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Case Report

A complex case of recurrent intracranial bleeds due to malaria-induced coagulopathy: A case report and literature review

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ABSTRACT

Background: Malaria, a prevalent disease in the developing world, is a significant cause of morbidity and mortality. Infection with *Plasmodium falciparum*, although uncommon, can lead to severe brain injury, including intracranial hemorrhages, resulting in serious neurological deficits. Malaria-induced coagulopathy, while rarely reported, poses a challenge in understanding the exact mechanisms behind the development of intracranial bleeds. Proposed mechanisms include sequestration of parasitized erythrocytes in the brain's microvasculature, leading to capillary occlusion, endothelial damage, cytokine activation, and dysregulation of the coagulation cascade.

Case Description: We present the case of a 53-year-old male rapidly deteriorating following a history of traumatic brain injury (TBI). Upon admission, a computed tomography scan revealed bilateral acute on chronic hematomas, necessitating a lifesaving craniotomy. Subsequently, the patient experienced three consecutive recurrent intracranial bleeds post-surgery, attributed to *Falciparum*-induced coagulopathy. Prompt recognition and intervention stabilized the patient's condition, leading to discharge on the 4th post-operative day.

Conclusion: This case underscores the challenges posed by consecutive recurrent intracranial bleeds following TBI exacerbated by *P. falciparum* infection. It highlights the obstinate nature of malaria-induced coagulopathy and underscores the importance of timely and aggressive interventions in managing such cases.

Keywords: Coagulopathy, Intracranial hemorrhage, Malaria, *Plasmodium falciparum*, Thrombocytopenia

INTRODUCTION

Malaria is one of the most significant parasitic diseases afflicting humanity, impacting over 500 million individuals annually and resulting in between one to three million deaths each year worldwide. Within Pakistan, from January to August 2022, a staggering 3.4 million suspected cases of Malaria were reported, with 170,000 cases confirmed through laboratory analysis, predominantly identified as *Plasmodium vivax*.[23] The disease tends to gravitate toward endemic regions, with the Sahara hosting a high prevalence among children under the age of 5 years, while Southeast Asia experiences a higher incidence among adults.[17] Notably, severe malaria manifests differently in adults, often leading to multi-organ failure, whereas children commonly experience severe anemia, respiratory distress, and cerebral malaria.[8]

Malaria operates as an intravascular disease, exerting profound alterations in vascular physiology, thus instigating heightened coagulation activation without direct organ invasion. Thrombocytopenia, a prevalent hematological abnormality in malaria, with an incidence ranging from 60% to 80%, frequently accompanies anemia, further compounding coagulation irregularities and escalating the risk of bleeding, notably intracranial hemorrhage.[9] Despite ongoing research efforts, the exact mechanisms triggering intracranial bleeding in Malaria remain partially understood and are hypothesized to involve a complex interplay of factors, including endothelial dysfunction, platelet abnormalities, and microvascular sequestration of infected erythrocytes.

This case study underscores the critical significance of the early detection and prompt treatment of malaria, particularly in high-risk regions. Here, a 53-year-old male initially presented with a brain hemorrhage and subsequently developed recurrent intracranial bleeding attributed to malaria-induced coagulopathy. This case emphasizes the pivotal role of proactive malaria management in averting the progression of coagulation abnormalities and associated complications.

CASE REPORT

A previously healthy 53-year-old male of average build and height was brought to the emergency department by his family due to a severe and continuous headache accompanied by vomiting persisting for 5 days. He reported feeling dizzy and experiencing difficulty walking. In addition, the patient had been in a drowsy state for 1 day. Upon inquiry, it was disclosed that the patient had been involved in a road traffic accident (RTA) 1 month prior, resulting in a mild contusion and right frontal lobe hematoma, which was managed conservatively [Figure 1a and b]. The patient had no known comorbid conditions and provided no significant drug history. Initially, his Glasgow Coma Scale (GCS) score was 13/15, with bilaterally equally reactive pupils. Laboratory workup revealed normal ranges, with hemoglobin of 10.9 g/dL and platelets of 169 × 10^3/mL. However, his GCS deteriorated rapidly, prompting a swift computed tomography (CT) scan, which revealed bilateral acute on chronic subdural hematomas (SDHs) with midline shift and subfalcine herniation toward the right side of the brain [Figure 2]**.** Consequently, a left frontotemporoparietal craniotomy and evacuation of the SDHs were promptly performed, and the patient was admitted to the trauma intensive care unit postoperatively and intubated.

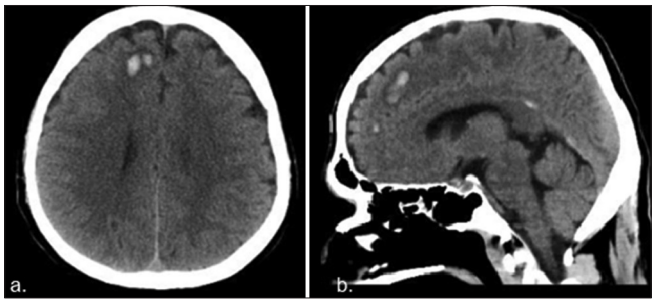

Figure 1: (a and b) Axial view and Sagittal view depicting a hematoma in the frontal lobe observed 1 month following a road traffic accident.

Postoperatively, the patient's level of consciousness deteriorated further, with a GCS dropping to E2VtM5. A repeat CT scan revealed a recurrent left SDH with a midline shift of 9.5 mm [Figure 3]. Subsequently, the patient underwent a second surgery to evacuate the newly formed SDH, during which an extradural hematoma was discovered beneath the bone flap. However, the patient's headache worsened postoperatively, and he became increasingly drowsy and confused. A repeat CT scan revealed a new intraparenchymal hematoma in the left frontal region, with a reduced SDH volume and midline shift [Figure 4], aligning with the second surgery. Due to the consecutive recurrent intracranial bleeds, a hematology consultation was sought. Platelet aggregation studies, fibrinogen, factor 13, and other clotting tests were conducted, alongside tests for malaria and dengue, which returned positive for *Falciparum* species. The remaining conventional clotting tests were normal, and dengue was negative. The patient received two units of packed cell volume and six units of platelets promptly, along

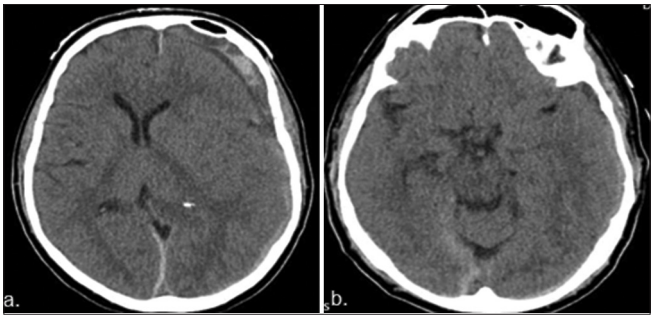

Figure 2: (a and b) Bilateral acute on chronic subdural hematomas with midline shift and subfalcine herniation towards the right.

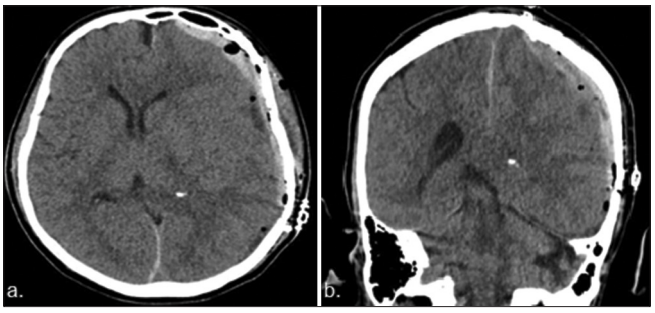

Figure 3: (a and b) Postoperative imaging demonstrating a recurrent subdural hematoma with a midline shift of 9.5 mm.

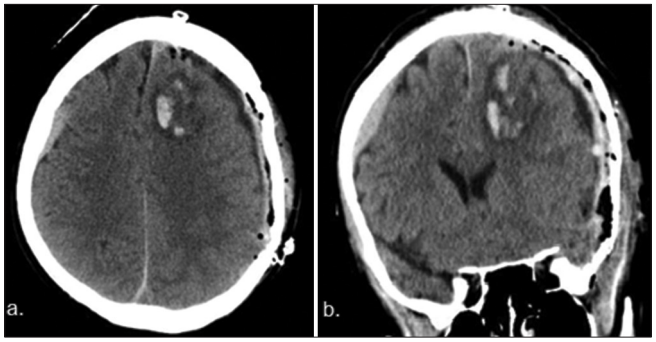

Figure 4: (a and b) Postoperative images illustrating a new intraparenchymal hematoma alongside reduced volume of the previous recurrent subdural hematoma and reduced midline shift following the second operation.

with initiation of intravenous artesunate therapy (2.4 mg/kg), followed by the same dose after 12 h and continued once daily for 5 days. Following the diagnosis of *Falciparum*-induced coagulopathy, the new intraparenchymal hemorrhage in the left frontal region was conservatively managed with antiepileptics and anti-edema drugs.

The patient was extubated after stabilization on the 5th postoperative day from the first craniotomy. Throughout platelet transfusions and antimalarial therapy, the patient's general condition and GCS significantly improved, with platelets reaching 138 × 10^3/mL. He was discharged home on the 6th postoperative day from the first craniotomy, in a stable condition, with oral Artemether/Lumefantrine 80/480 mg twice daily for 3 days after consulting with infectious disease specialists. In subsequent follow-up after a month, his GCS remained stable, he reported no new complaints, and the hematoma was completely resolved. Repeated malarial parasite and dengue tests also came out negative.

DISCUSSION

Pakistan ranks among the top countries globally in terms of traumatic brain injury (TBI) incidence. According to the 2004 National Injury Survey, the rate of RTAs associated with TBI stands at approximately 1500/100,000 individuals annually.[2] Malaria, a potentially fatal disease prevalent in tropical regions, necessitates prompt medical intervention for survival. Delayed diagnosis can exacerbate its severity. In 2022, an estimated 249 million people across 85 countries contracted malaria, resulting in approximately 608,000 deaths.[22] Transmission occurs exclusively through the bite of female Anopheles mosquitoes, with approximately 400 Anopheles species identified, 40 of which are capable of transmitting the disease. *Plasmodium falciparum* and *P. vivax* are particularly notorious for their lethal complications among the five species identified. Notably, in 2022, four sub-Saharan African countries accounted for half of global malaria-related deaths: Nigeria (31.1%), the Democratic Republic of the Congo (11.6%), Niger (5.6%), and the United Republic of Tanzania (4.4%).[22] Vulnerable populations include pregnant women, human immunodeficiency virus patients, infants, and children under 5 years of age. In addition, individuals traveling from high-risk areas without immunity or chemopreventive therapies face increased susceptibility. Cerebral malaria, the most severe neurological manifestation, predominantly affects preschool children.[8]

After inoculation with protozoans, symptoms such as headache, fever, and chills typically emerge within 10–15 days. Approximately 1% of these symptomatic infections progress to severe malaria, characterized by hypoglycemia, metabolic acidosis, anemia, seizures, electrolyte imbalances, coma, or multiple organ failure, resulting in an estimated one million deaths annually.[16] Cerebral malaria, a fatal complication of severe malaria, presents with acute loss of consciousness and coma, primarily due to metabolic factors and the sequestration of infected erythrocytes in the cerebral microcirculation. In children, coma can develop 1–3 days after fever onset, accompanied by progressive weakness. Additional manifestations may include intracranial hypertension, retinal hemorrhage, macular pallor, papilledema, and brainstem signs. In adults, symptoms may start with fever and body aches, progressing to delirium and coma.[8] Complications such as jaundice, hemoglobinuria, renal failure, lactic acidosis, abnormal bleeding, and adult respiratory distress syndrome can further worsen disease outcomes. This multisystemic disease state can lead to cortical infarcts and dural sinus thrombosis due to dysregulated coagulation.[8]

Metabolic derangements predispose patients to bleeding, which is often associated with severe anemia, hyperparasitemia, thrombocytopenia, and coagulopathy, typically occurring late in the disease course, with an incidence ranging from 10% to 20%.[1] Approximately 5% of adults with cerebral malaria experience overt bleeding, commonly in the gastrointestinal tract.[21] Rare and severe bleeding episodes such as purpura fulminans, pulmonary hemorrhage, and intracranial bleeding have been reported.[5,24] While few reports discuss gross thrombotic events at autopsy, intracranial bleeding, notably acute on chronic SDH, was the sole presentation in our patient, who initially presented with brain hemorrhage and subsequently experienced multiple rebleeds. Therefore, symptoms such as headaches should not be disregarded because patients may later present with chronic SDH and epidural hematoma. Chronic SDH can stem from coagulation defects, intracranial hypotension, long-term use of antiplatelets and anticoagulants, anti-inflammatory drugs such as ibuprofen, chronic alcohol consumption, and trauma, as observed in our patient. Acute spontaneous SDH is a rare pathological entity, accounting for 5% of all cases.[20] SDH

cases have also been reported in young individuals with risk factors such as hypertension, vascular malformations, and dural metastasis from solid tumors.[5] Any maneuver causing a sudden increase in intravenous pressure can precipitate SDH.[3] However, in our patient, known risk factors were absent, and the development of SDH was attributed to coagulation defects and thrombocytopenia associated with malaria *Falciparum*. TBI remains a manifestation of coagulation dysregulation due to hypocoagulopathy and the prothrombotic nature of malaria.

Thrombocytopenia is the most prevalent hematological anomaly associated with malaria and was initially linked primarily to *P. falciparum* until the late 1990s when studies revealed a significant association with *P. vivax*.[10] The overall incidence of thrombocytopenia in malaria ranges from 60% to 80%.[20] Although the precise mechanism remains elusive, factors such as splenic sequestration, oxidative stress, diminished platelet production, and abnormal platelet interaction with parasites have been implicated. Recent findings suggest that von Willebrand factor (vWF)-mediated GP1b shedding in early malaria contributes to thrombocytopenia, typically preventing excessive adhesion of platelets and infected erythrocytes. Interaction between normal platelets and *Falciparum*-infected erythrocytes can induce adenosine diphosphate (ADP) release from infected red blood cells (RBCs), thereby exacerbating hypersensitivity. Impaired platelet aggregation in response to ADP, epinephrine, and collagen further complicates the scenario.[14]

Malaria triggers coagulation activation through endothelial activation and damage, which is facilitated by circulating microparticles and interactions between parasite-derived proteins and coagulation receptors on the endothelium and circulating RBCs. Tumor necrosis factor-alpha and histamine, which are released during acute severe infection, promote fibrin formation and contribute to coagulation defects.[18] Activation of the intrinsic pathway releases bradykinin and PMN-derived elastase and activates the complement system. Diminished levels of anticoagulants, such as protein C, protein S, and antithrombin, exacerbate pathogenesis, particularly in *P. falciparum* infections. Plasma levels of plasminogen activator inhibitor-1 are notably elevated in *P. falciparum* infections compared with those in *P. vivax* infections, potentially impairing fibrinolysis. Elevated levels of the vWF and its propeptides directly reflect disease burden and endothelial damage.[6,11]

Severe malaria induces the assembly of multi-molecular coagulation complexes through increased tissue factor expression in endothelial cells by infected RBCs.[4] Tumor necrosis factor, extensively studied in cerebral malaria, enhances the adhesion of infected erythrocytes to the brain vascular endothelium by upregulating intercellular adhesion molecule-1 expression, complicating disease progression, and regulating synaptic transmission.[7] Neuronal dysfunction may also result from parasite sequestration in the cerebral microvasculature, impairing local perfusion to neurons and initiating inflammatory cascades, blood–brain barrier dysfunction, brain swelling, and intracranial hypertension. Research gaps in cerebral malaria pathophysiology hinder our understanding of biochemical changes and outcomes.

Malarial parasites can be identified using various methods such as blood smears, immunological tests (including rapid diagnostic tests), and polymerase chain reaction (PCR). These testing kits and dipsticks enable early detection, whereas PCR confirms parasite species post-diagnosis. Indirect immunofluorescence and enzyme-linked immunosorbent assays can detect antibodies, confirming past exposure. In cases of cerebral malaria, magnetic resonance imaging can be used to assess structural, metabolic, and biochemical factors in the brain.[13] Advanced techniques such as flight angiography, diffusion-weighted imaging, and arterial spin labeling can be used to evaluate cerebral blood flow obstruction and local effects. Magnetic resonance spectroscopy enables the measurement of substrates and metabolites.

The cornerstone of reversing coagulopathy in malaria lies in immediate and effective anti-malarial therapy. Quinine and artemisinin derivatives, commonly used in Southeast Asia, are sufficient for treating hemostatic alterations and eradicating the disease. Widespread spontaneous bleeding may require screened blood products or exchange transfusions to manage fluid overload. Vitamin K can address prolonged prothrombin time and activated partial thromboplastin time, although steroids lack documented efficacy for thrombocytopenia.[12] Heparin use is generally limited to disseminated intravascular coagulation and systemic thrombosis cases, such as purpura fulminans and acral ischemia. While activated Protein C was previously employed for multiple organ failure in *Falciparum* malaria, it was withdrawn because of the lack of benefit in follow-up trials.[15] As per the 2015 World Health Organization guidelines, artesunate serves as the first-line therapy for severe malaria, including cerebral malaria, in both children and adults and is administered intravenously for 24 hours in severe cases. In areas without artesunate availability, artemether can be utilized, followed by oral artemisinin-based combination therapy for 3 days.[24] Respiratory support and artificial ventilation are crucial, and benzodiazepines may manage seizures because 70% of children with severe malaria are prone to them, potentially reducing long-term secondary neuronal damage.[19]

In addition to treatment, preventing malaria remains a pressing priority. Implementing vector control measures such as insecticide-treated nets and indoor residual spraying, alongside chemoprophylaxis, is crucial to maximize prevention and

protect communities in both endemic and non-endemic regions.[22] Ongoing trials aim to enhance immunity against malaria, including Mosquirix™, the first-ever malaria vaccine. It has been administered in a four-dose regimen and has demonstrated partial protection against severe and cerebral malaria in 32.2% of children aged between 5 and 17 months.[16]

CONCLUSION

We followed the course of a 1-week hospital stay of a 53-year-old patient infected with *P. falciparum* who developed three recurrent intracranial bleedings, a SDH, an extradural hematoma, and an intraparenchymal hematoma after craniotomy for bilateral SDHs at presentation. We accentuated the disruption of clotting mechanisms in the human body by the malarial parasite and how it can exacerbate secondary brain injury after TBI, highlighting the need for judicious and timely interventions given the obstinate and severe nature of malaria-induced coagulopathy.

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics approval

Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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