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Case Report

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Case report

Transfusion-Requiring Delayed Hemolytic Anemia After Artemether/Lumefantrine Treatment for Low-Parasitemia Uncomplicated Malaria in a Japanese Patient with Multiple Previous Malaria Episodes

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Abstract

Background: Artemisinin-based combination therapy (ACT) is the first-line treatment for falciparum malaria. However, post-artemisinin delayed hemolysis (PADH) is a recognized complication that typically occurs 1–4 weeks after treatment, particularly in patients with severe malaria and high parasitemia.

Case presentation: A 38-year-old Japanese man with a history of multiple episodes of *Plasmodium falciparum* malaria presented with fever after traveling to Tanzania. The patient was diagnosed with uncomplicated *Plasmodium falciparum* malaria with low parasitemia. After treatment with artemether–lumefantrine, parasitemia cleared within 72 hours, and the patient was discharged on hospital day 7. Ten days after discharge (approximately 17 days after initial

admission), the patient was readmitted with exertional dyspnea, hematuria, and fatigue. Laboratory investigations revealed hemolytic anemia (hemoglobin nadir 7.2 g/dL) and renal dysfunction, whereas repeat malaria testing and both direct and indirect Coombs tests were negative. PADH was diagnosed based on the clinical course, and the patient was managed with supportive therapy, including red blood cell transfusion.

Conclusions: This case illustrates that PADH can occur after treatment of uncomplicated falciparum malaria with low parasitemia, and that a history of multiple malaria episodes should not be assumed to confer protection against this complication. Clinicians should maintain awareness of delayed hemolysis after ACT regardless of initial disease severity.

Keywords: Artemisinin-based combination therapy, malaria, post-artemisinin delayed hemolysis, *Plasmodium falciparum*

Introduction[1]

Malaria is a vector-borne infectious disease transmitted by *Anopheles* mosquitoes. Falciparum malaria, caused by *Plasmodium falciparum*, is associated with a high risk of severe disease and can be fatal if appropriate treatment is delayed [1]. It is endemic mainly to sub-Saharan Africa and Southeast Asia. Although malaria is not endemic in Japan, it remains an important imported infectious disease among Japanese travelers.

The recommended treatment for falciparum malaria is artemisinin-based combination therapy [2]. However, some patients with severe malaria and high parasitemia develop post-artemisinin delayed hemolysis (PADH) [3]. The proposed mechanism involves the splenic pitting of parasitized erythrocytes during artemisinin treatment: once-infected erythrocytes are cleared of parasites but remain in circulation with a shortened lifespan, and their delayed, synchronized destruction results in hemolysis [4,5]. PADH has also been reported in patients with low parasitemia and uncomplicated malaria, indicating that its development cannot be reliably

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[1] **Abbreviations**

ACT: Artemisinin-based combination therapy

PADH: Post-artemisinin delayed hemolysis

IFAT: Indirect fluorescent antibody test

63 predicted based solely on disease severity. In contrast, PADH is less likely in patients with a semi-
64 immune state [1,6]. Here, we report a case of PADH developing after artemether–lumefantrine
65 treatment for uncomplicated falciparum malaria with low parasitemia in a Japanese patient with
66 a history of several prior episodes of falciparum malaria. Despite his malaria history, serological
67 testing suggested that he had not acquired significant anti-malarial immunity.
68
69 **Case presentation**
70 The patient was a 38-year-old Japanese man with persistent fever, headache, and fatigue
71 who was referred to us by another hospital. He visited Dar es Salaam, Tanzania, in 2024 for 8
72 days for overseas consulting work. His medical history included approximately five previous
73 episodes of falciparum malaria, with the most recent infection in 2019. He also had a history of
74 multiple trips to malaria-endemic countries, including Benin and Rwanda (2013). The purpose of
75 his 2024 trip was mainly to attend meetings, and he stayed exclusively in the urban areas of Dar
76 es Salaam, lodging at a hotel. The travel period coincided with the rainy season in Tanzania, and
77 although the patient reported mosquito exposure while dining outdoors during his stay, he did not
78 use insect repellents or take any malaria chemoprophylaxis, nor did he receive pretravel
79 vaccinations.
80 At admission, the patient was conscious and oriented. His vital signs were as follows:

temperature, 38.1°C; blood pressure, 83/42 mmHg; heart rate, 85 beats per minute; and oxygen saturation, 100% on ambient air. His blood pressure rapidly improved to 103/54 mmHg following intravenous fluid resuscitation. Physical examination revealed no pallor of the palpebral conjunctiva, no scleral icterus, and no neck stiffness. Cardiac examination revealed normal heart sounds without murmurs, and lung auscultation revealed clear bilateral breath sounds. The abdomen was flat and soft, with no tenderness or rebound tenderness. Murphy's sign was negative, and there was no hepatic or costovertebral angle tenderness. Examination of the extremities revealed peripheral coldness and multiple insect bite marks on both lower extremities. No focal neurological deficits were observed. Laboratory investigations showed a white blood cell count of 14,100 /μL, hemoglobin level of 16.0 g/dL, and platelet count of 39,000 /μL. Biochemical analysis revealed elevated liver enzyme levels, with total bilirubin, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase levels of 1.5 mg/dL, 272 U/L, 222 U/L, and 712 U/L, respectively. Furthermore, his blood urea nitrogen, creatinine, blood glucose, and C-reactive protein levels were 27.6, 1.67, 113, and 19.93 mg/dL, respectively. Urinalysis was negative for occult blood and nitrites. Chest and abdomen computed tomography revealed hepatosplenomegaly. A fully automated hematology analyzer (XN-31) detected *P. falciparum* with a parasitemia of 0.1091%. Polymerase chain reaction testing confirmed *P. falciparum* infection (Figure 1). Conventional microscopic examination of thick and thin blood smears

revealed ring forms within erythrocytes.

Based on these findings, the patient was clinically diagnosed with uncomplicated falciparum malaria. Because disease severity was assessed as non-severe, Artemether–lumefantrine was administered at a dose of [80/480 mg] twice daily for 3 days (six doses total). Given the relative bradycardia, concomitant infections such as typhoid fever or non-typhoidal *Salmonella* infection were considered, and ceftriaxone at 2 g/day was initiated. However, the blood cultures remained negative, and ceftriaxone was discontinued on hospital day 6. The parasite clearance time was 72 h, and the fever resolution time was 120 h. The patient showed clinical improvement and was discharged on hospital day 7 with outpatient follow-up.

Ten days after discharge, the patient developed exertional dyspnea, hematuria, and generalized fatigue, prompting readmission for further evaluation and management. Laboratory tests revealed findings indicative of hemolytic anemia and renal dysfunction: white blood cells, 6,120/μL; hemoglobin, 8.0 g/dL; reticulocyte percentage, 8.28%; platelets, 426,000/μL; total bilirubin, 1.5 mg/dL; aspartate aminotransferase, 168 U/L; lactate dehydrogenase, 3,055 U/L; creatinine, 1.72 mg/dL; and C-reactive protein, 1.71 mg/dL. Repeated malaria testing using XN-31 was negative, and microscopic examination of blood smears revealed no malaria parasites. Both direct and indirect Coombs tests were also negative. Urinalysis was positive for occult blood, and urine sediment examination revealed >100 red blood cells per high-power field. Based on the

117 clinical course and laboratory findings, a diagnosis of PADH was made. The patient was managed
118 with supportive therapy, including transfusion of 6 units of packed red blood cells and intravenous
119 fluid administration. The hemoglobin nadir was 7.2 g/dL. Hematuria subsequently resolved, and
120 renal function improved, allowing discharge on hospital day 5 after readmission (Figure 2). At
121 the outpatient follow-up visit, 6 days after discharge, hemoglobin level had improved to 10.1 g/dL,
122 and serum creatinine level had returned to 1.17 mg/dL.

123 To investigate whether the patient was in a semi-immune state, antibody titers against *P.*
124 *falciparum* were determined using an indirect fluorescent antibody test (IFAT) [7] (Additional file
125 Supplemental material). IFAT showed a titer of 1:16, indicating no significant elevation despite a
126 history of multiple malaria infections. During the convalescent phase, the antibody titer against
127 falciparum malaria antigens increased to 1:1024.

128

129 **Discussion and Conclusions**

130 In the case of our patient, PADH developed after treatment of uncomplicated falciparum
131 malaria contracted during a short trip to Dar es Salaam, Tanzania. Although malaria transmission
132 intensity in Dar es Salaam is lower than in rural parts of Tanzania [8], the case illustrates that
133 malaria risk persists in urban settings, particularly during the rainy season and in the absence of
134 chemoprophylaxis.

The risk of PADH was considered low in this case given the uncomplicated presentation, low parasitemia, absence of relevant comorbidities, and self-reported history of multiple malaria episodes suggestive of semi-immunity. PADH is most commonly reported in patients with severe *P. falciparum* malaria and high levels of parasitemia. Previous studies have shown that the risk of PADH increases with parasite burden, particularly in patients with high parasitemia who require parenteral therapy [3]. The proposed mechanism involves the “pitting” phenomenon, in which once-infected erythrocytes are cleared of parasites in the spleen after artemisinin treatment but remain in circulation with a shortened lifespan. The accumulation of these damaged erythrocytes results in delayed and synchronized hemolysis, which occurs 1–4 weeks after treatment [4,5]. Although PADH after oral ACT for uncomplicated malaria has been reported, Kurth et al. found that the decrease in hemoglobin levels was generally modest and often not clinically relevant [9]. Nevertheless, fatal PADH after oral ACT in uncomplicated falciparum malaria has been reported. Notably, the previously reported fatal case was accompanied by a positive direct antiglobulin test [10], suggesting a possible autoimmune component that was not evident in the present case. Glucose-6-phosphate dehydrogenase (G6PD) deficiency was considered unlikely given its low prevalence in the Japanese population [11], although it was not formally excluded by enzymatic testing. Although high parasitemia, elevated lactate dehydrogenase levels, and thrombocytopenia have been reported as possible predictors of PADH in uncomplicated malaria, none of these risk

153 factors was evident in the present case [12]. Accordingly, PADH was not readily predictable, and
154 its progression to transfusion-requiring severe anemia was unexpected. Therefore, careful follow-
155 up after ACT remains important.

156 Given his history of repeated malaria episodes, uncomplicated presentation, and low
157 parasitemia, the patient was initially considered to be semi-immune. Generally, PADH develops
158 less frequently and is less severe in semi-immune individuals. Although a significantly lower risk
159 of PADH has not been observed in semi-immune patients with uncomplicated malaria [9], such
160 patients are generally less likely to develop high parasitemia [13]. Hence, there is less
161 accumulation of infected red blood cells, resulting in fewer red blood cells undergoing hemolysis.
162 In addition, because some degree of immunity is present in these patients, severe disease is less
163 likely to develop, and pretreatment red blood cell damage may also be reduced [14]. Repeated
164 malarial infections are generally thought to result in partial immunity, often referred to as a semi-
165 immune state. However, this concept is primarily used in a clinical context, and there are no
166 established definitions or objective diagnostic criteria for semi-immunity [9]. Antibody titers
167 against crude *P. falciparum* antigens are known to increase approximately 1 week after infection
168 and gradually decline over about 1 year, although repeated infections may lead to sustained
169 elevation [15]. Although IFAT titers do not directly reflect protective immunity, they are often
170 elevated in semi-immune individuals from malaria-endemic regions in Africa [16]. In the present

171 case, nearly 5 years had elapsed since the last malaria episode, which may have contributed to a
172 decline in antibody titers. Furthermore, despite repeated infections in the past, the patient's IFAT
173 titer was not markedly elevated at presentation, suggesting that his immune status was
174 inconsistent with that typically observed in semi-immune individuals.

175 Macroscopic hematuria or hemoglobinuria is not a typical feature of PADH. This is because
176 hemolysis in PADH is predominantly extravascular, with damaged red blood cells removed by
177 the spleen and other components of the reticuloendothelial system rather than being destroyed
178 within the circulation. However, several reports have described cases of PADH accompanied by
179 renal dysfunction and hematuria [17,18]. One possible explanation is that free hemoglobin
180 released during intravascular hemolysis causes renal tubular injury and hemoglobinuria. However,
181 in the present case, urine sediment examination revealed abundant red blood cells (>100/HPF),
182 indicating true hematuria rather than isolated hemoglobinuria. The mechanism underlying
183 hematuria in this context remains uncertain, and a contribution from glomerular or other renal
184 parenchymal involvement cannot be excluded. When hemolysis is severe, clinicians should be
185 aware of the potential for hematuria through this mechanism. Appropriate supportive management
186 – including adequate fluid therapy and blood transfusion when indicated – is therefore important.

187 In conclusion, we report a case of severe, transfusion-requiring PADH that developed after
188 treatment for uncomplicated falciparum malaria in a patient initially considered to be at low risk.

189 This case illustrates that PADH may occur in settings where clinical risk factors are absent or not
190 apparent, and cannot be reliably predicted based solely on initial disease severity, and highlights
191 the importance of maintaining clinical vigilance for delayed hemolysis after artemisinin-based
192 therapy, regardless of initial parasitemia level or presumed immune status.
193
194

195 **List of Abbreviations**

196 **ACT**: Artemisinin-based combination therapy; **PADH**: Post-artemisinin delayed hemolysis;

197 **IFAT**: Indirect fluorescent antibody test; **PCR**: Polymerase chain reaction; **DNA**:

198 Deoxyribonucleic acid; **bp**: Base pairs; **Hb**: Hemoglobin; **Cre**: Creatinine; **LDH**: Lactate

199 dehydrogenase

200

Declarations

Ethics approval and consent to participate

Ethics approval was not required for this case report in accordance with the institutional guidelines.

Consent for publication

Written informed consent for publication was obtained from the patient.

Availability of data and materials

None.

Conflict of interest

None.

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Author contributions

K.Y. and S.K. supervised the study. K.Y., H.N., S.K., N.O. were involved in the clinical care and management of the patient, collection of data, and drafting of the manuscript. All authors approved the final version of the manuscript. All authors meet the ICMJE authorship criteria.

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Declaration of generative AI in scientific writing

During the preparation of this work, the authors used ChatGPT (OpenAI) to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Figure legends

Figure 1. Polymerase chain reaction testing of the patient's blood sample for *Plasmodium* spp

(a) PCR using universal primers for *Plasmodium* spp.

Lane M, 100-bp DNA ladder; lane 1, patient sample; lane 2, negative control; lanes 3–7, positive controls for *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*, respectively. The patient's sample was found to be positive on using universal primers, as indicated by the arrows.

(b) Species-specific PCR for *Plasmodium* spp.

Lane M, 100-bp DNA ladder. Patient samples were loaded in lanes 8, 12, 16, 20, and 24 for *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*-specific primers, respectively. The corresponding positive controls were loaded in lanes 9, 13, 17, 21, and 25; the negative controls from the first PCR were loaded in lanes 10, 14, 18, 22, and 26; and the water controls were loaded in lanes 11, 15, 19, 23, and 27. No species-specific amplification was detected in the patient samples. The patient's sample was only positive for *P. falciparum*, as indicated by the arrow.

PCR: Polymerase chain reaction

Figure 2. Temporal changes in laboratory parameters from the initial admission

317 The patient’s hemoglobin (Hb), creatinine (Cre), and lactate dehydrogenase (LDH) levels were
318 monitored over time. The horizontal axis represents the days after admission. Hb and Cre are
319 shown on the left y-axis, and LDH is shown on the right y-axis. A marked decrease in Hb and an
320 increase in LDH were observed around day 17, which was consistent with delayed hemolysis.

Figures

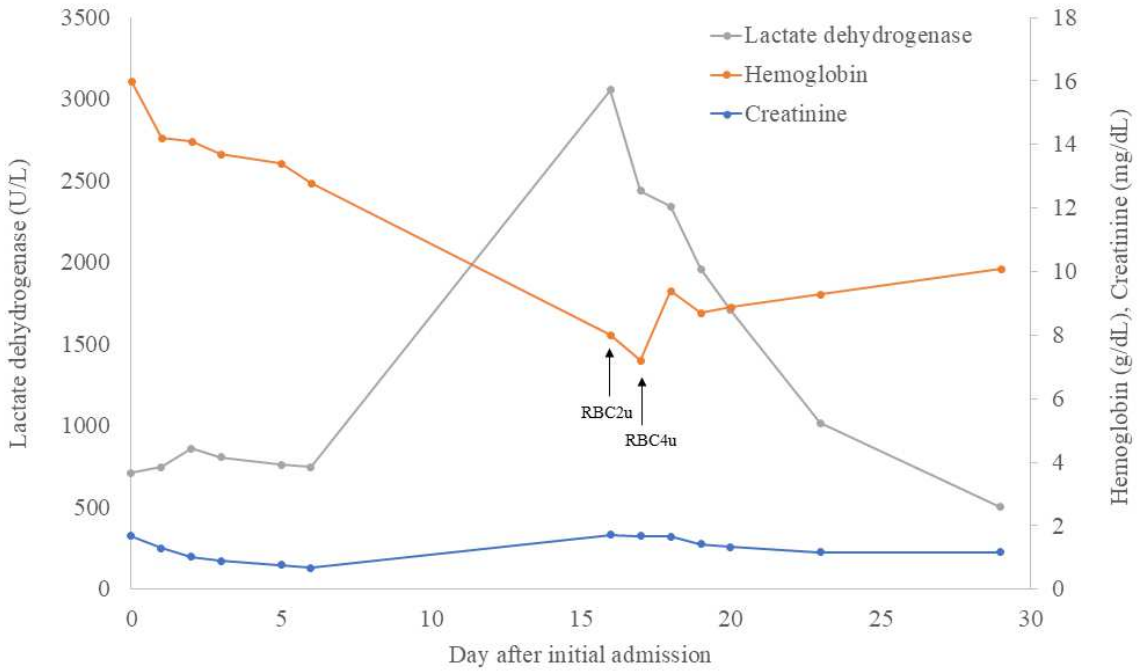


Figure 2

Temporal changes in laboratory parameters from the initial admission

The patient's hemoglobin (Hb), creatinine (Cre), and lactate dehydrogenase (LDH) levels were monitored over time. The horizontal axis represents the days after admission. Hb and Cre are shown on the left y-axis, and LDH is shown on the right y-axis. A marked decrease in Hb and an increase in LDH were observed around day 17, which was consistent with delayed hemolysis.

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