The clinical, hematological, and biochemical profiles of patients with complications due to Plasmodium vivax malaria: A case series

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ABSTRACT

Malaria, a protozoal infection caused by the six species of the genus Plasmodium, is one of the most important diseases known to humankind, with most infections caused by either of the two species – Plasmodium vivax and Plasmodium falciparum. Previously, it was held that falciparum malaria was responsible for causing severe, life-threatening disease, with vivax malaria causing mild or uncomplicated infections. In this case series, the clinical, hematological, and biochemical profiles of eight patients with features of complications due to P. vivax malaria, along with their clinical course, response to treatment, and clinical outcomes have been described. Among these, the most common clinical features were fever, headache, and myalgias. Five patients had altered mental status, two were prostrated, two were hypotensive, and one had recurrent generalized seizures. Three patients had pancytopenia, two had both anemia and thrombocytopenia, and one had evidence of disseminated intravascular coagulation. Six patients had clinical jaundice, four had elevated transaminases, and four had acute kidney injury. All cases showed excellent response to anti-malarial therapy. Hence, this case series revealed that P. vivax is capable of causing severe, life-threatening organ dysfunction akin to those seen in P. falciparum malaria and that early diagnosis and treatment initiation are associated with positive patient end outcomes.

Key words: Malaria; Plasmodium vivax; Pancytopenia; Hyponatremia

INTRODUCTION

Malaria is one of the most important protozoal infections afflicting humankind, caused by the six species of the genus Plasmodium, namely vivax, falciparum, ovale (curtisi and wallikeri), malariae, and knowlesi, and transmitted through the bite of the female Anopheles mosquitoes. The global burden of malaria cases in the year 2022, across 85 countries in which it is endemic, was 249 million cases.¹ In 2022, 2% of this global burden was accounted for by the South-east Asia region, to which India alone accounted for 66% of the total cases.¹

Clinical presentations may range from mild, uncomplicated cases to severe, life-threatening infections that may result in death if not treated early with definitive anti-malarial drugs and aggressive supportive measures.² Recent trends demonstrate an increasing number of severe malarial infections attributable to vivax infections,³,⁴ previously believed to cause milder cases. Severe Plasmodium falciparum malaria is considered to present with features such as unarousable coma, cerebral malaria, acidemia/acidosis, renal failure, non-cardiogenic pulmonary edema, hypoglycemia, hypotension or shock, bleeding manifestations or disseminated intravascular coagulation (DIC), repeated convulsions, hemoglobinuria, extreme weakness or prostration, hyperparasitemia or clinical jaundice with serum bilirubin >3 mg/dL, in the presence of other vital organ dysfunction or parasite density >100,000/µL.⁵ The increasing demonstration of similar
presentations in *Plasmodium vivax* malaria implies that the failure to recognize the risk of severe organ dysfunction and unfamiliarity with such clinical presentations may cause an avoidable compromise in patient care due to lapses in early and effective institution of definitive parenteral anti-malarial therapy and supportive measures, adequate monitoring of the emergence of complications, prognostication and thereby, clinical end outcomes.

This article presents eight cases of *P. vivax* infection, describing their clinical, hematological, and biochemical profiles, highlighting the existence of implicit complications, their recognition, and management, resulting in positive end outcomes.

**MATERIALS AND METHODS**

The current study was conducted in the general medicine wards of Medical College and Hospital, Kolkata, including patients with *P. vivax* malaria admitted therein, in the time period from August 2022 to November 2023. All patients above the age of 12 years, presenting with fever, headache, malaise, myalgias, and features of organ dysfunction, with a positive test for *P. vivax* malaria by malarial parasite dual antigen detection kit or a peripheral blood smear examination were included, with the exclusion of cases with dual vivax and falciparum malaria, and fever attributable to another concomitant cause. Clinical investigations were conducted free of cost at the hospital laboratory. Sociodemographic parameters and clinical data were collected through patient records, clinical examination, and relevant investigations, respectively.

Data were obtained and analyzed and response to treatment was noted.

We present the history, clinical findings, investigations, and clinical course of eight patients with complications due to *P. vivax* malaria. Tables 1-3 summarize the data pertaining to the patients.

**CASE 1**

A 16-year-old female presented with complaints of high-grade fever and recurrent seizures for 3 days. At presentation, the patient was stuporous with failure to appropriately localize noxious stimuli, pulse rate: 112/min, regular, blood pressure: Unrecordable, capillary blood glucose (CBG): 269 mg/dL, skin turgor: Decreased, pupils: Bilateral equal, reactive to light, plantar unresponsive, neck rigidity – absent. The absence of response to volume resuscitation prompted the institution of intravenous vasopressor support. Intravenous lorazepam was administered to terminate the ongoing seizure. Routine blood investigations and a comprehensive fever profile including MP/MPDA, Dengue NS1Ag, Scrub typhus Immunoglobulin M (IgM), *Leptospira* IgM, Chikungunya IgM, and urine and...
Table 3: Table summarizing the clinical, hematological, and biochemical profiles of eight patients with Plasmodium vivax malaria

<table>
<thead>
<tr>
<th>Parameter/S. No.</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
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</thead>
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<tr>
<td>Age (yrs)</td>
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<td>66</td>
<td>35</td>
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<td>17</td>
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<td>Gender</td>
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<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Blood Pressure</td>
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<td>120/70</td>
<td>118/70</td>
<td>120/70</td>
<td>112/60</td>
<td>113/70</td>
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<td>Capillary Blood</td>
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<td>Normal</td>
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<td>Normal</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.7</td>
<td>8.9</td>
<td>9.3</td>
<td>8.7</td>
<td>8.9</td>
<td>8.7</td>
<td>8.5</td>
<td>8.9</td>
</tr>
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<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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<td>Normal</td>
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<tr>
<td>Platelets (per mm³)</td>
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<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Ur/cr (mg/dl)</td>
<td>13.2</td>
<td>15.6</td>
<td>13.5</td>
<td>14.7</td>
<td>12.8</td>
<td>13.0</td>
<td>13.0</td>
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<td>Serum glutamic-oxaloacetic transaminase (SGOT)</td>
<td>230</td>
<td>220</td>
<td>200</td>
<td>210</td>
<td>220</td>
<td>230</td>
<td>240</td>
<td>250</td>
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<tr>
<td>Serum glutamic-pyruvic transaminase (SGPT)</td>
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<td>190</td>
<td>200</td>
<td>180</td>
<td>190</td>
<td>200</td>
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<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

CASE 2

A 59-year-old male, hypertensive, with known ischemic heart disease, presented with complaints of undocumented fever associated with chills and rigor, dull frontal headache, with mild body ache for 5 days before presentation, associated with a decreased urine output for 2 days, unaccompanied by dysuria, rash, bleeding manifestations, altered sensorium, seizures, abdominal pain, and vomiting. On examination, the patient was conscious, alert, and cooperative, pallor was absent, mild icterus was noted, blood pressure: 112/58 mm of Hg, pulse rate: 80/min, regular, CBG: 156 mg/dL. Routine blood investigations and a comprehensive fever profile were sent. Vitals and urine output were measured at timely intervals. A decreased urine output was noted. Reports revealed P. vivax by MPDA kit, isolated thrombocytopenia with normal hematocrit and total and differential counts, deranged liver function test, raised urea, and creatinine values. Serum sodium and potassium values were 133 meq/L and 5 meq/L, respectively. The following day serum creatinine rose to 3.1 mg/dL, and serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) were raised at 139 and 77, respectively. PT was prolonged at 22 s with INR 1.59, and APTT was prolonged at 50.7 s, with elevated fibrinogen and no evidence of DIC. The patient responded to a course of intravenous artesunate with intravenous hydration followed by area-specific oral artemisinin combination therapy, with the gradual recovery of renal function and normalization of laboratory parameters. He was discharged in a clinically stable condition with a prescription for a 14-day course of oral primaquine.

CASE 3

A 22-year-old male with no known comorbidities, and with an undocumented history of cerebral malaria 6 years ago
and an episode of treated uncomplicated *P. vivax* malaria 2 months before presentation, was admitted with complaints of high-grade fever with chills, associated with dull frontal headache, myalgia, and three episodes of vomiting. For 3 days with extreme weakness leading to inability to sit or stand unaided and diminution of consciousness over 2 days before presentation. On examination, the patient was drowsy, pulse, blood pressure, CBG within normal limits, pallor was absent, mild icterus was noted, and the abdomen was soft, non-tender with the liver palpable 3 cm below the right costal margin. He was diagnosed with vivax infection by dual antigen detection kit, and laboratory investigations revealed isolated thrombocytopenia, elevated total serum bilirubin, and rising serum creatinine from 2.5 mg/dL to 3.3 mg/dL with serum urea 50 mg/dL. He was treated with intravenous artesunate with supportive measures followed by area-specific oral artemisinin combination therapy and was discharged on recovery in a clinically stable condition with a 2-week course of oral primaquine after ascertaining normal G-6-P D enzyme activity.

**CASE 5**

A 17-year-old female presented with undocumented fever associated with chills and rigor for 3 days before presentation and alteration of sensorium for the preceding 12 h. This was not associated with seizures, vomiting, abdominal pain, or bleeding manifestations. On examination, the patient was stuporous with response only to noxious stimuli, febrile, and icteric, with blood pressure 120/92 mmHg and a regular pulse rate of 74/min. Neck rigidity was absent. She was diagnosed with vivax infection by dual antigen detection kit and was started on parenteral artesunate followed by 3 days of artemisinin combination therapy. Reports demonstrated jaundice and normocytic normochromic anemia with the development of thrombocytopenia. The patient responded to treatment, recovered, and was discharged with a 2-week course of oral primaquine therapy.

**CASE 6**

A 70-year-old female presented with complaints of fever rising to 103°F, associated with chills and dull frontal headache. On examination, the patient’s vitals were stable, pallor, and icterus were noted. Her blood reports were notable for jaundice, normocytic normochromic anemia, and thrombocytopenia. She was diagnosed with *P. vivax* infection by dual antigen detection kit and was started on oral artemisinin combination therapy and recovered and was discharged with an oral primaquine course.

**CASE 7**

A 59-year-old female patient planned for chemoradiotherapy for breast carcinoma, presented with complaints of high-grade continuous fever with chills for 5 days before presentation, with persistent vomiting and progressive drowsiness for 3 days. Her vitals were stable and she was found to have pallor. Her reports demonstrated pancytopenia. She was diagnosed with *P. vivax* malaria using the dual antigen detection kit and was started on parenteral artesunate followed by 3 days of area-specific artemisinin combination therapy. The patient recovered clinically and her blood picture improved. She was discharged in a hemodynamically stable condition and directed to the oncology and radiotherapy departments.

**CASE 8**

A 41-year-old female on regular antihypertensive medications presented with a history of undocumented fever associated with chills about 3 weeks before presentation that was accompanied by anorexia and mild upper abdominal discomfort. After the fever subsided, she developed a gradually deepening yellowish discoloration of her eyes and urine with the passage of normally colored stools. This was not associated with any bleeding manifestations or alteration of the sensorium. There was no prior history of blood transfusions or high-risk behavior. There was no history of community aggregation of
similar cases. The patient had a report stating hepatitis A IgM positive but remarkably, liver enzymes were not found to be significantly elevated. On examination, her vitals were stable and she was found to have pallor and icterus. Her liver was palpable 3 cm below the right costal margin and was soft and tender. Her reports were notable for normocytic normochromic anemia. Serum total bilirubin was raised with elevated direct fraction, and liver enzymes were normal. She was found to be negative for hepatitis B surface antigen and anti-hepatitis C virus, anti-hepatitis E virus, and positive for *P. vivax* malaria by dual antigen detection kit. She received 3 days of oral artemisinin combination therapy and demonstrated a recovery of her clinical, hematological, and biochemical parameters. She was discharged in a hemodynamically stable condition with an oral primaquine course.

**DISCUSSION**

Malaria remains a major public health problem in India and globally, with the majority of cases being accounted for by two species, *P. falciparum* and *P. vivax*. The global burden of cases due to *P. vivax* declined from 8% in 2000 to 3% in 2022. The South-east Asia region, of which India is a part, saw about 46% of malaria cases attributable to *P. vivax* in the year 2022.

Furthermore, India and Indonesia accounted for 94% of all malaria deaths in the region in the same year, highlighting the impact of the disease on the Indian population. The state of West Bengal, in which this study was conducted saw a rise in malaria cases between 2017 and 2021 in contrast to the overall decline seen at the national level. Furthermore, in West Bengal, the percentage of cases due to *P. falciparum* stood at 33% which is lower than the national average of 63%, thereby highlighting the fact that most cases in the state, in fact, are due to *P. vivax*.

The pathophysiologic mechanism behind the complications seen in *P. falciparum* malaria was attributed to the property of cytoadherence, causing microvascular occlusion in critical organs, leading to organ dysfunction and resultant complications in addition to enabling escape from host immune mechanisms. As previously noted, of late, it is being increasingly recognized that *P. vivax*, too, can cause severe malaria with features similar to severe *P. falciparum* malaria.

The pathogenesis of severe malaria due to *P. vivax* infection is less clear. Unlike in *P. falciparum* malaria, red blood cells infected with *P. vivax* malaria do not exhibit significant sequestration in the capillary beds of vital organs; however, there is evidence that some degree of cytoadherence is indeed noted in red blood cells infected with *P. vivax*, albeit at a lower frequency. Therefore, theories regarding other pathophysiological mechanisms have been postulated and include endothelial dysfunction, cytokine-mediated inflammation, and thrombotic microangiopathy, among others.

In this case series, eight documented cases of severe *P. vivax* malaria have been included in which features of cerebral malaria, renal dysfunction, jaundice, prostration, hypotension, pancytopenia, anemia with thrombocytopenia, isolated anemia, and overt DIC without bleeding were seen.

In the present study conducted among adult patients, the subjects’ ages ranged between 16 and 79, the mean age being 45.37 years, demonstrating that persons of all age groups may be affected. All patients had presented with fever. The mean duration of fever was found to be 4±1.91 days.

Five patients (62.5%) presented with altered mental status and 2 patients (25%) were hypotensive at presentation and required fluid and vasopressor support. One (12.5%) patient had repeated generalized seizures and also laboratory features of DIC.

A systematic review and meta-analysis of clinical studies since 1990 showed jaundice to be the most common abnormality encountered in severe *P. vivax* malaria, followed by cerebral malaria, hematological abnormalities like anemia, thrombocytopenia, and DIC with or without overt bleeding, renal dysfunction, hypoglycemia, generalized seizures, hypotension, or shock.

In this study, the most common abnormalities were thrombocytopenia (100%) and jaundice (75%).

Direct hyperbilirubinemia was noted in five of the six patients. Transaminitis was noted in 5 (62.5%) of patients, four had elevated SGOT and SGPT, and one had only elevated SGOT. The mean among those with raised values was 344.8±543.018 IU/mL for SGOT and 316.75±472.864 IU/mL for SGPT. Jaundice in malaria is believed to be due to hepatocellular injury, cholestasis as well as hemolysis. Three patients had prolonged PT, more than or equal to 4 s.

Three patients (37.5%) presented with pancytopenia. Two patients (25%) had anemia and thrombocytopenia. One (12.5%) had only anemia. The mean hemoglobin value considering the least recorded value for each patient was 8.525±2.073 g/dL. The mean platelet value taking into account the lowest recorded value for each patient was 344.8±543.018 IU/mL. Anemia in malaria is due to both increased destruction of infected and uninfected red blood cells as well as an inappropriate bone marrow response to the anemia, with *P. vivax* infections causing
an earlier dip in hemoglobin levels than falciparum infections. Thrombocytopenia has been seen to be the most common hematological abnormality in various studies previously, which is consistent with the result in our series. A systematic review and meta-analysis conducted by Naing and Whittaker revealed an equal risk of developing severe thrombocytopenia and consequent bleeding in patients with *P. vivax* and *P. falciparum* malaria.

Four (50%) patients had acute renal dysfunction. Renal dysfunction in malaria is usually due to acute tubular necrosis and may be attributable to volume depletion, microcirculatory blockage due to sequestered parasites, and immune-mediated injury. The most common electrolyte abnormality noted was hyponatremia noted in five patients, mean value of sodium being 133.73±3.640. A hospital-based cross-sectional study conducted by Parida et al., at SCB Medical College, Cuttack, showed a greater occurrence of hyponatremia in mixed severe malaria infections than those due to *P. falciparum* alone and was a predictor of higher mortality. Two (25%) patients in this series were severely prostrated.

**CONCLUSION**

*P. vivax* infection can cause systemic complications due to organ dysfunction. Early diagnosis and treatment initiation lead to complete recovery in cases of severe *P. vivax* malaria and hence it is imperative that such presentations of *P. vivax* malaria and their management are known to internists and primary care physicians alike.

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**REFERENCES**

Authors Contribution:
AJ- Definition of intellectual content, literature survey, prepared the first draft of the manuscript, implementation of the study protocol, data collection, data analysis, manuscript preparation, and submission of the article; SKM- Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; RM- Coordination and manuscript revision; SB- Review manuscript and statistical analysis; GM- Review manuscript; and KD- Review manuscript.

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