CASE REPORT

NEONATAL MALARIA PRESENTING AS NEONATAL SEPSIS: A CASE REPORT

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Abstract

Neonatal malaria may be overlooked likely due to its non-specific features and low prevalence in Malaysia. In this case report, we detail a case of neonatal malaria in an 18-day old baby girl of Myanmar origin who presented with 6 days of intermittent fever but was otherwise well. Initially, she was treated as neonatal sepsis. She then developed thrombocytopaenia and severe anaemia with persistent spikes of temperature. This prompted a series of investigations and multiple changes of antibiotics. The diagnosis of neonatal malaria surfaced when her peripheral blood film incidentally revealed the presence of *Plasmodium vivax* parasites. Peripheral blood smears are simple and inexpensive. Therefore practising especially in endemic areas for malaria, we need to consider this diagnosis when dealing with neonatal sepsis that does not respond to standard treatment.

Keywords: Congenital Malaria, Neonatal Malaria, Malaria, Neonatal

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Introduction

Based on the latest statistic by World Health Organization (WHO), 198 million cases of malaria were reported globally in 2013 with 58400 deaths reported. The disease burden is heaviest in the WHO African region in which it accounted for approximately 90% of all malarial deaths [1]. Neonatal malaria is uncommon with reported incidences varying between 0.3 to 33.0% in both endemic and non-endemic countries [2]. Most of the cases reported were from the African region. In Malaysia this entity is rarely reported.

Case Report

An 18-day old Myanmar baby girl initially presented to the local clinic with intermittent fever since day 12 of life with a documented temperature of 37.9°C. She was then referred to the neonatal unit of Hospital Tengku Ampuan Rahimah, Klang (HTAR) for presumed sepsis. She is the second child of a 30-year old mother, born term at 39...
weeks gestation via normal vaginal delivery in Hospital Temenggung Seri Maharaja Tun Ibrahim, Kulai, Johor. Her birth weight was 2.9 kilogram. Birth and postnatal history were uneventful. Mother’s antenatal care was unremarkable and she denied being unwell at any time throughout the pregnancy or perinatal period. Both father and mother are Rohingya people, a group of indigenous Muslims in northern Rakhine, Myanmar who migrated to Malaysia, 6 and 3 years ago. She was residing with both parents in an oil palm estate in Skudai, Johor since birth till day 17 of life before coming to Klang to visit their relatives. Apart from the fever, baby was well and had no feeding difficulties. She passed urine and motion normally. There were no symptoms or signs that suggest respiratory or urinary tract infections. She did not have any history of ill contact. On admission she was afebrile (axillary temperature was 36.7°C) with a heart rate of 150 beats/minute and respiratory rate of 38 breaths/minute. She was pink and non-icteric. Examinations of the cardiovascular and respiratory systems were unremarkable. Abdomen was soft and there was no hepatosplenomegaly. Her initial full blood count (FBC) showed haemoglobin (Hb) 14.1 g/dL, white blood cell (WBC) 18.5 x 10^9/L, haematocrit (HCT) 42.6% and platelet (PLT) 298 x 10^9/L. Her C-reactive protein (CRP) was 11.36 mg/L. She was first started on intravenous (IV) c-penicillin and gentamicin. Her temperaturesettled initially but spiked again after 48 hours, which prompted us to change IV gentamicin to IV cefotaxime. Despite changing antibiotics, she had another spike of temperature on day 7 of admission associated with rising CRP (136.05 mg/L), anaemia and thrombocytopenia (FBC: WBC 8.29 x 10^9/L, Hb 9.0 g/dL, PLT 93 x 10^9/L). Antibiotic was changed to meningitic dose of IV meropenem. Initial urine culture grew a sensitive strain of Klebsiella species (repeated subsequently was negative).

In view of thrombocytopenia and the current outbreak of dengue in Klang Valley, dengue serology was also sent. However both dengue non-structural protein-1 (NS-1) antigen and dengue immunoglobulin M (IgM) tests were negative. Her blood sample was also sent for peripheral blood film to investigate the anaemia and thrombocytopenia.

On day 11 of admission, we noted her fever followed a cyclical pattern with spikes at every 48 hours (Figure 1) and her peripheral blood film incidentally showed malaria parasites. We proceeded with ‘Blood Film for Malaria Parasites’ (BFMP) and it revealed Plasmodium vivax (P. vivax) (Figure 2) (11461 asexual and 115 sexual per-ml of blood). The diagnosis of P. vivax malaria was further confirmed by nested polymerase chain reaction (PCR) done in the Institute for Medical Research Malaysia, (IMR). This test is highly sensitive and specific and the primer that this laboratory useds, does not share the same sequences with any other malarial parasites [3]. The test has a sensitivity of 99.55% and specificity of 80.06 % (with 95% confidence interval). The case was discussed with a Paediatric Infectious Disease consultant and she was started on IV artesunate stat, then 12 hours and every 24 hours thereafter for 6 days. She was also started on oral primaquine base daily for 2 weeks. Mother’s BFMP and PCR test were negative for any malarial parasites.
Figure 1. Temperature trend followed a tertian fever pattern with spikes at every 48 hours
Figure 2. Patient’s blood smear showing multiple schizonts with close up of 4 schizonts (arrows) containing numerous merozoites

Following the initiation of anti-malarial medications, her temperature settled and her platelet count improved (Table 1). However, during the course of disease her haemoglobin level decreased to 6.3g/dL on day 14 of admission, in which packed cell transfusion was required. BFMP was repeated on 3 consecutive days after completing 7 days of IV artesunate and all 3 were negative for malaria parasites. She was subsequently discharged healthy.

Table 1. Serial full blood count and CRP level for the infant. Antimalarial started on day 11 of admission

<table>
<thead>
<tr>
<th>Days since admission</th>
<th>WBC (x 10^9/L)</th>
<th>Hb (g/dL)</th>
<th>PLT (x 10^9/L)</th>
<th>CRP (&lt; 0.5 mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>18.5</td>
<td>14.1</td>
<td>298</td>
<td>11.86</td>
</tr>
<tr>
<td>Day 5</td>
<td>11.64</td>
<td>11.2</td>
<td>82</td>
<td>106.88</td>
</tr>
</tbody>
</table>

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Discussion

Neonatal malaria is described as malaria occurring within the first 28 days of life [4]. It can be acquired via blood transfusion, a bite of an infected *Anopheles* mosquito or transmitted congenitally. Congenitally acquired infection or congenital malaria is defined as the presence of asexual stages of the malarial parasites in the cord blood at the time of delivery or in the peripheral smear of the infant in the first 7 days of life [4]. One literature study has reported that the onset of symptoms occurred between 8 to 30 days [5]. In congenital malaria the parasites may be transmitted through placental passage or when the baby passes through the birth canal during labour [5,3]. The prevalence of congenital malaria varies between 0 to 23% in endemic areas [6-9]. Meanwhile the prevalence of neonatal malaria is just below 25% in a study done in Nigeria [10]. Even among those born to pregnant women with blood smears positive for malaria parasites, the incidence of congenital malaria is very low [11]. Low prevalence of malaria is postulated to be the result of protection from passive transfer of maternal antibodies and also the presence of fetal haemoglobin [4]. In addition, spontaneous clearance has also been observed in about 62% of neonates with patent parasitaemia (i.e. parasites visible on microscopy) in a multicentred study done in Nigeria [12].

Features of neonatal malaria especially *P. vivax* infection are highly non-specific. The most common presenting symptoms of neonatal malaria is fever with studies showing it as the sole presenting feature in about 77% of the cases [10, 13]. Other common features are anaemia, jaundice, pallor and hepatosplenomegaly [5]. Meanwhile features such as respiratory difficulty, convulsion, bleeding (disseminated intravascular coagulopathy), diarrhoea, vomiting and cyanosis are akin to diagnosis of severe malaria in which, most of the time are caused by *P. falciparum* [13]. To date, there are no studies reporting differences in clinical manifestations between congenital malaria and postnatally acquired neonatal malaria (either via *Anopheles* mosquitos’ bites or blood transfusion).

Owing to non-specificity of symptoms and low prevalence rate, neonatal malaria may be overlooked in low endemic areas such as Malaysia. Therefore, delay in diagnosis is not uncommon. Like most cases reported, our case was initially treated as neonatal sepsis and the patient was started on intravenous antibiotics [4, 14, 15]. The only clue that pointed towards a diagnosis of malaria is the cyclical fever pattern (Figure 1). Her fever followed a tertian fever pattern that is common in *P. vivax* infection [16]. Despite not being treated with antimalarials during the first 10 days of admission, she did not show other symptoms and signs suggestive of malaria (e.g. jaundice, feeding
difficulty and hepatosplenomegaly). Although her initial urine culture grew a sensitive strain *Klebsiella* species, it is most likely due to contamination since her urinalysis was normal and her fever did not respond despite treatment with appropriate antibiotics. In addition, a concurrent urinary tract infection would have caused a constant fever but her fever followed a cyclical pattern since admission.

As an aid for further discussion, the life cycle of *P. vivax* is described according to Mendis et al [17]: Two hosts are involved; human and female *Anopheles* mosquito. During a blood meal, a malaria infected female *Anopheles* inoculates sporozoites into the human host. These sporozoites invade the hepatocytes and then either enter a dormant hypnozoite phase or mature into schizonts. These schizonts rupture and release merozoites into the blood stream. This initial replication in the liver is known as exo-erythrocytic phase. Merozoites then invade red blood cells and evolve into trophozoites. At this stage trophozoites undergo asexual multiplication and form schizonts which will perpetuate this erythrocytic phase. Some trophozoites differentiate into gametocytes that would be taken up by a female *Anopheles* mosquito when it bites the infected human host. Inside the female *Anopheles* mosquito, these gametocytes mature into either microgametes (male) or macrogametes (female) and undergo sexual reproduction which eventually form sporozoites. These sporozoites reside in the salivary gland while waiting to inoculate another human host. The usual incubation period of *P. vivax* is between 12 to 18 days but can take up to months or years because of the presence of latent hypnozoites in the liver [18]. When *P. vivax* is transmitted via blood (eg. vertical transmission, or blood transfusion) rather than by mosquito bites, no latent hypnozoite phase occurs, as it is the sporozoites that form hypnozoites in infected hepatocytes.
In our present case, it is difficult to accurately identify the mode of transmission because, as there was no peripheral blood smear in the first week of life. The fact that she presented with fever as early as day 12 of life, suggested vertical transmission. We postulated that her mother most likely had an asymptomatic infection in the form of latent hypnozoite phase. These hypnozoites then reactivated into trophozoites that crossed the placenta and inoculated the fetus. This reactivation may have been of low parasitaemia load with mild illness that was easily dismissed. This transient parasitaemia was then cleared by the mother’s own immune system thus the BFMP and PCR test for the mother did not detect any malarial parasite. With this, it seemed likely that the baby had acquired the infection congenitally. However we were unable to completely rule out that the baby might have acquired the infection via the bite of a malarial-infected Anopheles.

The World Health Organisation (WHO) recommends chloroquine as the first line treatment to clear the erythrocytic phase of *P. vivax* and 14 days of primaquine to clear the hypnozoites of the exoerythrocytic phase [20]. Although WHO outlines treatment recommendations for malaria in children and infants less than 5 kilogram, there are
none specific for neonatal or congenital malaria. The “Management Guidelines of Malaria in Malaysia 2nd edition (2013)” which was based on the WHO “Guidelines for The Treatment of Malaria 2nd edition” (2010) recommends chloroquine as the first line treatment for congenital malaria caused by *P. vivax* [2]. Chloroquine is to be given at an initial dose of 10 mg base/kg body weight followed by 5 mg/kg at 6 hours, 24 hours and 48 hours [2]. Primaquine is not required in congenital malaria because of the absence of hypnozoites [2]. In contrast, the latest WHO guidelines published in 2015 recommends chloroquine at an initial dose of 10 mg base/kg dose followed by 10 mg/kg on the second day and 5 mg/kg on the third day [20]. Reason for change in dosing regime was not specified.

However, in regions where there is chloroquine resistance *P. vivax* malaria, an artemisinin base compound is recommended instead of chloroquine [20, 21]. In our case, IV artemunate (an artemisinin base compound) and oral primaquine was used. IV artemunate was chosen over oral chloroquine because artemisinin compounds demonstrate superior defervescence and clearance of parasitaemia [22]. In addition chloroquine resistance cases have been reported in 9 countries in which two of them are Myanmar and Malaysia [21]. Primaquine was added because there was still a possibility that the infection was transmitted via malaria-infected *Anopheles* mosquito. The dose for IV artemunate is 2.4mg/kg stat, then 12 hours and every 24 hours thereafter for 6 days. As for oral primaquine, the dose is 0.5mg base/kg once daily for 14 days. The recommended dosing regimes for IV artemunate and oral primaquine are the same for both the Malaysian and WHO guidelines.

**Conclusion**

Neonatal malaria is an uncommon disease in Malaysia. It usually presents with non-specific features such as fever and poor feeding thus leading the attending clinician to misdiagnose it as neonatal sepsis and start antibiotic at the initial point of contact. Therefore, awareness and high index of suspicion among doctors working closely with neonates is particularly important in cases of unresolved fever to avoid delay in accurate diagnosis and treatment.

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**References**


