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Cerebral Malaria from a *Plasmodium falciparum* and *Plasmodium malariae* Co-Infection: A Case Report on a Diagnostic Challenge

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A B S T R A C T

Severe malaria, primarily caused by *Plasmodium falciparum*, is a life-threatening medical emergency. Its diagnosis can be significantly complicated by mixed-species infections, where the presence of a less virulent *Plasmodium* species may mask the true etiological agent of the severe disease, leading to potential delays in appropriate therapy. This report details a case of cerebral malaria where such a diagnostic challenge occurred. An 18-year-old male with a recent travel history to a malaria-endemic area in Indonesia presented with a one-day history of decreased consciousness (Glasgow Coma Scale score of 9) following a week-long febrile illness. The clinical presentation met the World Health Organization's criteria for severe malaria, specifically cerebral malaria. Initial microscopic examination of a peripheral blood smear exclusively identified *Plasmodium malariae*. However, a concurrently performed rapid diagnostic test (RDT) was positive for both the pan-malarial antigen and the *P. falciparum*-specific histidine-rich protein 2 (HRP-2) antigen. This critical discordance prompted treatment for severe falciparum malaria with intravenous artesunate and triggered an expert re-evaluation of the blood smears. Subsequent analysis confirmed a co-infection with both *P. falciparum* and *P. malariae*. The patient showed significant clinical improvement within three days of initiating appropriate therapy. In conclusion, this case underscores the peril of diagnostic anchoring in severe malaria. Clinical severity must supersede laboratory findings that are incongruent with the patient's condition. The presence of a *Plasmodium* species other than *falciparum* on an initial smear does not rule it out as the cause of a severe syndrome. Discordant results between microscopy and RDTs are a critical red flag for mixed infections and mandate immediate, expert parasitological re-evaluation to ensure timely, life-saving treatment.

1. Introduction

Malaria remains a formidable global health challenge, with an estimated 249 million cases and 608,000 deaths reported in 2022.[1] The archipelagic nation of Indonesia continues to bear a significant portion of this burden outside the African continent, with 418,546 cases reported in 2023, predominantly from its eastern provinces like Papua. While five *Plasmodium* species are known to infect humans, *Plasmodium falciparum* is the undisputed principal agent of severe and fatal malaria.[2] Its virulence is rooted in a unique pathophysiology involving the sequestration of parasitized erythrocytes in the microvasculature of vital organs, leading to catastrophic syndromes such as cerebral malaria, acute respiratory distress syndrome (ARDS), and

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multi-organ failure.[3] Cerebral malaria, characterized by unarousable coma, represents the most severe neurological complication of *P. falciparum* infection and carries a mortality rate of 15-20%, even with optimal treatment. The diagnosis and management of this condition are a race against time, where every hour of delay in administering effective antimalarial therapy, specifically parenteral artesunate, increases the risk of death and long-term neurological sequelae.[4] In stark contrast, *Plasmodium malariae*, the causative agent of quartan malaria, is typically associated with a chronic, low-density, and often asymptomatic or mildly symptomatic infection.[5] While it can cause significant morbidity through complications like nephrotic syndrome and chronic anemia, it is rarely implicated as a sole cause of severe or fatal malaria.

The diagnostic landscape is further complicated by the phenomenon of mixed-species malaria infections, which are increasingly recognized as being more common than previously thought, particularly in high-transmission settings.[6] A co-infection presents a unique and perilous diagnostic challenge. The presence of a more readily identifiable or numerically dominant species, such as *P. malariae*, on a peripheral blood smear can lead to "diagnostic anchoring," a cognitive bias where clinicians and laboratorians prematurely stop their search, thereby missing a concurrent, more virulent infection.[7] This is especially dangerous when a low-density or sequestered *P. falciparum* infection is the true driver of a patient's severe clinical state. While the existence of mixed infections is known, there is a gap in the literature emphasizing the critical decision-making process required when profound clinical severity is starkly discordant with an initial laboratory finding of a less virulent species.[8] The novelty of this report lies in its detailed dissection of this specific clinical quandary: a patient with fulminant cerebral malaria whose initial microscopy pointed away from the true culprit, *P. falciparum*. We illustrate, step-by-step, how the integrated use of a complementary diagnostic tool—the rapid diagnostic test (RDT)—served as the pivotal trigger to question the initial findings and avert a potentially fatal therapeutic delay.[9,10] Therefore, the aim of this study is to use this case as an educational tool to underscore the primacy of clinical judgment over incongruent laboratory results in severe febrile illness. We seek to demonstrate that a systematic diagnostic approach, leveraging the strengths of both microscopy and RDTs, is essential to navigate the complexities of mixed malaria infections and ensure the timely administration of life-saving therapy.

2. Case Presentation

Written informed consent was obtained from the patient for the collection of clinical data and the publication of this case report, including any accompanying images, in an anonymized format. The case is reported in accordance with the CARE guidelines.

An 18-year-old male was brought to the Emergency Department of Prof. Dr. I.G.N.G. Ngoerah General Hospital in Denpasar, Bali, with the chief complaint of a decreased level of consciousness. According to his family, the patient had become progressively lethargic and difficult to communicate with over the 5 hours prior to admission. The patient's illness began seven days earlier with the sudden onset of a high-grade fever, which occurred daily. These febrile episodes were accompanied by intense shivering, particularly at night, and were only temporarily relieved by paracetamol. For the week leading up to his admission, he had been profoundly weak and had significantly reduced his daily activities. On the morning of admission, his family noted he was excessively drowsy, would only open his eyes briefly when called, and would not engage in conversation. Upon arrival at the emergency department, he was largely unresponsive, only groaning to painful stimuli.

The family denied any associated cough, shortness of breath, nausea, vomiting, seizures, focal weakness, or sensory disturbances. The patient was a resident of

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West Sumba, an area highly endemic for malaria in East Nusa Tenggara, and had traveled to Bali two weeks prior for construction work in the Jimbaran area. He had a history of being treated for falciparum malaria at the age of 13. His parents had also previously had malaria. Prior to this hospital visit, he had been taken to a local clinic where a malaria test was reportedly performed, but the family could not recall the result or the treatment given, other than paracetamol.

Table 1. Summary of clinical findings on admission.

Parameter	Patient's Finding	Significance & Interpretation
Clinical Presentation		
Chief Complaint	Decreased consciousness (5 hours)	Acute, severe neurological change indicating a critical illness.
History	7-day high-grade fever with nightly rigors	Classic history suggestive of malarial paroxysms.
Travel History	From West Sumba (endemic area) to Bali (2 weeks prior)	Crucial epidemiological link for malaria.
Vital Signs & Physical Exam		
Temperature	39.0 °C	High-grade fever, a hallmark of acute infection.
Heart Rate	124 bpm	Tachycardia, likely secondary to fever and systemic illness.
Physical Finding	Marked conjunctival pallor	Clinical sign of significant anemia.
Neurological Assessment		
Glasgow Coma Scale (GCS)	9 (E3, V2, M4)	Meets WHO criteria for Cerebral Malaria (GCS < 11). This is a life-threatening emergency.
Cerebrospinal Fluid (CSF)	Normal	Absence of pleocytosis or high protein makes bacterial meningitis less likely, strengthening the diagnosis of cerebral malaria.
Laboratory Findings		
Hemoglobin	8.6 g/dL	Moderate anemia, a classic complication of malaria due to hemolysis and bone marrow suppression.
Platelet Count	10,000 /µL	Severe thrombocytopenia, very common in falciparum malaria and a criterion for severity.
BUN / Creatinine	57.1 / 1.34 mg/dL	Acute Kidney Injury (AKI), another criterion for severe malaria.
Blood Glucose	77 mg/dL	Hypoglycemia, a metabolic complication of severe malaria.
Parasitology		
Initial Microscopy	*P. malariae* trophozoites (13,760/µL)	Highly discordant with the clinical picture of cerebral malaria. A diagnostic red flag.
Rapid Diagnostic Test (RDT)	Positive (3 Lines: Control, Pf, Pan)	Pivotal finding. Unambiguously indicates a P. falciparum infection, overriding the initial microscopy and guiding immediate, appropriate treatment.
Final Diagnosis	Mixed Infection: *P. falciparum* & *P. malariae*	Confirms the RDT result and explains the full clinical and laboratory picture.

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On examination, the patient was acutely ill. His vital signs were blood pressure 105/65 mmHg, heart rate 124 beats/minute (tachycardia), respiratory rate 20 breaths/minute, and an axillary temperature of 39.0°C. His oxygen saturation was 98% on room air. His body weight was 50 kg.

Neurologically, his consciousness was severely impaired, with a Glasgow Coma Scale (GCS) score of 9 (Eyes 3, Verbal 2, Motor 4). There were no signs of meningeal irritation, and no focal neurological deficits were observed. Examination of the head and neck revealed marked conjunctival pallor (anemia) but no scleral icterus. The remainder of the examination, including cardiovascular, respiratory, and abdominal systems, was unremarkable. Notably, there was no palpable hepatomegaly or splenomegaly. His extremities were warm and well-perfused (table 1).

The initial diagnostic framework was broad, centered on an undifferentiated febrile coma in a patient from a malaria-endemic area. The primary differential diagnoses included cerebral malaria and other central nervous system infections like bacterial meningitis or viral encephalitis.

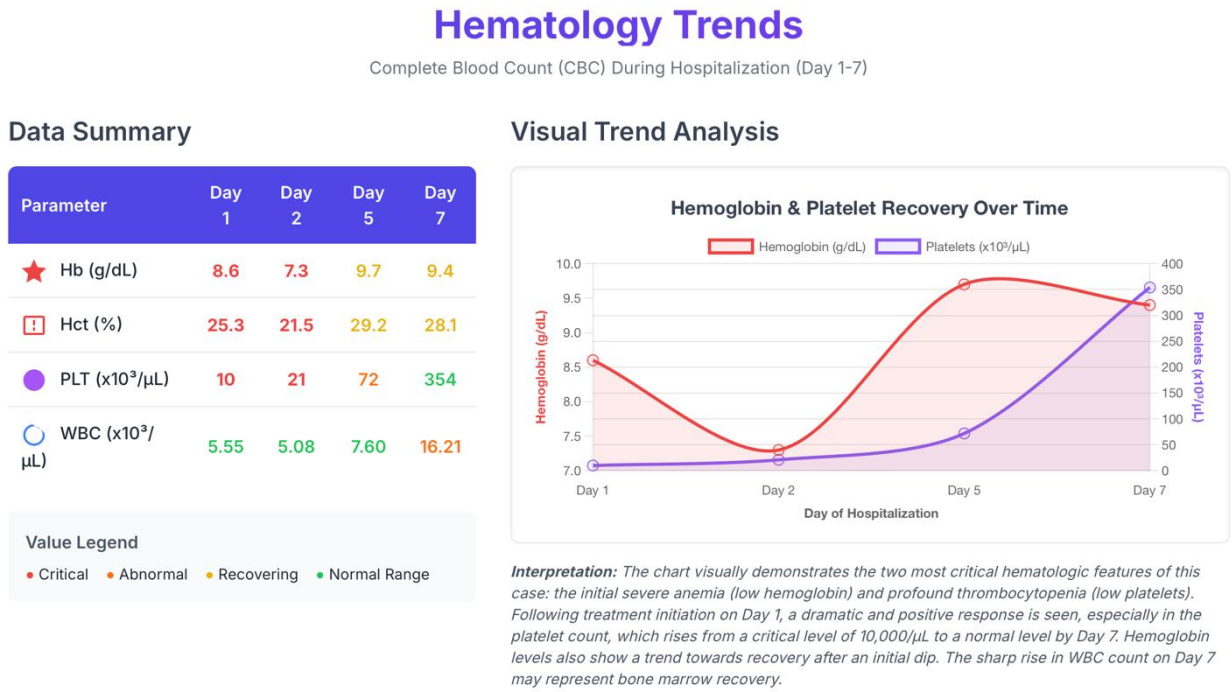

Figure 1. Complete blood count during hospitalization.

Figure 1 provides a compelling visual narrative of the patient's hematological crisis and subsequent recovery. It highlights the two cardinal features of severe falciparum malaria on admission: profound thrombocytopenia (platelets at a critical 10,000/µL) and significant anemia (hemoglobin dipping to 7.3 g/dL). The most dramatic trend is the robust and rapid recovery of the platelet count, which surges from a life-threatening level to normal by Day 7. This serves as a powerful visual biomarker of the patient's positive response to the intravenous artesunate therapy initiated on Day 1. While hemoglobin recovery is more gradual, as expected, the upward trend is evident. The sharp increase in white blood cells by Day 7 suggests a healthy bone marrow rebound following the suppression from the acute infection. Together, these trends vividly confirm the successful and timely management of this critical illness.

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Table 2. Biochemical & parasitology summary during hospitalization.

Biochemical & Parasitology Summary

Key Diagnostic Markers During Hospitalization

Parameter	Finding	Normal Range	Clinical Interpretation
Organ Function & Metabolic Status (on Admission)			
BUN (mg/dL)	57.1	7 - 20	Significantly elevated, indicating Acute Kidney Injury (AKI), a criterion for severe malaria.
Creatinine (mg/dL)	1.34	0.7 - 1.3	Elevated, confirming renal impairment consistent with AKI.
SGOT (U/L)	54.0	< 40	Mildly elevated, suggesting some degree of liver involvement or hepatocellular injury.
Blood Glucose (mg/dL)	77	70 - 140	Borderline low (hypoglycemia), a known metabolic complication of severe malaria.
Parasitological Evaluation & Evolution			
Initial Microscopy (Day 1)	*P. malariae* only	N/A	A misleading finding, highly inconsistent with the clinical diagnosis of cerebral malaria.
Rapid Diagnostic Test (Day 1)	Positive (3 Lines)	N/A	The pivotal diagnostic clue.Confirmed P. falciparum (Pf line) and another species (Pan line), revealing the mixed infection.
Expert Microscopy Review (Day 1 smear)	*P. falciparum* + *P. malariae*	N/A	The definitive diagnosis, confirming the RDT result and explaining the full clinical picture.
Parasite Density Trend	13,760 → 6,180 → 2,107 /µL	N/A	Demonstrates a steady decline in parasite load, indicating a positive therapeutic response to artesunate.

Table 2 powerfully illustrates the multi-systemic crisis of severe malaria and the critical diagnostic pathway. The biochemical data from Day 1 reveal clear evidence of organ failure, with Acute Kidney Injury (AKI) and hypoglycemia—both classic hallmarks of life-threatening *P. falciparum* infection. The parasitology section tells the most crucial story. It traces the journey from a misleading initial microscopy finding, which was dangerously inconsistent with the patient's severe state, to the pivotal RDT result that correctly identified *P. falciparum*. The initial microscopic examination, performed on the day of admission identified parasites morphologically consistent with *Plasmodium malariae* at the trophozoite stage. The parasite density was calculated to be 13,760 parasites/µL. No other *Plasmodium* species were reported at this time (Figure 2).

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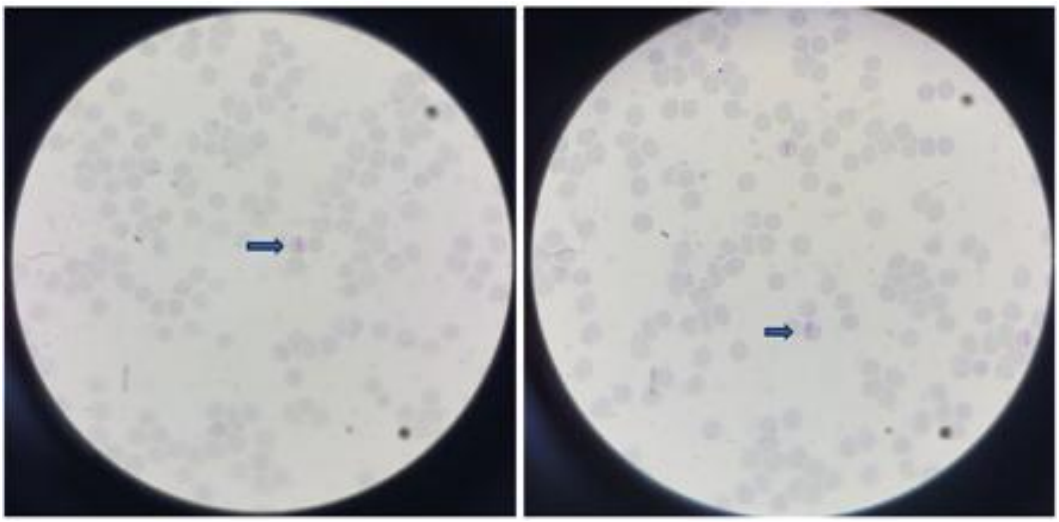

Figure 2. Initial blood smear. Micrograph from the initial thin blood smear showing a red blood cell infected with a *Plasmodium malariae* trophozoite, characterized by its compact cytoplasm and large chromatin dot, forming a "band" or "basket" shape.

A commercial immunochromatographic RDT was performed concurrently on the same blood sample. The result was starkly discordant with the initial microscopy. The RDT cassette showed three distinct positive lines: the control line, the line specific for *P. falciparum* histidine-rich protein 2 (Pf-HRP2), and the pan-malarial line, which detects lactate dehydrogenase (pLDH) common to all human *Plasmodium* species. This result strongly indicated the presence of a *P. falciparum* infection, likely in conjunction with another species.

To investigate other potential causes of coma, a lumbar puncture was performed. The cerebrospinal fluid (CSF) was clear and colorless, with a normal cell count (3 leukocytes/mm^3), normal protein (Nonne and Pandy reactions negative), and normal glucose, effectively ruling out acute bacterial meningitis. Serological testing for the Dengue virus (IgM and IgG) was negative.

Based on the constellation of findings—a profound neurological deficit (GCS 9) meeting the WHO definition of cerebral malaria, a travel history from a highly endemic region, and a Pf-positive RDT—a working diagnosis of Severe Malaria due to *P. falciparum* was established, with the understanding that a co-infection was highly probable. The clinical severity and the RDT result were given precedence over the initial, conflicting microscopy report.

The patient was immediately admitted to the high-care unit and management was initiated according to the WHO guidelines for severe malaria. He was started on intravenous (IV) Artesunate at a dose of 2.4 mg/kg body weight (120 mg total). This was administered at 0, 12, and 24 hours on the first day, followed by a once-daily infusion. Supportive care included cautious intravenous fluid resuscitation, fever control with paracetamol, and plans for nutritional support. Serial blood smears were performed to monitor the therapeutic response.

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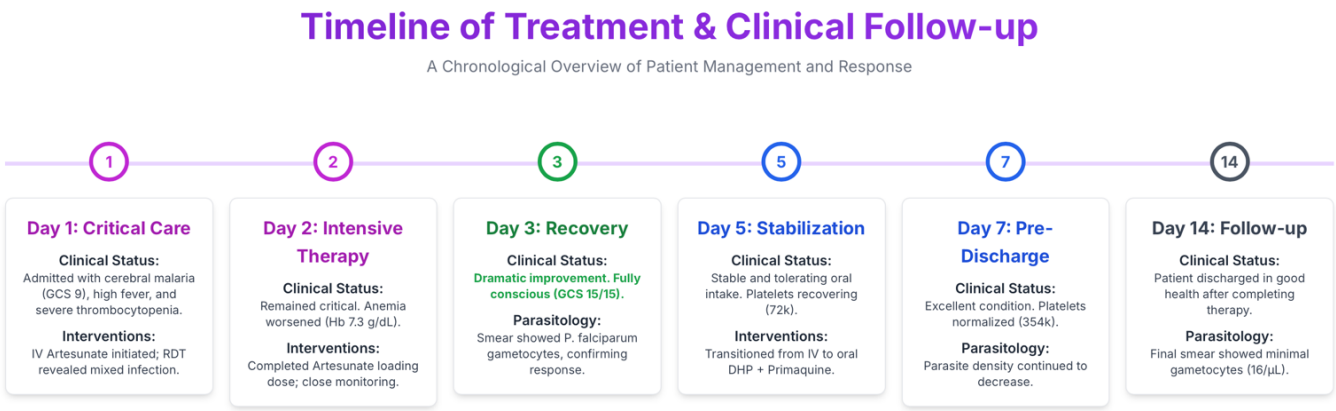

Figure 3. Timeline of treatment and clinical follow-up.

On day 3 of treatment, the smear revealed parasites morphologically identified as *P. falciparum* gametocytes, with a density of 6,180 parasites/µL (Figure 4-6). The initial blood smear was retrieved and subjected to a re-examination by a senior clinical pathologist. This expert review, prompted by the RDT/microscopy discordance and the clinical picture, yielded a revised and definitive diagnosis. In addition to the previously noted *P. malariae* trophozoites, the smear was found to contain sparse but definite *P. falciparum* ring-form trophozoites and characteristic crescent-shaped *P. falciparum* gametocytes. Subsequent smears on days 5, 7, and 14 showed a progressive decline in the density of *P. falciparum* gametocytes, consistent with a positive therapeutic response. The patient's clinical condition improved dramatically in response to treatment. By the third day of hospitalization, his fever had resolved, and his mental status had returned to normal (GCS 15/15). He was transitioned to oral therapy with dihydroartemisinin-piperaquine (DHP) plus primaquine to complete the treatment course and was eventually discharged in good health.

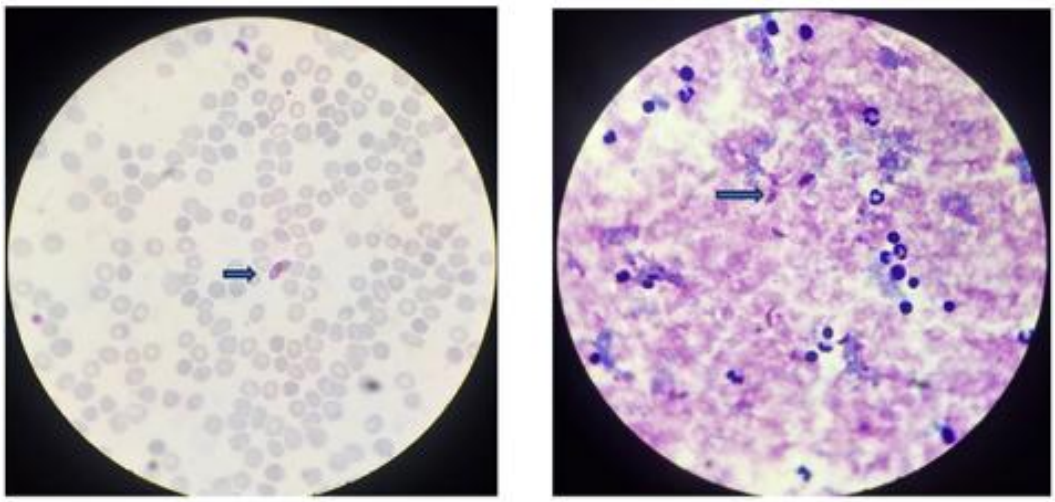

Figure 4. Blood smear on day 3 of treatment. Micrograph from the thin blood smear after two days of treatment, clearly showing a crescent-shaped *Plasmodium falciparum* gametocyte. The appearance of gametocytes is common after initiation of artemisinin-based therapy.

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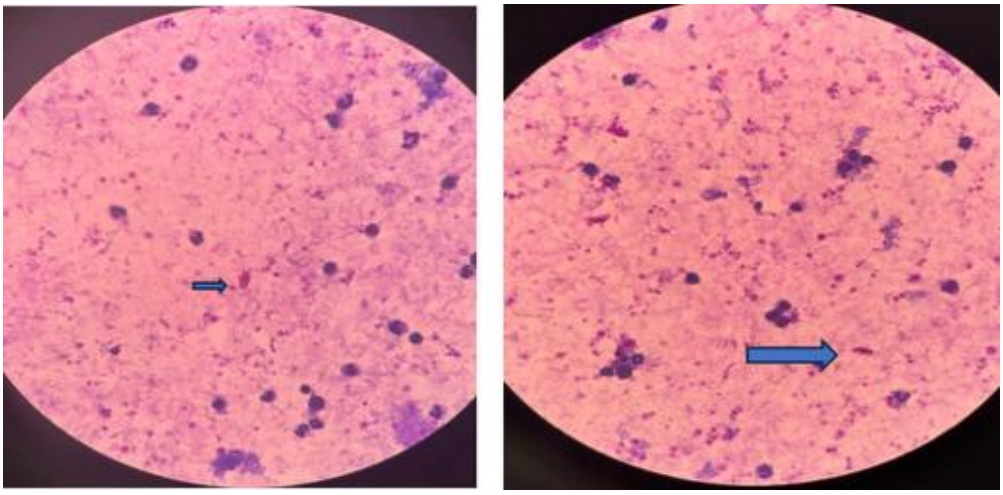

Figure 5. Blood smear on day 7 of treatment. Follow-up blood smear demonstrating a significant reduction in parasite density. A single *P. falciparum* gametocyte is visible, indicating a positive response to therapy.

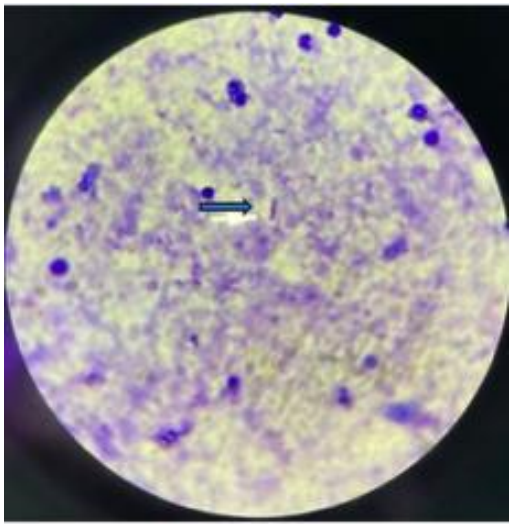

Figure 6. Fourth blood smear imaging. Micrographs from the expert re-evaluation of the first day's blood smear. A subtle but definite ring-form trophozoite of *P. falciparum,* characterized by its delicate cytoplasm and small chromatin dot; A classic crescentic gametocyte of *P. falciparum*; A compact trophozoite of *P. malariae*. This retrospective analysis confirmed the mixed-species infection that was initially missed.

3. Discussion

This case report presents a compelling and educational narrative of a near-miss in the diagnosis of cerebral malaria. The central clinical problem was the profound discordance between the patient's life-threatening presentation (a GCS of 9) and the initial laboratory finding of *P. malariae*, a species not typically associated with such severe neurological impairment.[9] The successful outcome hinged on the clinical team's refusal to accept this incongruent diagnosis, a decision buttressed by a revelatory RDT result, which ultimately led to the correct diagnosis of a mixed infection and the administration of appropriate, life-saving therapy. This case serves as a

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powerful illustration of the pathophysiological and human factors that can conspire to create a diagnostic trap in severe malaria.[10]

The primary reason *P. falciparum* was initially missed on microscopy is almost certainly due to its core pathogenic mechanism: sequestration. Mature asexual stages of *P. falciparum* (trophozoites and schizonts) express a unique, antigenically variable protein on the surface of the infected erythrocyte called *P. falciparum* erythrocyte membrane protein 1 (PfEMP1).[11] This protein acts as a ligand, mediating the adherence of infected red blood cells to the endothelial lining of capillaries and post-capillary venules in deep vascular beds, a process known as cytoadherence. This sequestration is most pronounced in the brain, lung, and placenta.

In the context of this patient, the cerebral malaria was a direct consequence of massive sequestration of parasitized erythrocytes within the cerebral microvasculature. This process leads to mechanical obstruction of blood flow, metabolic derangements, endothelial activation, and a cascade of neuroinflammation, culminating in the clinical syndrome of coma.[12] A critical consequence of this pathophysiology is that the parasite biomass becomes concentrated in the organs, while the density of these mature, pathogenic stages in the peripheral circulation can become remarkably low, sometimes even falling below the limit of microscopic detection.[13] In contrast, *P. malariae* does not sequester; its developmental stages circulate freely in the bloodstream, making them readily detectable on a peripheral smear.

Therefore, the biological plausibility of the initial findings is high. Upon admission, the patient's peripheral blood likely contained a relatively high number of circulating *P. malariae* trophozoites, which were easily identified. Simultaneously, the vast majority of the pathogenic *P. falciparum* trophozoites were sequestered in his brain, leaving only very sparse, early ring-form trophozoites and non-sequestering, crescent-shaped gametocytes in the peripheral circulation.[14] These few *P. falciparum* elements were likely overlooked in the initial examination, especially when the microscopist's attention was captured by the more numerous and morphologically distinct *P. malariae* parasites—a classic example of diagnostic anchoring.

This case champions the foremost principle of clinical medicine: treat the patient, not the laboratory result.[15] The most important diagnostic clue was the patient's profound clinical severity. A GCS of 9 in a patient with a febrile illness from a malaria-endemic area is cerebral malaria until proven otherwise, and cerebral malaria is overwhelmingly caused by *P. falciparum*. The initial report of *P. malariae* was a diagnostic outlier that simply did not fit the clinical picture. This incongruity should be an immediate red flag for any clinician, prompting a critical reassessment of the data.[16]

The turning point in this case was the Rapid Diagnostic Test. While microscopy remains the gold standard for its ability to speciate, quantify, and assess for different parasite stages, it is highly operator-dependent and can be fallible. The RDT served as an essential, objective cross-check. The three-band positive result (Control, Pf-HRP2, Pan-pLDH) was unambiguous evidence of a *P. falciparum* infection co-existing with another *Plasmodium* species. Modern RDTs targeting HRP-2 have a very high sensitivity (>95%) for detecting clinical *P. falciparum* malaria.[17] The RDT result provided the definitive impetus to override the initial microscopy report and initiate treatment for severe falciparum malaria without delay. This case powerfully argues for the routine use of RDTs alongside microscopy, not as a replacement, but as a crucial safety net to catch discordant results and prevent misdiagnosis.

Microscopy is a skill that requires expertise, time, and meticulousness.[18] This case highlights its inherent limitations. Identifying sparse parasites, especially the delicate, often faint ring forms of *P.*

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falciparum, in a thick smear containing debris and other elements, is challenging. When a more prominent parasite like *P. malariae* is also present, it is easy to see how the initial reader might have identified it and concluded the examination. The WHO recommends examining at least 100 high-power fields before declaring a slide negative.[19] It is plausible that in a busy clinical setting, this standard may not always be met once a positive finding is made. The subsequent re-evaluation of the original slide by a senior pathologist, which correctly identified all parasite forms, underscores the value of quality control and the indispensable role of expert consultation in resolving complex or discordant parasitological findings.

The management of the patient was exemplary. The immediate initiation of intravenous artesunate, the drug of choice for severe malaria, was appropriate and life-saving.[20] The patient's rapid defervescence and neurological recovery within three days of starting artesunate therapy is a hallmark of the drug's potent, fast-acting schizonticidal activity against *P. falciparum*. This excellent clinical response serves as a *post-hoc* confirmation that the sequestered *P. falciparum* parasites were indeed the cause of his cerebral syndrome, and that their rapid clearance by artesunate led to his recovery.

This report's primary limitation is the absence of molecular confirmation via polymerase chain reaction (PCR). PCR is the most sensitive and specific method for detecting and speciating *Plasmodium* DNA and would have provided definitive confirmation of the mixed infection and potentially even the relative proportion of each species.[20] However, PCR is not widely available in many resource-limited settings where malaria is prevalent, including at our institution at the time of the patient's admission. This case, therefore, reflects a realistic clinical scenario where clinicians and laboratorians must rely on microscopy, RDTs, and clinical judgment to make critical, time-sensitive decisions.

4. Conclusion

This case of cerebral malaria due to a *P. falciparum* and *P. malariae* co-infection highlights the critical danger of diagnostic anchoring on an initial, seemingly straightforward microscopic finding. The successful outcome was driven by adherence to three fundamental principles of care. First, clinicians must maintain a high index of suspicion for falciparum malaria in all patients presenting with severe symptoms from endemic areas; clinical severity must always guide management. Second, the integrated use of complementary diagnostic tools is essential. Discordant results between microscopy and RDTs are a critical alert for a potential mixed infection and demand immediate investigation. Third, meticulous laboratory practice, including a low threshold for expert re-evaluation of slides in complex or discordant cases, is paramount. This report underscores that in the diagnostic battle against severe malaria, the most virulent pathogen may not be the most visible, and a systematic, multi-faceted approach is required to prevent life-threatening delays in treatment.

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