Case Report: Malaria Transmission Under an Unusual Circumstance Causing Death in Two Siblings

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Abstract. Two school-going siblings from a family residing in a presumed malaria non-endemic locality ~90 km from Mangalore city in southwestern India contracted *Plasmodium falciparum* infection. In both cases, misunderstanding of initial clinical symptoms as due to viral hepatitis resulted in progression to severe malaria before malaria treatment was initiated. Despite treatment at a tertiary hospital, the children died of cerebral malaria and multi-organ dysfunction. Active case detection in the affected locality suggested that the infection was transmitted from infected individuals who worked in nearby malaria-endemic areas and periodically visited their families. A lesson from this study is that lethal falciparum malaria can be transmitted in regions of India, believed to be non-endemic for the disease, resulting in fatal outcomes if diagnosis is missed or delayed. Implementation of effective surveillance and control measures as well as preparedness for malaria detection and diagnosis are necessary in areas that are potentially disposed to malaria transmission even though they are presumed to be non-endemic.

Malaria is a substantial public health problem in most parts of the tropics and nearly half of the world population is at risk of contracting the disease.^{1–3} Five parasite species of the genus *Plasmodium* can infect humans, but a vast majority of the infections are caused by *Plasmodium falciparum* and *Plasmodium vivax*.⁴ Although *P. falciparum* is the predominant species in Africa, both *P. vivax* and *P. falciparum* are prevalent in other parts of the world, including the Indian subcontinent.^{1–3} *Plasmodium falciparum* often causes severe malaria and organ-related pathologies, causing deaths, particularly in young children and nonimmune adults, whereas *P. vivax* causes relatively less complications. However, in recent years, complicated and fatal cases of *P. vivax* infection have been increasingly reported.^{5–8}

The locality of the malaria cases reported herein is a remote village called Shishila, situated in a forest area (12°54'2"N75°30'15"E) at ~90 km east of Mangalore city in south India. Mangalore is a coastal city along the Arabian Seashore in Dakshina Kannada district of Karnataka State, India. The city and several towns in the area are endemic for malaria; however, the Shishila village had not recorded any malaria cases previously. The medical records of malaria clinical cases available at the Dakshina Kannada District Health Office indicate the prevalence of *P. vivax* at ~90% and of *P. falciparum* at ~10% in and around Mangalore city. Much of the malaria spreading in the city and its surrounding may be linked to building constructions, which provide breeding grounds for the prevailing malaria vector *Anopheles stephensi*,⁹ and also to infected construction workers coming from northeastern parts of India, where malaria is highly endemic. Recently, the city has been under a rapid expansion phase with many ongoing building and road infrastructure constructions, providing many employment opportunities in

hotels, constructions, and other industries. People from nearby and remote villages as far as ~100 km come to work and reside in Mangalore city and in other malaria-endemic towns, and visit their families at villages weekly or once or twice a month. These people are at high risk of contracting malaria at Mangalore and become potential infection carriers. In addition, people from villages travel to endemic towns and cities for shopping and worshipping at temples and thus, they are also at risk of contracting malaria. Therefore, studies directed at understanding malaria infection dynamics under these evolving changes in demographics among endemic localities and presumed non-endemic areas are needed in implementing appropriate control measures and diagnosis.

Here, we report two cases of *P. falciparum* infections in school-going siblings, which occurred in an unusual transmitting circumstance, either on the same day or within 1–2 days apart. The two siblings, a girl aged 11 years (Case 1) and her brother aged 9 years (Case 2), were from a socioeconomically disadvantaged family, residing in the Shishila village.

During initial periods of infection, Case 1 exhibited fever, headache, and malaise. The family suspected that the symptoms were due to exhaustion (previous day the child had gone for a school trip to Mangalore) and as such treated with paracetamol (acetaminophen) to relieve fever and pain. However, fever continued to rise and the child was taken to the nearby primary health center (PHC) with a complaint of abdominal pain and vomiting. The PHC was not equipped for malaria testing as the area was considered to be malaria free and hence, the case was not tested for malaria. Urine analysis revealed bilirubinuria, and the PHC suspected the case to be a viral hepatitis and/or leptospirosis infection. Therefore, the members of her household gave herbal remedy for jaundice. The child developed severe clinical complications by 6th day of the illness, and was admitted to the tertiary hospital, Wenlock District Government Hospital, Mangalore.

At the time of admission to the hospital, Case 1 had fever history of 6 days, abdominal pain and vomiting, pallor, repeated episodes of involuntary movements, and altered sensorium. Physical examination revealed that the girl had fever of 104°F, 7/15 on Glasgow Coma Scale (GCS), tonic

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posturing with uprolling of eye balls, hyperventilation, splenomegaly, and severe jaundice. Peripheral blood smear examination showed high levels of the ring-stage and noticeable levels of the trophozoite-stage *P. falciparum*. IgM-based enzyme-linked immunosorbent assay ruled out dengue and leptospirosis infections. Hematological and serological clinical tests revealed severe anemia with low platelet counts and high levels of urea, serum bilirubin, and creatinine (Table 1). Thus, the patient was diagnosed to have several manifestations of severe malaria, including cerebral malaria.

Case 2 had a similar initial history as that of Case 1 and was also suspected of having viral hepatitis and/or leptospirosis infection by the PHC, and the family gave herbal medicine for jaundice. This patient also developed severe clinical complications and was admitted to Wenlock District Government Hospital along with Case 1. At the time of admission to the hospital, Case 2 had fever for 6 days, pallor, acute respiratory distress syndrome, and reddish discoloration of urine. Physical examination revealed fever, semi consciousness (Glasgow Coma Scale 10/15), hyperventilation, prostration, and jaundice. Peripheral blood smears showed, as in Case 1, the presence of high density of the ring-stage *P. falciparum*. Dengue and leptospirosis infections were absent. Hematological and serological clinical tests revealed severe anemia with low platelet counts, high levels of urea, serum bilirubin, and creatinine, and liver enzymes (Table 1).

At the hospital, both the patients were immediately given intravenous artesunate, valproate, platelet and blood transfusion, and other supportive therapy including mechanical ventilation. Despite the treatment and the supportive care given, both patients died due to multiorgan dysfunction; the girl died 7 hours post-admission and the boy after 3 days.

According to World Health Organization (WHO) definition of severe malaria,¹⁰ the two cases reported here can be classified as having cerebral malaria and multiorgan complications. The children shared a common bedroom and stayed together most times before and after school time. The other members of the family, who stayed in other rooms, were not infected. The malaria symptoms in both children started within a day apart. Furthermore, progression to severe malaria and worsening of the conditions in both cases occurred at more or less similar time points, although they died 3 days apart. Thus, it appears that both children were infected either on the same day or 1–2 days apart by a vector carrying *P. falciparum*.

In infected people, the trophozoite- and schizont-stage *P. falciparum* is known to sequester in microvascular capillaries of brain and other organs.¹¹ In nonimmune people, these forms of *P. falciparum* do not usually circulate because of their adherence to vascular endothelia through adhesive proteins expressed on the surface of infected erythrocytes, whereas the ring-stage parasites, which are still non-adherent, circulate. Thus, the presence of very high levels of ring-stage *P. falciparum* in the patients suggested that in both subjects, parasites were heavily sequestered in the microvascular capillaries of the brain and possibly in other organs as well.

Since the locality where the patients and their family lived had remained malaria free earlier, it was puzzling as to how the infection occurred. Also, the siblings had not traveled to endemic areas before symptoms appeared, ruling out the possibility that they got infected in an endemic area. To determine how the siblings contracted infection, soon after deaths, peripheral blood smear examination and bivalent rapid diagnostic test for *P. vivax* and *P. falciparum* detection kits were conducted on the household members, the people residing in the radius of up to 2 km from the house of the family and those in and around the areas where the children attended school. Altogether, 253 adults and 144 children in the area were screened. Tests were also performed a month after on 116 adults and 166 children. A group of 14 quarry workers, belonging to a small town about 36 km from the affected village, but had been residing at the affected locality for 2 months on work were also tested. In all these screens, none tested positive for either *P. falciparum* or *P. vivax* by blood smear examination and rapid diagnostic test. Also, none in the locality had recent history of fever or treatment of malaria. These results suggested the possibility of infection transmitted from infected people coming from endemic areas. Accordingly, we identified and tested 10 village natives who had been working in Mangalore city and had been visiting the family in the village on alternative weeks. Of these, three individuals had history of malaria infection; one individual had malaria infection 6 months prior to the infection of the siblings, another had 1 month before, and the third individual had ongoing infection during the siblings' malaria illness; all three returned to the village during their infection and stayed for ~10 days for recuperation. Thus, either ongoing infection and/or gametocytemia in people who returned from endemic areas after working or visiting might have been the source of infection for the children.

Furthermore, entomologists from the National Institute of Malaria Research, Bangalore, performed a detailed entomological study in the affected village. Adult mosquitoes were collected from four human dwellings and four cattle sheds between 6:00 and 8:00 AM by oral aspirator. Pyrethrum spray collections were also done from one human dwelling and a cattle shed in each surrounding village. The mosquito species were identified at the National Institute of Malaria Research, Bangalore.¹² Larval sampling was also performed at the breeding habitats (streams and water wells) at the locality using the standard WHO method.¹³ The collected larvae from each breeding site were separately reared at the laboratory until adult emergence and species identified according to the published procedure.¹² Among several localities from which samples were collected, one stream and four water wells were the main breeding habitats. *Anopheles culicifacies* and *Anopheles jeyporiensis* were found

TABLE 1
Hematological clinical profiles of the cases

Clinical parameters	Case 1	Case 2	Normal range
Hemoglobin level (g/dL)	6.9	5.2	13–18 (males); 11–15 (females)
Total leukocyte counts	16,900	15,900	150,000–400,000
Platelets (cells/mm ³)	3,000	8,000	150,000–400,000
Urea (mg/dL)	198	416	10–45
Creatinine (mg/dL)	1.7	5.0	0.4–1.4
Total bilirubin (mg/dL)	15.5	27.1	0.3–1.2
Direct bilirubin (mg/dL)	10.5	21.0	up to 0.2
Alanine transaminase (IU/L)	122	123	5–40
Aspartate transaminase (IU/L)	63	80	5–40
Alkaline phosphatase (IU/L)	249	236	up to 462
Total protein (g/dL)	5.0	5.1	6.3–8.3
Albumin (g/dL)	2.7	2.6	3.5–5.5

to be the malaria vector species at the locality. The vectors were separated and per man-hour densities and per structure densities were calculated. Per man-hour densities of *An. culicifacies* and *An. jeyporiensis* were 2 and 8, respectively. Thus, the locality is potentially disposed to malaria transmission. *Anopheles jeyporiensis* is known to be a vector for malaria transmission and has been reported to be prevalent at markedly higher abundance during dry and relatively cooler months (October–April) in other parts of India, with climate and geography similar to the locality studied here.^{14–16} Further, the malaria cases reported here have occurred during the last week of December and the first of week January, correlating with season at which *An. jeyporiensis* prevalence reaches high levels. Hence, it is likely that *An. jeyporiensis* is a malaria transmittable vector in the locality.

In conclusion, the Mangalore city and several neighboring towns are endemic for malaria. In recent years, there has been exponential growth of urbanization in the region, providing numerous job opportunities in hotels and construction industries. Many people from non-endemic rural areas take up these jobs and frequently visit their families. Notably, when infected with malaria, these people usually go back to villages and stay there for 1–2 weeks for recuperation. Because of this situation and the prevalence of transmittable vectors in villages, there is likelihood of increased malaria transmission, leading to severe malaria complications and fatalities, as had happened in the two cases reported herein. Therefore, in the wake of these changing demographics, more thoughtful planning of surveillance, and control measures as well as implementation of diagnostic measures at PHC levels in rural areas are increasingly becoming a basic necessity. It is also equally important that healthcare personnel at PHCs are informed about malaria.

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