Human *Plasmodium Knowlesi* Infections in Klang Valley, Peninsula Malaysia: A Case Series

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SUMMARY

We report seven cases of naturally acquired human *Plasmodium knowlesi* infections which were admitted to our centre from July 2007 till June 2008. Diagnosis was confirmed by nested PCR. Cases of *P. knowlesi* infections, dubbed the fifth type of human malaria, have been reported in East Malaysia (Sabah and Sarawak) as well as in the state of Pahang in Peninsula Malaysia. These seven patients appear to be the first few reported cases of *P. knowlesi* infection in the Klang valley, Peninsula Malaysia. We then discuss the characteristics of human *P. knowlesi* infections, which include its natural hosts, responsible vectors, clinical presentation, and the treatment of such infections.

KEY WORDS:
Malaria, Monkey malaria, Plasmodium infection, Plasmodium knowlesi

INTRODUCTION

Plasmodium knowlesi has been described as the fifth human malaria parasite since Knowles and Das Gupta's[1] success in transmitting to humans this monkey malaria they had discovered in 1932. Cases of *P. knowlesi* infections have been dubbed as the fifth type of human malaria[2].

Previous reports of *P. knowlesi* infection were mainly in rural settings with the largest case series in East Malaysia [3,4]. However, this parasite has been gaining importance as a cause of malaria in suburban and urban areas, as shown in our report as well as in Singapore[5].

The diagnosis of *P. knowlesi* infection may be missed by blood film microscopy because the early blood stages of *P. knowlesi* appear similar to that of *P. falciparum*, while the mature stages and gametocytes morphologically resemble those of P. malariae [4].

P. knowlesi has a 24-hour asexual life cycle, the shortest of all known primate malarias, resulting in daily schizont rupture, hence the daily fever spikes and increased parasite load, which is unprecedented in human malaria. Therefore, rapid diagnosis and intensive treatment as appropriate for falciparum malaria should be instituted.

CASE SERIES

Seven cases of *P. knowlesi* infections were admitted to University Malaya Medical Centre from July 2007 till June 2008. All seven patients had a history of traveling into jungles or staying in areas with close proximity to jungles. These patients were initially misdiagnosed to have *P. malariae* or *P. falciparum* infections. High parasitaemia level was a common feature in several cases. Diagnosis of *P. knowlesi* infection was later confirmed by nested PCR.

Case One. A 17-year-old high school student with no prior medical illness presented on 27/7/07 with 11 days' history of fever, chills and rigors, associated with headache, myalgia, reduced oral intake and mild abdominal pain. He had attended a camping trip, including jungle-trekking and swimming in a nearby river four weeks prior to presentation. A friend was also recently admitted in a different hospital for malaria. He was treated with quinine and doxycycline since Day 1 of admission, and subsequently discharged well on Day 4.

Case Two. A 58-year-old Indonesian Chinese presented on 27/8/07 with seven days' history of fever, associated with chills and rigors. His last visit to his hometown in Kalimantan was in 2003. He is married to an East Malaysian and regularly visits his in-laws in Bario, Sarawak. He was given quinine and doxycycline for seven days, started from Day 1 of admission. His stay was however complicated by acute renal failure as well as upper GI bleed secondary to gastric and duodenal ulcers. He required a total of eight units packed cell transfusion during his hospital stay. Renal function improved gradually, no inotrope support was needed and he was discharged well on Day 15.

Case Three. A 54-year-old karaoke centre owner with underlying ischaemic heart disease, hypertension and hyperlipidaemia presented on 13/3/08 with nine days' history of fever, chills and rigors, associated with headache, myalgia and jaundice. He goes for hunting trips regularly in the forests of Pahang, the last trip being one month earlier. He was initially dehydrated and hypotensive (90/55 mmHg), which responded to fluid therapy. Quinine and doxycycline were started on Day 2 of admission. His hospital stay was also complicated by acute renal failure, fluid overload and persistent hypotension, requiring two days' inotrope support and ICU care. His condition improved gradually, renal function normalised and he was discharged on Day 7.

Case Four. A 22-year-old travel agency clerk with a history of anxiety disorder presented on 7/5/08 with five days' history of fever and chills associated with arthralgia, myalgia, reduced appetite, vomiting and headache. He had traveled into a jungle in Ampang four weeks prior to presentation. Quinine and doxycycline were started on Day 1 of admission,

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Table I: Summary of vital signs and laboratory investigations

Detail		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Duration of hospital stay (days)		4	15	7	6	9	6	7
Initial blood pressure (mmHg)		110/70	140/84	90/55	126/60	74/47	134/70	106/64
Pulse rate (per minute)		100	100	100	120	100	110	120
Temperature, oral (ºC)		37.0	37.1	36.6	37.0	36.9	40.2	37.9
Haemoglobin (g/dL)		14.1	14.9	12.0	15.8	13.7	12.4	10.7
WBC count (x10^3 cells/μL)	(N: 4-11)	5.5	9.4	6.1	4.5	8.0	2.9	6.1
Platelet count (x10^3 cells/μL)	(N: 150-400)	99	5	7	35	29	39	44
Serum urea (mmol/L)	(N: <6.4)	2.9	35.4	26.3	4.0	35.7	3.0	1.3
Serum creatinine (μmol/L)	(N: <132)	82	546	263	70	613	96	66
Total serum bilirubin (μmol/L)	(N: <17)	17	73	77	36	10	10	73
Serum albumin (g/L)	(N: 35-50)	30	23	25	36	23	25	24
Serum ALT (IU/L)	(N: 30-65)	39	85	92	197	96	54	50
Serum AST (IU/L)	(N: 15-37)	29	97	99	101	70	34	43
Initial misdiagnosis		*falciparum*	*falciparum*	*malariae*	*falciparum*	*malariae*	*malariae*	*malariae*
Parasite load		0.001%	4%	2.2%	0.2%	3.8%	0.1%	0.02%

Data of tests performed within 24 hours of presentation.
Laboratory reference values given in parentheses.

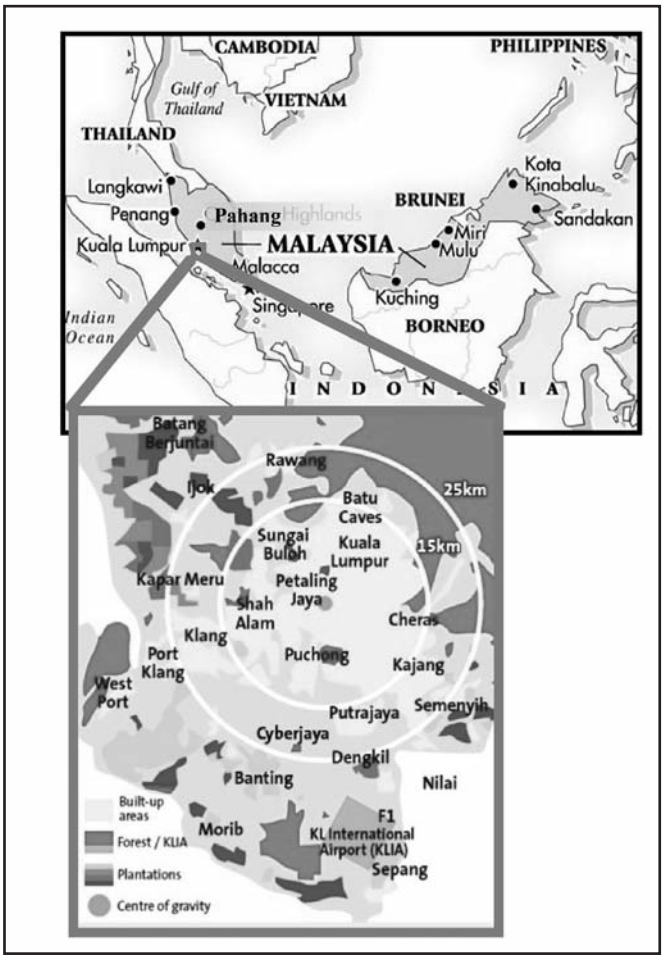

Fig. 1: Map of Malaysia, showing position of Klang Valley and Malaysian Borneo.

but was subsequently changed to chloroquine (150mg base, 10 tablets in total) on Day 3 of admission. He was discharged well on Day 6.

Case Five. A 55-year-old accountant with underlying Type 2 diabetes, hypertension, and hyperlipidaemia presented on 28/5/08 with eight days' history of fever, with hypotension (74/47 mmHg), thrombocytopaenia, hypoglycaemia, lactic acidosis, acute renal failure and acute hepatitis. He had gone jungle-trekking in several places recently, being in Thailand and Australia one month earlier and in Labuan, Borneo two weeks back. He required inotropic support, empirical antibiotics, and four days of assisted ventilation (BIPAP) in an ICU ward for one week. Quinine, Riamet (artemether+lumefantrine) and doxycycline were started on Day 1 of admission. Renal function normalised, inotrope as well as ventilatory support were weaned off, and he was finally discharged on Day 9.

Case Six. A 27-year-old welder with no prior illness presented on 5/6/08 with seven days' history of fever, chills and rigors, associated with arthralgia, myalgia, headache and two days' cough. He went fishing about two weeks ago in Kuala Kubu Bharu, located in the state of Selangor. Intravenous ceftriaxone and oral doxycycline were commenced for pneumonia, and chloroquine was added on Day 2 when the blood film result came back positive for malaria parasite. He responded well and was discharged on Day 6 of admission.

Case Seven. A 24-year-old convenience store (7-Eleven) cashier, admitted on 5/6/08 to Kuala Kubu Bharu Hospital, was referred to our centre on 7/6/08. She presented initially with 10 days' history of fever associated with myalgia, reduced appetite and vomiting. She goes back frequently to her hometown in KKB, the last trip being two weeks earlier. Chloroquine was started on Day 2 of admission to our centre (8/6/08). Her hospital stay was uneventful and she was subsequently discharged on Day 5.

DISCUSSION

The patients reported above presented initially with symptoms of a non-specific viral illness. In a dengue-endemic area where the incidence in Malaysia is 181 per 100,000 population (2007), the diagnosis of dengue illness was top on the list of differential diagnoses. However, features against this diagnosis are the absence of leucopaenia (except Case 6) and a longer, protracted duration of illness which would be atypical for dengue. Patients with a dengue illness also rarely present with renal impairment unless there is severe dehydration.

The diagnosis of malaria was only confirmed via blood film microscopy, which was done based on the clinical presentation, in association with a history of recent traveling into jungles or staying in areas with close proximity to a jungle. In such patients with a recent history of travel, the diagnosis of leptospirosis should also be ruled out, especially when there is associated renal and liver involvement. Differential diagnoses to consider would include HIV seroconversion illness, typhoid, typhus and other viral illnesses.

P. knowlesi, a simian parasite, is naturally found in long-tailed macaques (Macaca fascicularis), pig-tailed macaques (Macaca nemestrina) and banded leaf monkeys (Presbytis malalophos), which are commonly found in the forested areas of South East Asia. Vector transmission of this disease is restricted to mosquitoes of the Anopheles leucosphyrus group, which are also present in South East Asian countries6. These mosquitoes are equally attracted to monkeys and humans, hence the potential for transmission of *P. knowlesi* infections to humans.

P. knowlesi is commonly mistaken for *P. malariae* by blood film microscopy due to the similarity of the mature stages and gametocytes[4]. The early blood stages can also be misdiagnosed as *P. falciparum* if only ring forms are identified[4]. Features which should raise the suspicion of *P. knowlesi* infection are:

- daily fever spikes (due to its 24-hour asexual life cycle)
- travel to forested areas within the range of long-tailed and pig-tailed macaques
- high parasitaemia level, which is not expected in a *'P. malariae'* infection
- pronounced symptoms which are atypical for a *'P. malariae'* infection

P. knowlesi infections respond well to the usual anti-malarial agents. However, they can be potentially life-threatening as shown by four recent fatalities in Sarawak, Malaysian Borneo [2]. Clinical features common to those four reported fatal cases in Sarawak included fever, abdominal pain, jaundice, thrombocytopaenia and renal impairment. These patients had all received a misdiagnosis of *P. malariae* infection. Hence, it is pertinent that clinicians be aware of the characteristics of *P. knowlesi* infection and clinical features that might lead to fatal outcomes.

This case series shows that the geographic range of human P. knowlesi infections in Peninsula Malaysia is not only confined to the eastern state of Pahang, but also extends to the Klang valley on the west coast. A recent report has confirmed the existence of human *P. knowlesi* infections throughout Peninsula Malaysia [7], although the monkeys caught in Selangor were not infected with *P. knowlesi*. In conclusion, human infections with *P. knowlesi* malaria in Peninsula Malaysia are not that uncommon and may have a wider distribution than previously thought.

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