Severe unresolving Plasmodium falciparum malaria following artemisinin combination therapy: Emergence of drug resistance in Saudi Arabia

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Abstract

A 5-year-old female child presented with fever of 1-week duration after visiting a malaria endemic zone without antimalarial prophylaxis. The patient presented with respiratory distress, decreased level of consciousness and high-grade fever. An elevated parasitaemia reaching 800,000/µl was observed. Antimalarial therapy was initiated with artesunate being administered intravenous (IV) along with IV clindamycin. Contrary to the expectations, there was no resolution of fever. Following a week of unresolved fever, the drug therapy was revised and altered to IV quinine dihydrochloride and IV clindamycin. Emergence of non-responsiveness to artesunate in Saudi Arabia is an alarming sign and requires revision of management protocols.

Key words: Artesunate, malaria, resistance

Introduction

A region of the world, usually acknowledged for its vast arid environment, would probably be a less likely place of interest for researchers investigating a disease such as malaria. Contrary to expectations, we wish to document an intriguing case study that not only chronicles the presence of such a disease in the bordering regions of Saudi Arabia but also archives the challenges encountered in the line of its treatment.

Case Report

A 5-year old female child was admitted to Aseer Central Hospital (ACH) located in the south-western region of Saudi Arabia, presented with fever for 1 week after visiting an area known to have cases of malaria (Al Raboobah district, bordering Yemen). The child had not received antimalarial prophylaxis before her travel to that area.

On admission, she was pale, jaundiced, in respiratory distress with decreased level of consciousness and hence required Paediatric Intensive Care Unit care. She was febrile

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with temperature of 39°C, respiratory rate 34/min, pulse 130/min, blood pressure 105/60 mmHg with saturation of oxygen at 69% in room air. On examination, she had significant hepatosplenomegaly.

As we are located in an area endemic for malaria, and based on the clinical suspicion of malaria, thin and thick blood smear examinations for malarial parasite were undertaken which showed ring forms of *Plasmodium falciparum* with a parasite count of 800,000/µL of blood [Figure 1] with a haemoglobin level of 6.6 g/dl.

Complete blood count showed white blood cell count 12,600/mm³ and platelet count 57,000/mm³. Other determined laboratory parameters were prothrombin time 23 s, activated partial thromboplastin time 59 s, international normalised ratio 3.2, blood glucose 23 mg/dl, serum creatinine 0.8 mg/dl, serum urea 64 mg/dl, serum transaminases SGOT 1731 IU/L, SGPT 186 IU/L, bilirubin (total) 18 mg/dl, bilirubin (direct) 10 mg/dl, serum albumin 2 g/dl. Venous blood gas measurements: pH = 7.2, PaCO₂ 24.9 kPa, HCO₃⁻ 17 mEq/L. Computed tomography of the abdomen showed enlargement of the spleen, diffuse hypodensity with multiple internal septations, depicting a picture of total splenic infarction [Figure 2].

The patient was managed as a case of severe malaria, and intravenous (IV) artesunate therapy was initiated (at specified dosage of 2.4 mg/kg IV on admission [time = 0], 1.2 mg/kg at 12 h and subsequently 1.2 mg/kg IV once daily) plus IV clindamycin (loading dosage 10 mg/kg IV followed by 15 mg/kg/day IV as divided doses every 8 h), following the Saudi national protocol and guidelines for treating severe malaria, in addition to providing supportive care that included intubation and inotropic support.

However, despite the administered antimalarial therapy for 7 days, the fever did not subside and the general condition of the patient did not improve. The parasite count continued to be high on day 7 at 42,105/µL [Figure 3]. A blood parasite count curve determined that the count

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**Figure 1:** Microscopic examination of thick blood smear on 14th May 2013 (day 1) showed predominantly trophozoites (ring stages; inset black arrows) of *Plasmodium falciparum*. Parasitic count 800,000/µL of blood (Giemsa stain [5%]; ×100)

**Figure 2:** Computed tomography of the abdomen showed enlargement of the spleen, diffuse hypodensity with multiple internal septations (inset black arrow), suggestive of splenic infarction

**Figure 3:** Microscopic examination of thick blood smear on 20th May 2013 (day 7) showed trophozoites (rings; inset black arrow) and gametocyte stages of *Plasmodium falciparum*. Parasitic count 42,105/µL of blood (Giemsa stain [5%]; ×100)

**Figure 4:** Day-wise decline in *Plasmodium falciparum* count/µL of blood. Quinine therapy was initiated on day 8 of hospitalisation
although had declined over a period of 7 days, complete remittance was not achieved [Figure 4]. Blood, urine and cerebrospinal fluid cultures were negative for bacterial pathogens.

On day 8 after admission, the drug therapy was revised to replace IV artesunate with IV quinine dihydrochloride (dosage of 20 mg/kg loading dose in 5% dextrose/4 h, followed by 10 mg/kg over 4 h/8 h) in addition to clindamycin, following which the patient started showing improvement clinically in terms of fever subsidence and recovery from multi-organ failure as well as dramatic drop in parasite count over the following days [Table 1]. She was afebrile by day 8 after initiation of IV quinine therapy.

On improvement of general condition and tolerance of oral intake, drugs (quinine and clindamycin) were administered orally for 10 days. Follow-up of blood films showed complete absence of parasites and the patient was discharged subsequently [Figure 5].

Table 1: Summary of clinical, laboratory findings and therapeutic interventions

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>Clinical information</th>
<th>Parasite count/µL blood</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14th May 2013</td>
<td>Fever, jaundice, pallor, drowsiness, respiratory distress, hepatomegaly, thrombocytopenia, anaemia, metabolic acidosis, renal impairment, liver function derangement, DIC</td>
<td>800,000</td>
<td>IV artesunate, IV clindamycin</td>
</tr>
<tr>
<td>2</td>
<td>15th May 2013</td>
<td>Febrile, intubated, in critical condition with multi-organ failure</td>
<td>65,901</td>
<td>IV artesunate, IV clindamycin</td>
</tr>
<tr>
<td>4</td>
<td>17th May 2013</td>
<td>Still febrile, still in critical condition with multi-organ failure, gangrenous tip of finger and toes</td>
<td>60,000</td>
<td>IV artesunate, IV clindamycin peritoneal dialysis, antibiotics</td>
</tr>
<tr>
<td>6</td>
<td>19th May 2013</td>
<td>Still febrile, still in critical condition with multi-organ failure, gangrenous tip of finger and toes, seizure</td>
<td>80000</td>
<td>IV artesunate, IV clindamycin, Keppra (Levetiracetam)</td>
</tr>
<tr>
<td>8</td>
<td>21st May 2013</td>
<td>Still febrile, still in critical condition with multi-organ failure, gangrenous tip of finger and toes, spontaneous partial splenic rupture, bacterial sepsis and meningitis ruled out</td>
<td>40,000</td>
<td>IV quinine, IV clindamycin</td>
</tr>
<tr>
<td>9</td>
<td>22nd May 2013</td>
<td>Still febrile, still in critical condition with multi-organ failure, gangrenous tip of finger and toes</td>
<td>32,250</td>
<td>IV quinine, IV clindamycin</td>
</tr>
<tr>
<td>10</td>
<td>23rd May 2013</td>
<td>Still febrile, still in critical condition with multi-organ failure, gangrenous tip of finger and toes</td>
<td>44,943</td>
<td>IV quinine, IV clindamycin</td>
</tr>
<tr>
<td>22</td>
<td>5th June 2013</td>
<td>Asymptomatic</td>
<td>256</td>
<td>IV quinine, IV clindamycin</td>
</tr>
<tr>
<td>23</td>
<td>6th June 2013</td>
<td>Asymptomatic</td>
<td>160</td>
<td>IV quinine, IV clindamycin</td>
</tr>
<tr>
<td>25</td>
<td>7th June 2013</td>
<td>Asymptomatic</td>
<td>96</td>
<td>IV quinine, IV clindamycin</td>
</tr>
<tr>
<td>26</td>
<td>8th June 2013</td>
<td>Asymptomatic</td>
<td>224</td>
<td>IV quinine, IV clindamycin</td>
</tr>
<tr>
<td>27</td>
<td>9th June 2013</td>
<td>Asymptomatic</td>
<td>160</td>
<td>IV quinine, IV clindamycin</td>
</tr>
<tr>
<td>28</td>
<td>10th June 2013</td>
<td>Asymptomatic</td>
<td>96</td>
<td>IV quinine, IV clindamycin</td>
</tr>
<tr>
<td>31</td>
<td>12th June 2013</td>
<td>Discharged from hospital</td>
<td>96</td>
<td>IV quinine, IV clindamycin</td>
</tr>
<tr>
<td>32</td>
<td>13th June 2013</td>
<td>Home</td>
<td>60</td>
<td>IV quinine, IV clindamycin</td>
</tr>
</tbody>
</table>

IV: Intravenous infusion, PO: Per oral, DIC: Disseminated intravascular coagulation
Discussion

In Saudi Arabia, *P. falciparum* accounts for more than 85% of malaria infections, with the majority of locally acquired cases in the south-west regions of Jazan and neighbouring Asser where ACH is located. The annual incidence rate varies widely depending on population movement and early arrival of heavy rainfall, with the peak of transmission occurring during autumn and early winter.[1]

Severe malaria is generally defined as acute malaria with high levels of parasitaemia (>5 per cent) and/or major signs of organ dysfunction,[2-4] altered consciousness with or without convulsions, deep breathing, respiratory distress (acidotic breathing, costal indrawing, use of accessory muscles, nasal alar flaring), metabolic acidosis (plasma bicarbonate level 15 mmol/l or whole blood lactate >5 mmol/l), circulatory collapse, pulmonary oedema or acute respiratory distress syndrome, renal failure, haemoglobinuria (“black water fever”), clinical jaundice, disseminated intravascular coagulation, severe anaemia and hypoglycaemia.

In areas where malaria is endemic, young children (aged 2–5 years) are at a high risk of developing severe malaria, as are pregnant women. Travellers to regions where malaria is endemic, who have no previous exposure to malarial parasites, are at a high risk of progression to severe disease if infected with *P. falciparum.[5,6] Several of the above-mentioned factors inclusive of age, previous lack of exposure, lack of chemo-prophylaxis, predisposed the patient under study for acquiring severe parasitic infection.

Immune deficiency or splenic dysfunction, whether congenital or acquired, frequently contributes to severe malaria. Considering this, the immune system function in our patient was assessed but was unrevealing. Partial splenic rupture and multiple splenic infarcts observed on imaging may have contributed significantly to a severe presentation by producing a compromised functionality of spleen.

There are two major classes of drugs available for parenteral treatment of severe malaria: Cinchona alkaloids (quinine and quinidine) and artemisinin derivatives (artesunate, artemether and artemotil).[2] Artemisinin derivatives are known to clear parasitaemia at a more rapid rate than quinine and are known to serve as blood schizonticidals as well as gametocidals.[7-9] Artemisinin derivatives include artesunate, artemether and artemotil. Artesunate remains to be the preferred artemisinin for treating severe malaria cases as clinical experience with artemether and artemotil drugs is rather limited.

Review of literature comparing quinine and artemisinins suggests that IV artesunate is preferable for treatment of adults and children with severe falciparum malaria (in areas where IV artesunate of reliable quality is readily available).[2,7,8] If IV artesunate is not an option, IV quinine (or quinidine in the United States) remains to be the drug of choice. This approach is based on studies suggesting that artesunate is superior to IV quinine for treatment of adults in Asia and children in Africa with severe malaria.[9]

According to the national drug policy for control of malaria in the Kingdom of Saudi Arabia, treatment of a complicated severe malaria patient such as in the above-mentioned case report should include in addition to supportive care, IV artesunate in combination with either clindamycin or doxycycline according to the age of the child.[10]

Emergence of artemisinin resistance, the core component of the combination therapy, has been identified in Southeast Asian countries such as Cambodia, Myanmar, Thailand and Viet Nam but not from the Middle Eastern countries. The presence of parasite after day 3 of artemisinin combination therapy (ACT) or failure to clear parasitaemia by day 8 was an alarming and unusual sign which strongly suggested a case of emerging drug resistance in the Kingdom. Urgent surveillance protocols are needed in the region to identify and eliminate resistant strains of the parasite and to ensure that ACTs remain effective.[10] To rule out any compromise on the quality of drugs, expiry date values and other manufacturing anomalies, the IV drugs administered were examined by the treating physicians but were found to be well within normal limits.

Conclusion

ACT is the recommended treatment for *P. falciparum* due to its rapid clearance of parasite and excellent safety profile. Emergence of non-responsiveness to artesunate in Saudi Arabia is an alarming sign although the same has been reported elsewhere from south-eastern countries in Asia earlier. It requires careful circumspection and planning with vigilant revision of management protocols to counter the
life-threatening infections, necessitating use of alternative drugs such as quinine.

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Conflicts of interest

There are no conflicts of interest.

References