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SIMILARITIES IN THE PRESENTATION OF SEVERE MALARIA AND THROMBOTIC THROMBOCYTOPENIC PURPURA: A CASE REPORT FROM A RURAL KENYAN HOSPITAL.

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Abstract
Severe malaria can present with clinical features strikingly similar to those of thrombotic thrombocytopenic purpura (TTP), including the "pentad" of fever, microangiopathic hemolytic anemia, severe thrombocytopenia, neurological deficits, and renal failure. This finding is believed to be due to a shared pathogenetic pathway involving thrombotic microangiopathy, resulting in increased von Willebrand factor levels and decreased ADAMTS13 activity. In this study, we present the case of a 56-year-old Kenyan woman who presented with the "TTP pentad," jaundice, hypoglycemia, shock, and repeatedly negative thin blood slide microscopy results for malaria, but her peripheral blood film revealed numerous Plasmodium falciparum malaria parasites. The patient was treated with intravenous artesunate and artemether-lumefantrine, as well as supportive care, with complete resolution of her symptoms and normalization of her laboratory derangements. We emphasize awareness of this shared pathogenesis and a high index of suspicion for either disease in appropriate clinical contexts to minimize delays in providing life-saving treatment.

INTRODUCTION

Severe malaria is defined by an increased risk of death at the time of assessment and is characterized by impaired consciousness, acidosis, hypoglycemia, severe anemia, acute kidney injury, hyperparasitemia, jaundice, pulmonary edema, coagulopathy, and shock (White, 2022). Of the 5 *Plasmodium* species that cause malaria, *Plasmodium falciparum* is the most virulent and responsible for most deaths (Bousema & Drakeley, 2011). In Kenya, malaria (including severe malaria) is mainly caused by *Plasmodium falciparum*, which accounts for >90% of all infections. Nearly 6.7 million people are infected annually in Kenya, with approximately 4,000 annual deaths, especially among children (Elnour et al., 2023). A diagnosis of malaria is established by thick and thin peripheral blood smear microscopy, peripheral blood film microscopy, rapid diagnostic tests (RDT), polymerase

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chain reaction, etc. (Tangpukdee et al., 2009). The main pathogenetic mechanisms of malaria include the sequestration of infected erythrocytes leading to mechanical microvascular obstruction, endothelial dysfunction, activation of pro-inflammatory immune cells and release of inflammatory cytokines, dysregulation of coagulation pathways, increased blood-brain barrier permeability with resulting cerebral edema, and thrombotic microangiopathy (Wassmer et al., 2015). These mechanisms lead to the clinical findings in severe malaria. On the other hand, thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy caused by a deficiency of the von Willebrand factor-cleaving metalloprotease called ADAMTS13 (**A** **D**isintegrin **A**nd **M**etalloprotease with a **T**hrombo**S**pondin type **1** motif, member **13**). Clinically, TTP is characterized by the "pentad" of fever, microangiopathic hemolytic anemia, severe thrombocytopenia, renal failure, and neurological deficits. The last 2 are due to ischemic end-organ injury caused by microvascular platelet-rich thrombi. A diagnosis of TTP is established when the ADAMTS13 activity is ≤10% by use of the PLASMIC score (Li et al., 2018). Similarities in the pathogenesis of thrombotic microangiopathy in severe malaria and TTP can lead to overlapping clinical syndromes. For example, the "pentad" of symptoms in TTP may also be observed in severe malaria, leading to challenges and delays in the management of either disease. These challenges have been reported in the literature (Ghadge & Khobragade, 2020; Kunwar et al., 2024; Kurek et al., 2023; Löwenberg et al., 2010). We present a case of severe *Plasmodium falciparum* malaria in a woman in rural Kenya, whose symptomatology mimicked the "pentad" of TTP.

Case Summary

History and Physical Examination

A 56-year-old single mother of 4 and a businesswoman from Mbaruk, Nakuru County, Kenya, with no history of significant comorbidities presented to us in early September 2024 with a 2-week non-specific history of lethargy, anorexia, and paresthesia of both legs. She had no history of traveling outside Nakuru County for the last 2 years. Her examination was unremarkable, and the baseline laboratory tests were all normal, including a complete blood count, creatinine, and a negative blood slide for malaria parasites. She was treated symptomatically. 4 days later, she was admitted with a history of profound lethargy (she could not stand without support), confusion, postprandial vomiting, dark-colored urine, and diaphoresis. Her vital signs were: blood pressure of 82/52 mmHg, pulse rate of 98 bpm, temperature of 37.9 ^{0}C, oxygen saturation by pulse oximetry of 94% in room air, and random blood glucose of 74 mg/dl. Clinically, she was acutely unwell, confused with a Glasgow Coma Scale of 12/15; she was pale, had scleral jaundice, had no peripheral lymphadenopathy, but was severely dehydrated. Her neurologic examination revealed no meningism or focal neurological deficits. Her abdominal examination revealed marked epigastric tenderness but no peritonism or organomegaly. The interval digital rectal examination showed no melena stool. She was in mild respiratory distress, with a respiratory rate of 22 breaths/min and bilateral transmitted chest sounds. Her cardiovascular system was remarkable for severe dehydration with a tachycardia of 112 bpm, normal S1 and S3, but with a hemic murmur. The skin and mucosal surfaces did not show petechial hemorrhage or ecchymoses.

Workup, Management, and Follow-up

Her laboratory tests included a complete blood count, creatinine, and a blood slide for malaria parasites, as shown in table 1 below. She had a negative HIV test, a normal prothrombin time and International Normalized Ratio (INR) of 1.3, elevated total bilirubin of 3.4 mg/dL (normal is up to 1.5), an indirect bilirubin of 2.5 mg/dL (normal is up to 0.7), an aspartate transaminase of 98 u/L (normal is up to 40), normal serum electrolytes, and urinalysis showing 5-10 leucocytes/hpf. She had negative screening for hepatitis B and C serology. She had negative direct and indirect Coombs tests to exclude autoimmune hemolytic anemia. A chest X-ray was unremarkable. Gastroscopy revealed hiatus hernia (Hill's grade 4) with antral gastritis. Abdominopelvic ultrasound revealed

normal renal sizes, preserved corticomedullary differentiation, mild ascites but no organomegaly, and normal visceral organs.

Table 1: Complete Blood Count, Creatinine, and Tests Results for Malaria

Date	**Complete Blood Count** **WBC**=white blood cells (4-11 x10^3/µL) **Hb**=hemoglobin (11-16 g/dL) **MCV**=mean corpuscular volume (80-99 fL)				**Creatinine** (0.5-1.0 mg/dL)	**Tests for malaria parasites:** ***BS for MPS***=blood slide for malaria parasites ***PBF***=peripheral blood film
	WBC	**Hb**	**MCV**	**Platelets** (x10^3/µL)		
09/09/2024	4.7	12.6	82	211	1.3	Negative BS for MPS
13/09/2024	4.1	8.4	77	40	-	Negative BS for MPS
14/09/2024	4.3	7.5	77	30	5.5	Negative BS for MPS
17/09/2024	4.9	8.9	81	51	1.8	PBF=4+malaria parasites, 2+ schistocytes
19/09/2024	7.1	7.4	83	48	1.3	-
22/09/2024	7.3	6.3	82	91	1.2	-
23/09/2024	5.8	9.2	91	245	-	-
11/10/2024	9.7	10.7	90	355	1.1	Negative BS for MPS

She was initially assessed as having sepsis secondary to cystitis and possible acute viral hepatitis, with the thrombocytopenia and acute kidney injury considered the complications of sepsis. The patient was started on intravenous ceftriaxone and metronidazole, fluids, omeprazole, paracetamol, and supportive therapy. The main differential diagnosis was thrombotic thrombocytopenic purpura (TTP), pending a peripheral blood film (PBF) to check for schistocytes. TTP was considered in the presence of thrombocytopenia, fever, confusion, and renal failure (pending the PBF report). Accordingly, she was started on intravenous dexamethasone (8 mg thrice daily) on the 3rd day of admission. On the 4th day of admission, she became more confused and subsequently developed 2 episodes of generalized tonic clonic seizures during bedside evaluation. The seizures were immediately aborted with 10 mg of intravenous diazepam, followed by a loading dose of intravenous phenytoin (1 g in a half-liter of saline administered as an infusion over 1 hour.) Her random blood sugar was 189 mg/dl. Following this, we started planning to refer her to a tertiary center in town with concerns for TTP for possible plasma exchange therapy. Meanwhile, we also began empirical therapy for malaria based on epidemiological probability, fever, possible hemolytic anemia due to the presence of jaundice, possible immune-mediated thrombocytopenia, acute kidney injury with Coca-Cola-colored urine which was possibly "Black water fever" caused by hemoglobinuria, and convulsions which would be due to cerebral malaria. We started with oral artemether-lumefantrine tablets administered via nasogastric tube despite repeatedly receiving negative blood slide results for malaria parasites. On the 5th day of admission, the PBF report revealed numerous *Plasmodium falciparum* malaria parasites. See figure 1 below.

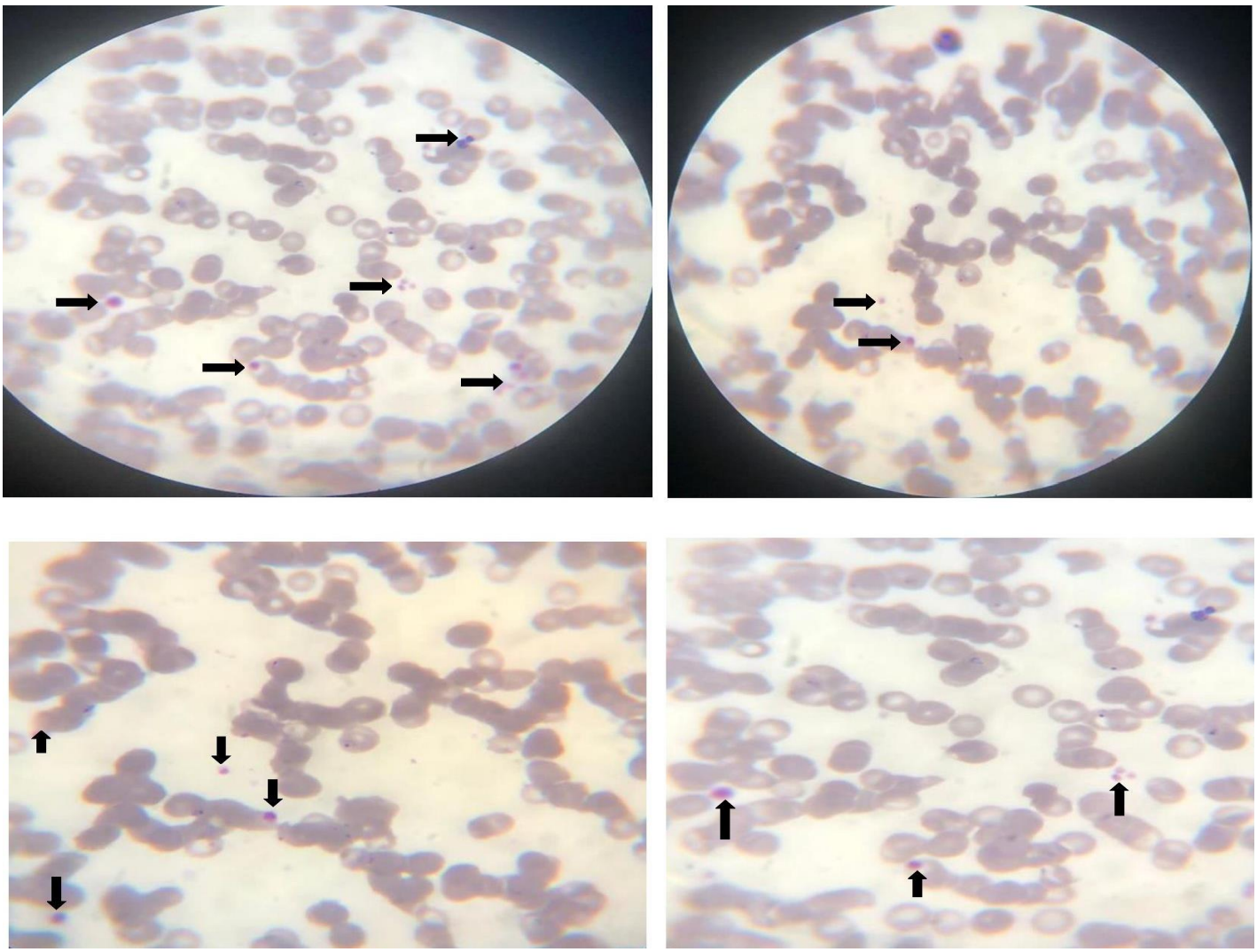

Figure 1: Peripheral blood film showing *Plasmodium falciparum* malaria trophozoites shaped as rings, commas, headphones, and dots.

We switched her to intravenous artesunate, loading at 2.4 mg/kg and given at 0, 12, and 24 hours, then daily for 3 more days. After that, she could take oral artemether-lumefantrine 4 tablets twice daily for 3 days to complete the full treatment dose. After 2 days of artesunate, she could take oral food and medications, and her renal function had improved, with daily urine outputs of more than 1.5-2.4 liters. Her GCS was 15 on the 3rd day of artesunate. She was transfused a total of 4 units of whole blood for symptomatic anemia. By the 10th day of admission, she had fully recovered clinically, and her platelets, creatinine, and bilirubin levels had normalized. We stopped administering the steroids on the 10th day of admission and discharged her on ferrous sulfate, folate, paracetamol, omeprazole, metoclopramide, and multivitamins. She was helped to acquire an insecticide-treated mosquito net and advised on measures to prevent malaria. During her 2-week review in the clinic, she was stable and had a near-normal complete blood count with normal platelets and creatinine, and a negative blood slide for malaria parasites.

DISCUSSION

Our patient presented with clinical features of severe malaria, including: fever of 37.9^{0}C, severe microangiopathic hemolytic anemia with a nadir hemoglobin of 6.3 g/dL and MCV of 82 fL, thrombocytopenia with a nadir platelet counts of 30 x10^3/µL, acute kidney injury with a peak creatinine of 5.5 mg/dL, altered mental status with confusion and convulsions, shock, and jaundice with a peak total bilirubin of 3.4 mg/dL. The first 5 clinical

features also constitute the "pentad" of TTP (Sukumar et al., 2021). This leads to a therapeutic challenge, which has also been reported in several similar case reports (Ghadge & Khobragade, 2020; Kunwar et al., 2024; Kurek et al., 2023). Severe malaria is managed with parenteral anti-malarial drugs until the patient can tolerate oral preparations. In Kenya, the first-line anti-malaria drugs are artemisinin-based combination therapy (ACT), e.g., artemether-lumefantrine. The parenteral forms of artemisinin-based drugs include intravenous artesunate and intramuscular artemether (Musuva et al., 2017). On the other hand, the mainstay therapies for TTP are plasma exchange therapy, immunosuppression (using steroids, rituximab, cyclosporin A, etc.), and anti-vWF agents (e.g., caplacizumab) (Sukumar et al., 2021). Both severe malaria and TTP share a similar pathogenesis involving thrombotic microangiopathy due to acute endothelial dysfunction. This is evidenced by high levels of von Willebrand factor (vWF) antibodies and decreased levels of ADAMTS13 in both conditions (Hollestelle et al., 2006; Kunwar et al., 2024; Löwenberg et al., 2010). In severe *Plasmodium falciparum* malaria, a yet-to-be-identified circulating inhibitor in malaria plasma is believed to reduce the activity of ADAMTS13 (Kunwar et al., 2024). *Plasmodium vivax* malaria has been reported to occur concurrently with TTP and require treatment for both diseases, with the possible link being the thrombotic microangiopathy pathway (Lalise Nemie et al.). We could not perform the ADAMTS13 test for our patient due to the unavailability of the test. The patient fully recovered after the administration of artesunate and artemether-lumefantrine. In malaria-endemic populations, it is reasonable to first offer effective malaria treatment and steroids for patients presenting with the "TTP pentad" first. When there is no clinical and/or laboratory improvement, TTP should be considered and managed. However, when ADAMTS13 levels are less than 10% in the presence of a confirmed severe malaria diagnosis, it is reasonable to treat both conditions in a multispecialty setting. It was curious that our patient repeatedly tested negative for malaria parasites on thin blood smear microscopy but had obvious *Plasmodium falciparum* parasites on PBF. This false-negative microscopy may be explained by several factors, including using non-peripheral blood for the tests, inappropriate timing of blood sample collection (malaria parasites, i.e., the merozoites, are released in burst-dispersal pulses/waves during their life cycle (Lew, 2005)), poor blood sample collection, preparation, and staining techniques, etc. This could have been resolved by the use of WHO-approved malaria rapid diagnostic tests (RDTs), which were unfortunately, not available to us (Maltha et al., 2013; Stauffer et al., 2009).

CONCLUSION

The possibility of a shared pathogenesis involving thrombotic microangiopathy pathways resulting in increased vWF levels and decreased ADAMTS13 may explain the remarkable similarities in the clinical presentation of severe malaria and TTP. In malaria-endemic populations, it is reasonable to first offer effective malaria treatment and steroids for patients presenting with the "TTP pentad" first. When there is no clinical and/or laboratory improvement, TTP should be considered and managed appropriately. Maintaining a high index of suspicion for either disease in appropriate clinical contexts can help minimize delays in providing life-saving treatment.

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Ethical Consideration

Informed consent was obtained from the patient for this case.

Conflict of interest

The authors declare no conflicts of interest.

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