**Plasmodium knowlesi** malaria infection in human

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**ABSTRACT**

*Plasmodium knowlesi* (*P. knowlesi*) is a species of Plasmodium that rarely infect humans compared to *P. vivax*, *falciparum*, *ovale* and *malariae*, and has been considered as the fifth malaria species. There is a large reservoir of *P. knowlesi* in the whole of Eastern Malaysia and in most states of Western Malaysia, particularly in Macaque monkeys. We report the rare case of a 58-year-old man who presented with septic shock secondary to *P. knowlesi* who was successfully treated.

**Keywords:** Malaria, septiceamia, acute kidney injury

**INTRODUCTION**

*Plasmodium knowlesi* (*P. knowlesi*) is considered the fifth malaria species. Unlike the other Plasmodium species, infections with *P. knowlesi* in human are rare. This species was first isolated in 1931 from a long tailed macaque monkey which was imported to India from Singapore. 1 It was first shown to be infectious to humans in 1932. 2 The first human infection was reported in 1965. 2

There is a large reservoir of *P. knowlesi* in the whole of Eastern Malaysia and in most states of Western Malaysia. 1 It has also been reported from Thailand, Myanmar, Singapore, the Philippines, Vietnam and Indonesia. Its natural hosts are the macaques and banded leaf monkeys. The vector for transmission to humans is the mosquito – *Anopheles leucosphyrus* group. Humans acquire this infection when they travel to forested areas where both the natural hosts and the vectors are present. Although the natural host is present in the urban setting, transmission is unusual due to absence of the vector.

We report the case of a 58-year-old man with *P. knowlesi* infection who presented with septicaemic shock, acute respiratory distress syndrome and acute kidney injury.

**CASE REPORT**

A 58-year-old farmer presented to the Accident and Emergency Department with a history of being unwell with loss of appetite for approximately a week. He had fever that was...
associated with dyspnoea for the previous three days. He also had coffee ground vomitus prior to admission. His oxygen saturation through a facemask with an oxygen flow rate of 8 L/minute, ranged between 62% and 64%.

He was immediately referred to the Critical Care Medicine Department. On examination he was conscious, and comfortable but was febrile (38.1°C) and had central cyanosis. He was haemodynamically stable (pulse rate 97/min and blood pressure 137/76mmHg). His oxygen saturation fluctuated between 70% and 100%, and he was transferred to the Intensive Care Unit (ICU). Urgent arterial blood gas analysis revealed metabolic acidosis with respiratory compensation (pH 7.341, PaO\textsubscript{2} 77.3mmHg, PCO\textsubscript{2} 22.3mHg, HCO\textsubscript{3} 11.8mmol/L and base excess of –11.6mmol/L). The serum lactate was elevated at 8.34mmol/L.

Admission chest radiograph was otherwise unremarkable. Laboratory investigations showed serum haemoglobin to be 13.2 gm/dL, markedly elevated white cell count of 39.5 x 10\textsuperscript{9} /L (7.0 to 11.0) and thrombocytopenia of 31 X 10\textsuperscript{9} /L (150 to 450). CRP was 26.09mg/dL (<0.2). Serum glucose was very low at 1.5mmol/L (4.5 to 6.5), and the renal profile was deranged (creatinine 360umol/L, urea 30mmol/L). The liver profile was mildly deranged. DCT was positive (IgG 2+, C3b, C3d+) and G6PD level was normal. Dengue IgM and IgG serology were negative and the NSI Ag was also negative. Viral hepatitis markers only indicated previous exposure (anti-HBe positive and anti-HBc total were positive). Blood culture did not isolate any organism. Ultrasound scan of the abdomen showed calculi in the gall bladder. The rest of the examination was normal.

Admission blood smear was positive for \textit{P. knowlesi} with a parasite index of 27.9%. Both trophozoites and schizonts were seen. He was immediately started on intravenous quinine with dose adjusted for renal and hepatic dysfunction. This was later changed to oral quinine after 48 hours of intravenous therapy. He was also started on intravenous

\begin{figure}[h]
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\caption{a) Blood film showing parasitised red blood cells (H&E stain, x10), and b) a magnified image showing \textit{Malaria knowlesi} inside the erythrocytes (H&E stain, x100).}
\end{figure}
antibiotics (ceftazidime and co-amoxiclav) and oral doxycycline to cover for concomitant bacterial infection. Blood and platelet transfusions were also given.

His condition was complicated by acute kidney injury with minimal urine output. Renal replacement therapy was started. On the third day of admission, he developed respiratory failure and required endotracheal intubation with mechanical ventilatory support. Chest radiograph revealed bilateral alveolar opacities with normal cardiac size, consistent with acute respiratory distress syndrome.

Forty-eight hours after starting quinine, the parasite index dropped to 1.6%. No parasites were seen on the fifth day. The platelet count normalised by the seventh day. On the eleventh day, his progress was complicated by gastrointestinal bleeding. An urgent upper gastrointestinal endoscopy only showed gastritis. His bleeding settled and a colonoscopy done two days later showed a circumferential ulcer with irregular edges in the sigmoid colon. Biopsies revealed broad fungal hyphae, aseptate with right angled branching consistent with mucormycosis. Intravenous Liposomal Amphotericin B was started. His condition improved and he was extubated on the 20th day and recovered without any further complications.

DISCUSSION

P. knowlesi is unusual among malaria parasite of primates in that it has relaxed host specificity (humans and monkeys) but is vector restricted to the Anopheles leucosphyrus group. It has the shortest erythrocytic cycle of all the malaria species affecting humans. Daily schizont rupture leads to pyrexia every 24 hours. Interestingly, due to its ability to induce daily pyrexia, it was used in the 1930s as a pyretic agent for the treatment of neurosyphilis. The early trophozoite stages (ring forms) are morphologically identical to P. falciparum, while the later stages (late trophozoites, schizonts and gametocytes) are identical to P. malariae. Unlike P. malariae which seldom exceeds 5000 parasites per ml of blood and has a benign clinical course, P. knowlesi causes very high parasitemia and can cause multiple organ dysfunction. A polymerase chain reaction-based assay is also available for definitive identification of P. knowlesi but is not recommended for routine use.

The incubation period of P. knowlesi is 9 to 12 days. The clinical features described in literature are similar to other plasmodial infections consisting of constitutional symptoms, pyrexia with chills and rigor. In contrast to other forms of malaria, the spike of fever in P. knowlesi is daily. Similar to the other forms of malaria, thrombocytopenia is a consistent feature. However, clinical bleeding due to the thrombocytopenia is rare. In our setting, where dengue fever is common, this needs to be excluded. Cerebral dysfunction has not been reported but depressed consciousness can occur due to hypoglycaemia. However, hypoglycaemia per se is unusual in this form of malaria. Multiple organ dysfunctions can occur in complicated cases, and renal function can be significantly deranged requiring renal replacement therapy.

P. knowlesi is sensitive to all anti-malarial medications. Chloroquine, quinine and artemether-lumefantrine combination and doxycycline have all been used in treatment.
No resistance, recrudescence or relapse has been reported to date. However, in severe malaria, the mortality was reported to be 27% as results of multiple organ dysfunctions. Since it has no late exo-erythrocytic hepatic phase, primaquine is not indicated in the treatment regime.

In conclusion, we report a rare case of *P. knowlesi* that presented with septicemic shock, acute respiratory distress syndrome and acute kidney injury. Our patient did not have any other comorbid conditions. Although we have encountered few rare cases of *P. knowlesi* in our local setting, a case with such presentation has never been reported. We hope this case will highlight to clinicians to consider this diagnosis in patients who are at risk of contracting malaria infection.

REFERENCES