence of non-viable parasitic remnants, as previously described in splenectomized patients treated with artemisinin derivatives (Table 2) [6,7,9].

Second, suspected artemisinin partial resistance in severe malaria requires systematic evaluation. Any apparent treatment failure, particularly rising parasitemia after appropriately administered artesunate, should prompt careful smear re-examination, verification of drug delivery, and, when feasible, molecular testing for resistance markers [3].

Third, clinicians should be aware of APIH, which may occur despite overall clinical improvement. This condition is characterized, like PADH, by delayed hemolysis but differs by the intensity of clinical and biological inflammatory features, the persistence of hearse-RBCs on smears beyond day 3, and the absence of once-infected (pitted) erythrocytes [5]. APIH can occur in patients with known conditions causing hyposplenism, or reveal previously unrecognized hyposplenism, as in our patient. In this case, persistent fever, sustained hemolysis and “hearse RBC” in circulation,

Table 2
Published cases of delayed parasite clearance associated with impaired splenic function following artemisinin-based therapy.

Reference	Type of splenic dysfunction	Key clinical/laboratory finding	Clinical outcome
Thu et al., *1997* [9]	Splenectomy	Persistent non-viable parasites	Recovery
Chotivanich et al., *2002* [6]	Splenectomy	Absent splenic pitting	Recovery (n = 4); Death (n = 1)
Marco-Hernández et al., *2019* [7]	Splenectomy	Rising parasitemia with pyknotic forms	Recovery
Roussel et al., *2023* (Case 1) [5]	Functional hyposplenism	Hearse RBC accumulation	Recovery
Roussel et al., *2023* (Case 2) [5]	Functional hyposplenism	Delayed parasite clearance	Recovery
Hommel et al., *2013* [10]	Functional hyposplenism	Hyposplenism revealed by malaria	Recovery
Present case	Functional hyposplenism	Persistent pyknotic parasites, presence of 61% pocked erythrocytes, APIH	Recovery

together with evidence of elevated proportion of vacuolated erythrocytes ("pocked cells"), were consistent with this syndrome. An additional diagnostic challenge is that pyknotic parasites may be difficult to distinguish from Howell-Jolly bodies on conventional Giemsa-stained blood smears. This distinction is particularly relevant in hyposplenic patients, in whom both findings may coexist and contribute to misinterpretation of persistent parasitemia.

This case highlights that persistent or apparently increasing parasitemia after intravenous artesunate does not necessarily indicate artemisinin resistance. In patients with impaired splenic function, persistent parasitic remnants may mimic treatment failure despite favorable clinical evolution. Interpretation of persistent parasitemia should therefore integrate the patient clinical course, parasite morphology, and splenic function.

Funding

No specific funding was received for this work. PB and CR are supported by French National Research Agency (ANR) Grant ANR-018-0001-GREx.

Ethical approval statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Arthur Cornet: Writing – review & editing, Writing – original draft, Conceptualization. **Jean-Marc Schwob:** Writing – review & editing, Investigation, Formal analysis. **Camille Roussel:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Romain Cordaillat:** Writing – review & editing, Validation, Data curation. **Christian Nsanzabana:** Writing – review & editing, Formal analysis. **Esther Kuenzli:** Writing – review & editing. **Rosalie Zimmermann:** Writing – review & editing, Investigation. **Andreas Neumayr:** Writing – review & editing. **Pierre Buffet:** Writing – review & editing, Methodology, Data curation. **Gilles Eperon:** Writing – review & editing, Validation, Supervision, Investigation, Data curation, Conceptualization. **Stefano Musumeci:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Acknowledgments

The authors thank Léa Ramu, Virna Rizzo, Simon Marceron, Domien Javier Calderon, and Lara Rasga for their technical support in the Parasitology Laboratory at Geneva University Hospitals.

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