

# Severe Plasmodium Falciparum Malaria Mimicking Thrombotic Thrombocytopenic Purpura (TTP): A Case Report From China

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**Background:** Plasmodium falciparum Malaria and Thrombocytopenic Purpura (TTP) are serious diseases associated with thrombotic microangiopathic anemia (TMA) pathogenesis. Therefore, clinical treatment is usually delayed because of the overlapping clinical manifestations. This case describes Plasmodium falciparum infection causing markedly elevated von Willebrand factor (vWF) levels but normal ADAMTS13 activity, which closely mimics the presentation of TTP.

**Case Presentation:** There is overlap in laboratory and clinical presentations, such as fever, thrombocytopenia, severe anemia, and intravascular coagulation between malaria and TTP. We present the case of a 51-year-old Chinese man who initially presented with fever that quickly progressed to a disturbance of consciousness. Laboratory tests showed a decreased platelet count, elevated lactate levels, and elevated indirect bilirubin levels. The patient's PLASMIC score for TTP was 7, suggesting a high possibility of TTP. There was markedly elevated vWF, but normal ADAMTS13 activity. Therefore, TTP was excluded. However, we found a large amount of P. falciparum in the peripheral blood smears. The patient's condition gradually improved after intravenous artesunate treatment.

**Conclusion:** Malaria and TTP have obvious laboratory and clinical resemblances, owing to the presence of TMA. It is important to quickly perform a differential laboratory diagnosis between malaria and TTP, which may lead to the early initiation of lifesaving treatment in some patients.

**Keywords:** plasmodium falciparum malaria, TTP, TMA, vWF

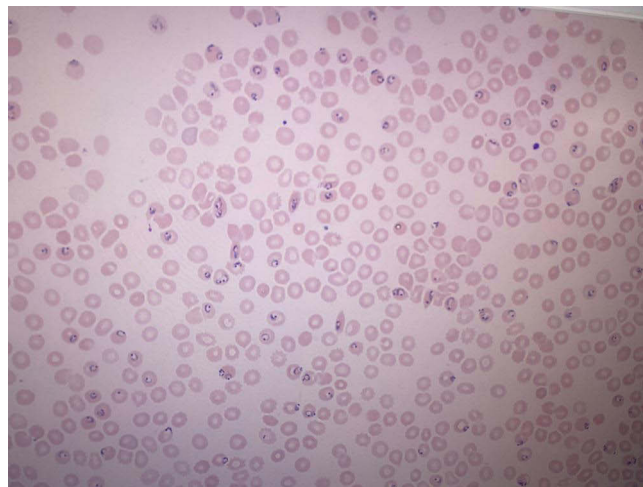
## Introduction

Malaria is an infectious disease caused by parasites of the Plasmodium genus, transmitted primarily by female Anopheles mosquitoes in regions such as Africa and Southeast Asia. Although there are over 120 species within the Plasmodium genus, only five are known to cause malaria in humans.<sup>1</sup> Among these, Plasmodium falciparum is particularly notable for its ability to cause multiple infections within individual red blood cells (RBCs) and to invade RBCs of any age. This capability facilitates rapid multiplication and increased virulence, often resulting in more severe manifestations of the disease.<sup>2</sup> Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening disorder characterized by microangiopathic hemolytic anemia, primarily caused by a severe deficiency in ADAMTS13, a specific protease responsible for cleaving von Willebrand factor (vWF).<sup>3</sup> VWF is a large multimeric plasma glycoprotein that binds to exposed collagen at sites of vascular injury, subsequently activating platelets and adhering to collagen fibers to form a thrombus, thereby arresting bleeding.<sup>4,5</sup> Plasmodium falciparum malaria presents with clinical manifestations similar to those of TTP, including microangiopathic hemolytic anemia, thrombocytopenia, fever, severe neuropsychiatric reactions, and acute kidney injury.<sup>6</sup> Both Plasmodium falciparum malaria and TTP are severe conditions associated with the pathogenesis of thrombotic microangiopathy (TMA).

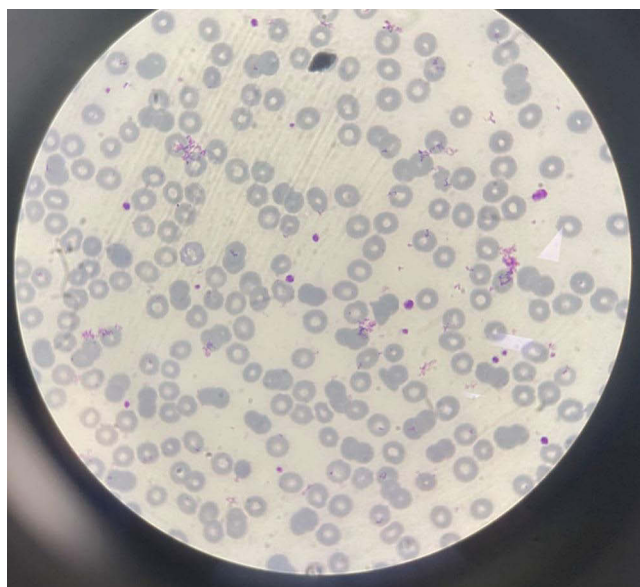
Consequently, clinical treatment is often delayed due to the overlapping clinical presentations. This case report describes an infection with *Plasmodium falciparum* that resulted in significantly elevated vWF levels while maintaining normal ADAMTS13 activity, closely resembling the clinical presentation of TTP.

## Case Presentation

A 51-year-old male of Chinese descent returned to Hubei Province, China, from Africa and remained at home for five days before traveling to Guangzhou, where he developed symptoms of fever, with a maximum body temperature of 39.9°C. He reported experiencing fatigue and nausea but did not exhibit a cough, chest tightness, or shortness of breath. Consequently, he was admitted to the hospital, where laboratory tests indicated thrombocytopenia and leukocytosis. The patient was advised to seek further evaluation at a higher-level medical facility. Subsequently, he presented to the emergency department of Tongji Hospital with a high fever during the night, altered consciousness, unresponsiveness to verbal stimuli, and was accompanied by convulsions and urinary incontinence. Electrocardiogram monitoring revealed a blood pressure of 80/60 mmHg, a respiratory rate of 26 breaths per minute, and an oxygen saturation level of 92%. Upon admission to the Intensive Care Unit, laboratory evaluations were conducted, revealing leukocytosis ( $11.71 \times 10^9/L$ ; reference range [RR] =  $3.5\text{--}9.5 \times 10^9/L$ ), thrombocytopenia ( $27 \times 10^9/L$ ; RR =  $125.0\text{--}350.0 \times 10^9/L$ ), normal hemoglobin levels (129 g/L; RR = 130.0–175.0 g/L), elevated lactate dehydrogenase (453 U/L; RR = 120–250 U/L), significantly elevated D-D dimer ( $> 21 \mu\text{g/mL}$ ; RR  $< 0.5 \mu\text{g/mL}$ ), increased free hemoglobin ( $> 400 \text{ mg/L}$ ; RR  $< 40 \text{ mg/L}$ ), and markedly elevated von Willebrand factor antigen (vWF:Ag) at 623.3% (RR = 50–200%) and von Willebrand factor activity (vWFACT) at 462.9% (RR = 50–200%). Initially, the clinician suspected severe fever with thrombocytopenia syndrome (SFTS), given the patient's recent stay in a region endemic for SFTS during the current season. However, SFTS was ruled out due to negative Dabie-Banda RNA test results. Furthermore, the patient exhibited a high likelihood of TTP, with a PLASMIC score of 7. In relevant clinical scenarios, an ADAMTS13 activity level of less than 10% would further substantiate a TTP diagnosis. The patient was determined to be free of TTP based on the results of the ADAMTS13 activity assay, which indicated a level of 95.8% (reference range: 65.0–135.0%). Concurrently, a significant presence of *Plasmodium falciparum* was detected in erythrocytes via microscopy (Figure 1), correlating with the observed thrombocytopenia. Consequently, the patient was diagnosed with *Plasmodium falciparum* infection and severe cerebral malaria. At midnight, the patient exhibited symptoms of confusion, intermittent convulsions, dyspnea, and reduced oxygen saturation. Sedation and immediate intubation were administered, followed by treatment with intravenous artesunate. After 24 hours, the patient's overall condition showed gradual improvement, and the parasitemia rate in erythrocytes decreased from 9.0% to 0.03% (Figure 2). Two days later, the patient, although still experiencing some cognitive disorientation, was verbally responsive and



**Figure 1** *Plasmodium falciparum*-infected red blood cells before intravenous artesunate administration.



**Figure 2** Plasmodium falciparum-infected red blood cells treated with intravenous artesunate 24 hours later.

subsequently extubated. The patient was discharged upon request after the platelet count increased to  $162 \times 10^9/L$ . Changes in laboratory markers during the hospital stay are detailed in [Table 1](#), which illustrates the progressive improvement and normalization of platelet counts, indirect bilirubin (IBIL), lactate dehydrogenase (LDH), free hemoglobin (HGB), and D-dimer levels following antimalarial treatment. However, the vWF:Ag and von Willebrand factor activity (vWF:AC) levels were markedly elevated.

**Table 1** Laboratory Marker Changes During Hospital Stay

Parameters	Reference Range	On Admission	day 1	day 2	day 3	Day 4
WBC ( $\times 10^9/L$ )	3.5–9.5	11.71	12.12	10.19	9.07	12.33
RBC ( $\times 10^9/L$ )	4.30–5.80	4.35	4.26	2.94	3.06	2.88
HGB g/L	130.0–175.0	129	92	86	89	82
PLT ( $\times 10^9/L$ )	125.0–350.0	27	36	54	88	162
LDH U/L	120–250	453	466	1123	NA	801
IBIL $\mu\text{mol/L}$	$\leq 16.8$	60.5	54.5	18.2	NA	9.2
Free HGB mg/L	<40	>400	>400	391.6	211.90	199.30
BUN $\mu\text{mol/L}$	3.1–8.0	11.9	11.20	7.7	6.6	6.2
CREA $\mu\text{mol/L}$	59–104	105	110	86	91	83
vWF:Ag (%)	50–200%	546.5	411.6	NA	NA	430.2
vWFAC (%)	50–200%	623.3	462.9	NA	NA	465.7
ADAMTS13 activity (%)	65.0–135.0	95.8	NA	NA	NA	NA
PT (s)	11.5–14.5	13.7	14.4	13.3	12.8	13.5
TT (s)	<21.0	18.7	21.1	33.9	17.8	17.7
APTT (s)	29.0–42.0	41.5	50.7	59.4	35.8	39
D-D dimer $\mu\text{g/mL}$	<0.5	>21	9.92	8.2	4.27	2.87
PLASMIC score		7				

**Abbreviations:** WBC, white blood count; RBC, red blood count; HGB, hemoglobin; LDH, lactate dehydrogenase; IBIL, indirect bilirubin; BUN, blood urea nitrogen; CREA, creatinine; vWF, von Willebrand factor; PT, prothrombin time; TT, thromboplastin time; APTT, activated partial thromboplastin time; NA, not applicable.

## Discussion

The overlap in laboratory and clinical manifestations, including fever, thrombocytopenia, severe anemia, and intravascular coagulation, observed in both malaria and TTP, may be attributed to the presence of TMA in both conditions.<sup>6,7</sup> Sinha et al<sup>8</sup> documented that renal histopathology in cases of *Plasmodium* infection exhibited features characteristic of TMA. In a case analogous to ours, Kurek et al<sup>9</sup> described a patient initially diagnosed with malaria but erroneously identified as having TTP. Malaria can manifest with TTP-like alterations; thus, administering treatment for TTP might ameliorate the patient's condition even in instances of misdiagnosis. Recently, Kunwar et al<sup>10</sup> reported a case involving a patient who had traveled to Nigeria and contracted malaria, with ADAMTS13 activity exceeding 10%. The patient received antimalarial therapy without undergoing plasmapheresis and was discharged approximately one week later following normalization of platelet counts and symptomatic improvement. Both cases demonstrated reduced ADAMTS13 activity, albeit greater than 10%, which contrasts with our findings. This discrepancy may be attributable to variations in disease stages and ethnic backgrounds. However, it is noteworthy that the von Willebrand factor antigen (vWF:Ag) and von Willebrand factor activity (vWF:AC) tests were not conducted in these cases.

In our study, the patient exhibited significantly elevated levels of vWF:Ag and vWF:AC, while maintaining normal ADAMTS13 activity. Serial measurements of vWF:Ag and vWF:AC were conducted thrice during the patient's hospitalization, revealing persistently elevated levels upon discharge. A review<sup>11</sup> showed studies conducted on healthy volunteers infected with *Plasmodium falciparum* revealed that the elevation in plasma von Willebrand factor antigen (vWF:Ag) and vWF propeptide (vWFpp) was increased from the early stages post-infection and these levels correspond closely with the severity of the disease. Hollestelle et al<sup>12</sup> have similarly reported that elevated levels of vWF and vWF propeptide (vWFPP) are most pronounced in patients with severe cerebral and non-cerebral malaria. Their study, which included 26 patients with cerebral malaria, assessed these levels after 24 hours and 3 days of treatment. They observed that vWFPP levels were significantly reduced compared to admission levels, with half of the patients returning to normal levels after three days of treatment. Although vWF levels did not significantly decrease after 24 hours of treatment, a significant reduction was noted by the third day. Nonetheless, vWF levels remained elevated in the majority of cases. These findings are consistent with our laboratory results, although we did not conduct vWFPP testing. Additional studies<sup>13,14</sup> have demonstrated that elevated vWF levels can precede the appearance of parasites in peripheral blood smears. Meanwhile, we observed that the patient had a high level of D-dimer on the date admission. A review<sup>15</sup> emphasizes a strong link between increased D-dimer levels and *Plasmodium* infections, particularly involving *P. falciparum*. Increased D-dimer levels were considered as indicative of coagulation activation and fibrinolysis. And they were noted in a significant portion of malaria patients. This points to an underlying hypercoagulable state that may contribute to the development of complications.

Malaria and TTP exhibit notable laboratory and clinical similarities, primarily due to the presence of TMA. This observation suggests a potential mechanism wherein elevated levels of vWF may induce TMA in malaria. The activation of endothelial cells (ECs) occurs when erythrocytes infected with *Plasmodium falciparum* adhere to these cells.<sup>16</sup> Subsequently, Weibel-Palade bodies (WPBs) release ultra-large vWF into the bloodstream. These ultra-large vWF strings facilitate the recruitment and sequestration of platelets, which in turn activate additional ECs, thereby enhancing WPB secretion. Mature *P. falciparum* parasites express the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), which is capable of binding to platelet-decorated vWF strings through platelet CD36. Consequently, the presence of ultra-large vWF increases endothelial cell permeability, leading to thrombosis.<sup>17,18</sup> In a study conducted by O'Regan et al, *Plasmodium berghei* ANKA was used to infect mice, resulting in a model that accurately replicates cerebral malaria in humans. The findings of this study revealed that, in comparison to wild-type controls, vWF-deficient (vWF<sup>-/-</sup>) mice exhibited protection against *Plasmodium berghei* infection.<sup>19</sup> These results suggest that vWF may play a critical role in the pathogenesis of cerebral malaria.

We also note some limitations of the study. Firstly, we cannot conduct vWFPP testing.

Maybe the level of vWFPP is more meaningful than vWF. Secondly, the patient recovered quickly so that the follow-up was short.

## Conclusion

Malaria and thrombotic thrombocytopenic purpura (TTP) exhibit notable laboratory and clinical similarities due to the presence of thrombotic microangiopathy (TMA). Prompt differential laboratory diagnosis between malaria and TTP is

crucial, as it may facilitate the early commencement of lifesaving interventions for certain patients. Therefore, it is essential to assess von Willebrand factor (vWF) levels and ADAMTS13 activity in individuals diagnosed with malaria.

## Ethics Approval and Consent

Institutional approval is not required for publication, so informed written consent for using patient information and case report publication was obtained from the patient as long as identifying data are anonymous. The patient has provided informed consent for the publication of this case report and accompanying images.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no conflicts of interest.

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