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CASE REPORT

The 24-hour crisis: rapidly fatal cerebral malaria due to *Plasmodium knowlesi* complicated by acute pontine infarction

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ABSTRACT

Plasmodium knowlesi is an emerging zoonotic malaria species and a leading cause of malaria in Malaysia. Although severe disease is increasingly recognised, cerebral malaria remains uncommon and is traditionally associated with *Plasmodium falciparum*. We report a fatal case of cerebral malaria caused by *P. knowlesi* in a previously healthy 61-year-old woman with a history of frequent orchard visits for peridomestic agricultural activities. She presented with rapid neurological deterioration and circulatory shock, complicated by an acute pontine infarction. Peripheral blood smear and polymerase chain reaction confirmed *P. knowlesi* infection with a parasite density of approximately 35,000 parasites/µL. The patient met World Health Organization criteria for severe malaria and was treated promptly with intravenous artesunate in accordance with international guidelines, alongside intensive supportive care for septic shock and multiorgan failure. Despite a rapid reduction in parasitaemia, her condition deteriorated, and she died within 24 hours of presentation. This case highlights the potential for *P. knowlesi* to cause rapidly progressive and fatal cerebral malaria. Clinicians in endemic regions should maintain a high index of suspicion for zoonotic malaria in patients presenting with acute neurological deterioration.

Keywords: *Plasmodium knowlesi*; neurological deterioration; cerebral malaria; critical care.

INTRODUCTION

Cerebral malaria is most commonly associated with *Plasmodium falciparum* and is rarely attributed to *Plasmodium knowlesi*. Although *P. knowlesi* infection can cause severe malaria, cerebral involvement remains uncommon and is defined by the presence of asexual parasitaemia together with clinical or laboratory evidence of vital organ dysfunction. While Sabah is a known epicenter for *P. knowlesi* in Malaysia, the interior district of Keningau represents a major endemic hotspot (Cooper *et al*., 2020), carrying a high burden of zoonotic malaria cases due to the close intersection of human activity and sylvatic vectors. Here, we report a classical neurological presentation of cerebral malaria caused by *P. knowlesi*, highlighting the interplay between parasite pathogenesis and clear behavioral risk factors–specifically, routine peridomestic agricultural activities during frequent, near-daily orchard visits. This case emphasizes the need for heightened clinical awareness of *P. knowlesi* as an emerging cause of severe and cerebral malaria.

CASE REPORT

A 61-year-old woman, previously healthy without known comorbidities, presented to the emergency department (ED) with a one-day history of fever, shortness of breath, and abnormal movements, followed by a sudden onset of generalized tonic–clonic seizures approximately 30 minutes prior to arrival. On initial assessment, she was comatose with a Glasgow Coma Scale (GCS) score of 3 over 15. Pupils were bilaterally 2 mm and sluggishly reactive. Her vital signs were: Blood pressure; 93/42 mmHg, heart rate; 118 beats/min, and respiratory rate 20 breadths/min, with oxygen saturation ($SPO_{2)}$ of 100% on room air and temperature of 37.8°C. Neurological examination revealed upper motor neuron signs, including hypertonia and a positive Babinski sign. Lung and abdominal examinations were unremarkable.

Approximately 20 minutes after arrival, she experienced another episode of generalized seizure lasted for 1 minute and was aborted with intravenous (IV) Diazepam 5mg. She was intubated

Table 1. Summary of blood investigation results

Parameters	Results	Normal range
Full blood count		
Haemoglobin	17.4	13–18 g/dL
White cell count	11.6	4.0–10.0'10y /L
Platelet	34	150–400'10y /L
Renal Profile		
Sodium	137	135–145 mmol/L
Potassium	3.7	3.5–4.1 mmol/L
Urea	9.7	2.8–8.0 mmol/L
Creatinine	239	44–89 mmol/L
Liver Function Test		
Albumin	39	35–50 g/L
Total bilirubin	46.8	< 23 mmol/L
Direct bilirubin	24.1	
Alanine Aminotransferase (ALT)	149	<44 U/L
Alkaline Phosphatase (ALP)	257	32–104 U/L
Aspartate Aminotransferase (AST)	412	<45 U/L
Lactate dehydrogenase	2514	120–250 U/L
Creatine Kinase	7842	30–150 U/L
Coagulation Profile		
Prothrombin Time	24.6	10–13 seconds
Activated Partial Thromboplastin Time	35.7	25–40 seconds
INR	2.2	0.9–1.1
Arterial blood gas (FiO_2: 1.0)		
pH	7.26	7.35 – 7.45
pCO_2	27.4	35–45 mmHg
pO_2	334.6	80–100 mmHg
HCO_3^-	12.6	22–28 mmol/L
Base excess	-12	-2 – +2
SaO_2	99	
C-reactive Protein	197.4	< 1.0 mg/dL
Blood smear malaria parasite	35000	
Peripheral Blood Glucose	3.5	4.0–8.0 mmol/L

for airway protection. Initial blood investigations, summarized in Table 1, revealed a capillary blood glucose of 3.5 mmol/L, leukocytosis (11.6×10^9/L), and severe thrombocytopenia (34×10^9/L). Her renal profile demonstrated acute kidney injury with an elevated creatinine (239 µmol/L) and urea (9.7 mmol/L). Liver function tests showed hyperbilirubinaemia (total bilirubin 46.8 µmol/L) with marked transaminitis (AST 412 U/L; ALT 149 U/L) and elevated alkaline phosphatase (257 U/L). Both lactate dehydrogenase (2514 U/L) and creatine kinase (7842 U/L) were markedly elevated. She also exhibited coagulopathy, with an INR of 2.2 and a prolonged PT of 24.6 seconds. Arterial blood gas (ABG) analysis revealed severe metabolic acidosis (pH 7.26, bicarbonate 12.6 mmol/L, pCO2 27.4 mmHg, base excess -12). Furthermore, her C-reactive protein (CRP) was markedly elevated at 197.4 mg/dL.

Chest radiography was unremarkable. Plain computed tomography of the brain demonstrated an acute pontine infarct (Figure 1). Prompted by her severe clinical manifestations and abnormal laboratory findings, further history was obtained from her family. They reported that she frequently gardened in an orchard situated near a jungle in Keningau, Sabah. Her residence was located approximately 100 metres from a dense forest and orchard that she routinely visited. Furthermore, monkeys were frequently sighted in the immediate vicinity. A peripheral blood smear was subsequently performed, revealing malaria parasites at

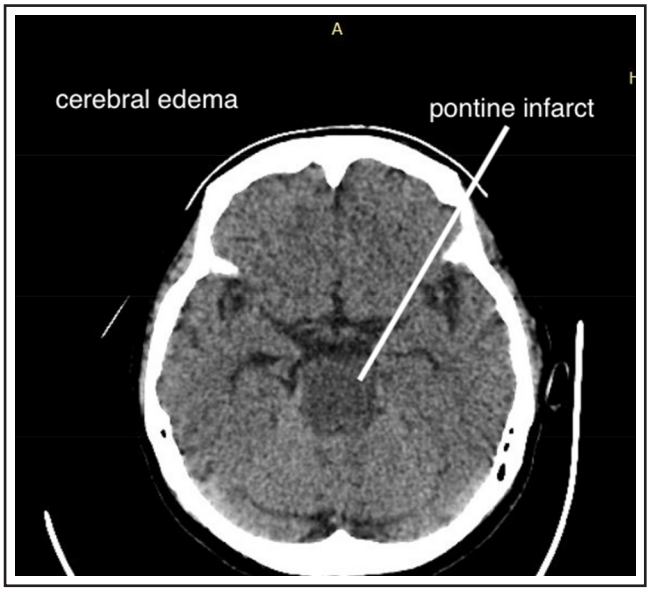
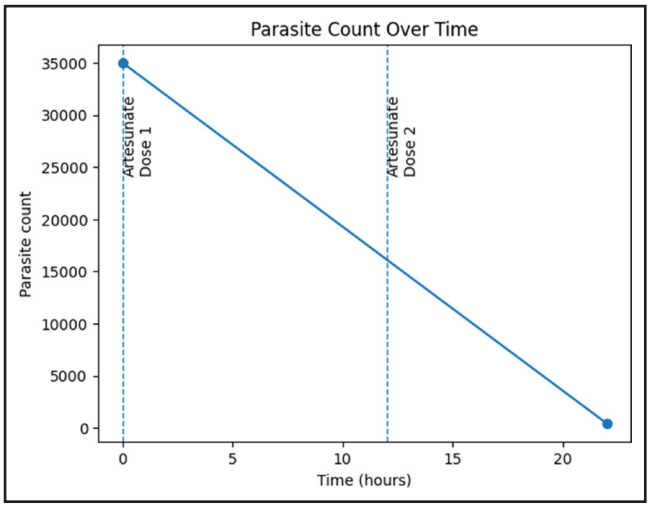


Figure 1. A plain CT brain: An arrow showing ill-defined hypodensities seen in the pons suggestive of an acute infarct with no associated hemorrhages and cerebral oedema.



Dashed vertical line at 0 hours → *Artesunate Dose 1*~ 156mg (2.4mg/kg)
Dashed vertical line at 12 hours → *Artesunate Dose 2* ~ 156mg (2.4mg/kg)

Figure 2. Parasite reduction over time after intravenous artesunate commenced.

the asexual stage with a density of approximately 35,000 parasites/µL. No specific morphological variants (such as distinct ring or band forms) or sexual stages (gametocytes) were explicitly distinguished in the initial pathology report. Because *P. knowlesi* morphologically replicates other *Plasmodium* species under light microscopy, molecular testing is essential for accurate speciation. Consequently, blood samples were referred to the Sabah Public Health Laboratory where polymerase chain reaction (PCR) analysis—utilizing both conventional and commercial real-time PCR assays–definitively confirmed the presence of *Plasmodium knowlesi* DNA.

The patient was promptly treated for septic shock secondary to severe malaria with multiorgan failure. An intravenous artesunate 156mg (2.4mg/kg) and doxycycline 200mg were administered. Lumbar puncture was deferred in view of the coagulopathy. Despite aggressive supportive care and a subsequent reduction in parasite density from 35,000 to 480 parasites/µL over 22 hours (Figure 2), her condition deteriorated rapidly due to progressive multiorgan failure, and she succumbed the following day.

DISCUSSION

Plasmodium knowlesi is now the predominant cause of malaria in Malaysia with zoonotic transmission accounting for the majority of reported cases (Ali *et al*., 2023). Although its capacity to cause severe and fatal disease is increasingly recognized, cerebral manifestations remain uncommon and may be misinterpreted as primary neurological events. The present case highlights this diagnostic challenge.

The World Health Organization (WHO) defines cerebral malaria as unarousable coma in the presence of confirmed malaria parasitaemia after exclusion of other causes of encephalopathy. In this case, the patient fulfilled multiple WHO criteria for the severe malaria, including impaired consciousness, shock, acute kidney injury, hepatic dysfunction with jaundice, severe thrombocytopenia, metabolic acidosis, hypoglycaemia, and coagulopathy. Her frequent engagement in peridomestic agricultural activities at the agro-forest interface further increased the risk of zoonotic transmission, as such settings provide suitable habitats for *Anopheles* mosquitoes of the *Leucosphyrus* group, the primary vectors of *P. knowlesi*, which feed on both macaque reservoirs and humans.

The patient's parasite density of 35,000 parasites/µL was below the WHO threshold for severe *P. falciparum* malaria, however *P. knowlesi* can cause severe disease even at lower parasitaemia (Barber *et al*., 2013). The *Management Guidelines of Malaria in Malaysia* (Ministry of Health Malaysia, 2013) define severe *P. knowlesi* malaria as a parasite density exceeding 20,000 parasites/µL. This threshold is supported by previous studies demonstrating that over 50% of patients with severe *P. knowlesi* infection had parasite counts above this level (Barber *et al*., 2013; Willmann *et al*., 2012). Reinforcing awareness of and adherence to these national guidelines is crucial for the timely diagnosis and prompt management of severe malaria, particularly in regions endemic for zoonotic transmission.

The patient's rapid deterioration was driven primarily by severe systemic malaria with multiorgan failure, within which cerebral involvement represented one of several critical manifestations. A key contributor to the rapid progression of severe disease in *P. knowlesi* infection is its 24-hour erythrocytic replication cycle, the shortest among human malaria species, which permits rapid rises in parasitaemia within a narrow clinical window. Unlike *P. falciparum*, in which cerebral malaria is largely mediated by ICAM-1-mediated cytoadherence of parasitized erythrocytes (Smith *et al*., 2000), cerebral involvement in *P. knowlesi* infection is increasingly recognized as a multifactorial process driven by systemic inflammation and widespread endothelial activation (Anstey *et al*., 2021; Bertran-Cobo *et al*., 2025). Post-mortem studies have demonstrated sequestration of pigmented parasitized red blood cells within the cerebral and cerebellar microvasculature; however, this process is ICAM-1 negative, with infected cells interspersed among uninfected erythrocytes rather than being marginalized against the endothelium (Cox-Singh, 2010).

Emergent evidence suggests that this unique pattern of microvascular congestion, along with elevated biomarkers of acute brain injury such as S100B and Tau, may contribute to neurovascular compromise in susceptible patients (Anstey *et al*., 2021; Bertran-Cobo *et al*., 2025). In our patient, this mechanism may plausibly have contributed to focal ischaemic injury when compounded by profound shock and haemoconcentration (Hb 17.4 g/dL), resulting in a pontine infarction that closely mimicked a primary acute ischemic stroke.

These pathophysiological mechanisms also help explain the diagnostic challenges encountered on neuroimaging. CT findings in cerebral malaria are frequently non-specific. The existing literature on *P. knowlesi* specifically is limited, with reported findings most commonly reflecting ischaemic involvement of the deep white matter, cerebral cortex, and basal ganglia (Dubey *et al*., 2017; Sakai & Barest, 2005; San Millan *et al*., 1993). While MRI remains the preferred radiological modality for detailed assessment, it is often unavailable at the clinical ground in many resource-limited settings where *P. knowlesi* is endemic (Anstey *et al*., 2021; Patankar *et al*., 2002; Wassmer *et al*., 2015). Our case is distinctive because it identifies a discrete infarct within the pons, a localization less frequently described than generalized cortical patterns, yet one that carries substantially higher risk of rapid brainstem failure.

Seizures in our patient likely reflected acute cerebral involvement occurring within the broader context of severe systemic malaria, rather than an underlying epileptic disorder. In keeping with current evidence, seizures were managed symptomatically without prophylactic antiepileptic therapy, using benzodiazepines as first-line treatment. This approach aligns with recommendations that discourage routine antiepileptic prophylaxis in cerebral malaria due to lack of benefit and potential harm. Agents such as levetiracetam or valproate may be considered if seizures are recurrent or refractory because of their favourable safety profiles and minimal interactions with antimalarial therapy (Idro *et al*., 2010; Alldredge *et al*., 2001; Meremikwu & Marson, 2002; WHO, 2022).

Our patient was treated with IV artesunate, the recommended first-line therapy for severe malaria of any species (WHO, 2022). This resulted in a rapid reduction in parasitaemia by the following day, consistent with the well-documented fast parasite clearance associated with artesunate therapy (Sinclair *et al*., 2012). Doxycycline was administered as adjunctive treatment to provide additional antimalarial activity and reduce the risk of recrudescence. Despite appropriate antimalarial therapy and demonstrable parasitological response, the patient's clinical condition continued to deteriorate due to progressive multiorgan failure, highlighting the severity of systemic disease at presentation rather than treatment failure.

CONCLUSION

Malaria in Malaysia remains geographically uneven, with East Malaysia carrying a far greater burden driven mainly by zoonotic *P. knowlesi*. Existing evidence indicates that the high mortality observed in adult *P. knowlesi* infections is primarily driven by rapid parasite multiplication, most frequently presenting with respiratory distress or acute kidney failure. However, this case serves as an important reminder that *P. knowlesi* can occasionally present with rare, atypical cerebral manifestations, such as focal neurological signs or a first-episode seizure, mimicking an acute stroke. The 24-hour erythrocytic cycle of *P. knowlesi* leaves clinicians with a very narrow window to act. A patient can deteriorate dramatically within hours, even when brain imaging is unremarkable. In endemic settings, malaria must remain high on the differential diagnosis for any patient presenting with altered consciousness or acute neurological symptoms, particularly when there is potential agro-forest exposure. Clinicians must maintain a high index of suspicion and a low threshold for initiating parenteral artesunate, guided by national guidelines rather than waiting for radiological evidence. Integrating this awareness into emergency and acute care, consistent with WHO and national guidelines, is critical to preventing the fatal 'diagnostic traps' that occur when rare atypical presentations are mistaken for primary vascular events.

Conflict of Interest

The author declares that they have no conflict of interests.

REFERENCES

Ali, R., Ali, W.N.W.M. & Putit, P.W. (2023). Updating the data on malaria vectors in Malaysia: protocol for a scoping review. *JMIR Research Protocols* **12**: e39798. https://doi.org/10.2196/39798

Alldredge, B.K., Gelb, A.M., Isaacs, S.M., Corry, M.D., Allen, F., Ulrich, S., Gottwald, M.D., O'Neil, N., Neuhaus, J.M., Segal, M.R. & Lowenstein, D.H. (2001). A comparison of Lorazepam, Diazepam, and Placebo for the treatment of out-of-hospital status epilepticus. *The New England Journal of Medicine* **345**: 631-637. https://doi.org/10.1056/NEJMoa002141

Anstey, N.M., Grigg, M.J., Rajahram, G.S., Cooper, D.J., William, T., Kho, S. & Barber, B.E. (2021). Knowlesi malaria: human risk factors, clinical spectrum, and pathophysiology. *Advances in Parasitology* **113**: 1-43. https://doi.org/10.1016/bs.apar.2021.08.001

Barber, B.E., William, T., Grigg, M.J., Menon, J., Auburn, S., Marfurt, J., Anstey, N.M. & Yeo, T.W. (2013). A prospective comparative study of Knowlesi, Falciparum, and Vivax malaria in Sabah, Malaysia: high proportion with severe disease from *Plasmodium knowlesi* and *Plasmodium vivax* but no mortality with early referral and artesunate therapy. *Clinical Infectious Diseases* **56**: 383-397. https://doi.org/10.1093/cid/cis902

Bertran-Cobo, C., Dumont, E., Noordin, N.R., Lai, M.-Y., Stone, W., Tetteh, K.K.A., Drakeley, C., Krishna, S., Lau, Y.-L. & Wassmer, S.C. (2025). *Plasmodium knowlesi* infection is associated with elevated circulating biomarkers of brain injury and endothelial activation. *The Journal of Infectious Diseases* **231**: e966-e975. https://doi.org/10.1093/infdis/jiae553

Cooper, D.J., Rajahram, G.S., William, T., Jelip, J., Mohammad, R., Benedict, J., Alaza, D.A., Malacova, E., Yeo, T.W., Grigg, M.J. *et al*. (2020). *Plasmodium knowlesi* malaria in Sabah, Malaysia, 2015-2017: ongoing increase in incidence despite near-elimination of the human-only *Plasmodium* species. *Clinical Infectious Diseases* **70**: 361-367. https://doi.org/10.1093/cid/ciz237

Cox-Singh, J. (2010). Malaria: what can apes teach humans? *Future Microbiology* **5**: 1157-1160. https://doi.org/10.2217/fmb.10.86

Dubey, A., Dubey, S. & Dhawale, R.G. (2017). Study of computed tomography in patients of cerebral malaria. *Journal of Neurology and Experimental Neural Science* **2017**: JNN-312. https://doi.org/10.29011/JNN-132.100032

Idro, R., Marsh, K., John, C.C. & Newton, C.R. (2010). Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. *Pediatric Research* **68**: 267-274. https://doi.org/10.1203/PDR.0b013e3181eee738

Meremikwu, M. & Marson, A.G. (2002). Routine anticonvulsants for treating cerebral malaria. *The Cochrane Database of Systematic Reviews* **2002**: CD002152. https://doi.org/10.1002/14651858.CD002152

Ministry of Health Malaysia. (2013). Management guidelines of malaria in Malaysia. Disease Control Division, Ministry of Health Malaysia.

Patankar, T.F., Karnad, D.R., Shetty, P.G., Desai, A.P. & Prasad, S.R. (2002). Adult cerebral malaria: prognostic importance of imaging findings and correlation with postmortem findings. *Radiology* **224**: 811-816. https://doi.org/10.1148/radiol.2243010588

Sakai, O. & Barest, G.D. (2005). Diffusion-weighted imaging of cerebral malaria. *Journal of Neuroimaging* **15**: 278-280. https://doi.org/10.1177/1051228405277341

San Millan, J.M., Muñoz, M., Navas, E. & Lopez-Velez, R. (1993). CNS complications in acute malaria: MR findings. *American Journal of Neuroradiology* **14**: 493-494.

Sinclair, D., Donegan, S., Isba, R. & Lalloo, D.G. (2012). Artesunate versus quinine for treating severe malaria. *The Cochrane Database of Systematic Reviews* **6**: CD005967. https://doi.org/10.1002/14651858.CD005967.pub4

Smith, J.D., Craig, A.G., Kriek, N., Hudson-Taylor, D., Kyes, S., Fagen, T., Pinches, R., Baruch, D.I., Newbold, C.I. & Miller, L.H. (2000). Identification of a *Plasmodium falciparum* intercellular adhesion molecule-1 binding domain: a parasite adhesion trait implicated in cerebral malaria. *Proceedings of the National Academy of Sciences* **97**: 1766-1771. https://doi.org/10.1073/pnas.040545897

Wassmer, S.C., Taylor, T.E., Rathod, P.K., Mishra, S.K., Mohanty, S., Arevalo-Herrera, M., Duraisingh, M.T. & Smith, J.D. (2015). Investigating the pathogenesis of severe malaria: a multidisciplinary and cross-geographical approach. *The American Journal of Tropical Medicine and Hygiene* **93**: 42-56. https://doi.org/10.4269/ajtmh.14-0841

Willmann, M., Ahmed, A., Siner, A., Wong, I.T., Woon, L.C., Singh, B., Krishna, S. & Cox-Singh, J. (2012). Laboratory markers of disease severity in *Plasmodium knowlesi* infection: a case control study. *Malaria Journal* **11**: 363. https://doi.org/10.1186/1475-2875-11-363

World Health Organization (WHO). (2022). Guidelines for malaria. Geneva: World Health Organization. https://iris.who.int/server/api/core/bitstreams/ee2530b8-73a1-4602-9a61-f38405086cf8/content.