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Severe *Plasmodium knowlesi* infection with multiorgan involvement in north east peninsular Malaysia

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Abstract. *Plasmodium knowlesi* has been recently identified as the "fifth human malaria species" following the discovery in Malaysian Borneo of a large focus of this simian malaria parasite in humans. Even though it shares microscopic similarities with *Plasmodium malariae*, it may cause severe illness with risk of fatality. We describe a case of *P. knowlesi* infection causing multi-organ failure in a patient who was successfully managed due to early recognition of the infection. Clinicians in this region should be more aware of the infection as it is not as rare as previously thought. This case write up highlight the case of severe malaria infection which presented with multi organ involvement which is caused by *P. knowlesi*.

INTRODUCTION

Plasmodium knowlesi is a simian parasite. It occurs in long-tailed and pig-tailed macaques (*Macaca fascilaris* and *Macaca nemestrina*) which are commonly found in south-east Asia (Garnham, 1966). *Plasmodium knowlesi* was first identified in 1931 and was shown to be infectious to humans by the inoculation of infected blood (Chin *et al.*, 1965). The first natural human infection was in 1965 (Chin *et al.*, 1965). Naturally acquired infection in humans were thought to be rare until recently when large focus of infection has been described in Malaysian Borneo (Singh *et al.*, 2004). *Plasmodium knowlesi* infection has also been reported in other countries in South East Asia namely Thailand (Jongwutives *et al.*, 2004), Singapore (Ong *et al.*, 2009), Indonesia (Erma *et al.*, 2010) and Philippines (Luchavez *et al.*, 2008). These findings have enhanced the perception that *P. knowlesi* infection is now the fifth malaria species causing infections in humans (Cox-Singh *et al.*, 2008).

Morphologically, *P. knowlesi* is similar to *Plasmodium malariae* making it difficult to distinguish between the two by routine examination of the blood film for malarial parasite (BFMP) using microscopy (Cox-Singh *et al.*, 2008; Wilairatana *et al.*, 2010). The development of *P. knowlesi* –specific primers allow accurate identification of the infection by nested PCR assay (Wilairatana *et al.*, 2010). However due to its cost, it is advocated to use this test only to differentiate the infection when the need arises and not to use as routine test in the diagnosis of malaria infections (Cox-Singh *et al.*, 2008).

The parasite has 24-hr life cycle which differs from that of *P. malariae*. This results in the ability of the parasite to reach dangerous densities in the blood. Initially, *P. knowlesi* infection was not known to cause severe infection in human. However in 2008, Cox-Singh *et al.* reported four fatal cases through retrospective cases reviewed in

Sarawak, Malaysia (Cox-Singh *et al.*, 2008). Daneshsvar *et al.* (2009) also reported a few cases of fatality resulting from *P. knowlesi* infection with a lower overall case fatality rate of 1.8%.

This case illustrates a severe case of *P. knowlesi* infection with multi-organ dysfunction which was managed successfully due to early recognition of this new parasitic pathogen.

Case Report

We report a case of a 26-year old man with severe *P. knowlesi* infection in the state of Kelantan, North- east of peninsular Malaysia, near the Malaysia-Thai border. The patient presented with fever for four days associated with chills, rigor, myalgia and arthralgia. He also had history of severe abdominal pain for the past three days, located at epigastric and hypochondriac areas. The patient was unable to tolerate orally since the onset of illness. There is also history of petechiae rash on bilateral lower limbs since day two of illness. The possible risk factor is that patient works as a rubber tapper. It wasn't clear whether the area where patient worked was a habitat for the macaque monkeys or not.

Clinically, the patient was afebrile, tacypnoeic and dehydrated. His blood pressure was 103/65 mmHg and his pulse rate was 73 beats per minute. He had mild jaundice with presence of hepatomegaly. Laboratory studies showed that he had normochromic normocytic anaemia with thrombocytopenia (Hemoglobin : 11.7 g/L, Platelet: 10 x 10^9/L). There was a sign of acute kidney injury with urea 36.9 mmol/L and creatinine 591mmol/L. He also showed derangement in liver function with raised alkaline phosphatase and transaminases, ALP: 143 IU/L, AST : 81 IU/L and ALT : 47 IU/L. His total bilirubin was 51mmol/L, direct bilirubin: 23mmol/L and indirect bilirubin : 36mmol/L. The respiratory system was also affected as the blood gas showed type 1 respiratory failure. Blood was also tested for dengue serology and was negative.

Plasmodium *malariae / knowlesi* parasitemia of 4800 parasites/ µl blood was noted on blood-smear examination. The chest and abdominal X-rays were normal. In view of his presentation of severe malaria mimicking falciparum malaria infection and the blood films reported as P. *malariae / knowlesi*, the patient was diagnosed as *P. knowlesi* clinically.

Patient was admitted to high dependency ward. Intravenous artesunate and tablet doxycycline were started. Over four days of admission, his renal function deteriorates necessitating haemodialysis. The renal function improved after the dialysis.

However, five days after admission, his condition deteriorated. He developed fever with temperature of 39°Celcius. He was dyspnoeic and his oxygen saturation was 93% under high flow mask oxygen. There was coarse crepitation at right lower zone which was consistent with chest X-ray finding of patchy opacities over right lower zone. Diagnosis of Hospital Acquired Pneumonia was made and patient was treated with intravenous meropenem.

Patient responded well to therapy. After one week of admission, his investigations normalized and BFMP was negative for three consecutive days. Tablet doxycycline was continued until day 14 and he was discharged. His PCR for *P. knowlesi* was confirmed two months later.

DISCUSSION

We describe an unusual severe presentation of *P. knowlesi* infection with multi-organ dysfunction which was successfully treated. This case demonstrates that *P. knowlesi* was not as rare as previously believed and it can be fatal if not recognized and treated early and appropriately. The severe cases that have been reported in Malaysia were mostly from Sarawak (Singh *et al.*, 2004; Cox-Singh *et al.*, 2008) and Sabah (William *et al.*, 2011). A retrospective study in Sabah conducted in 2009 reported 22 out of 56 (39%) patients admitted with PCR-confirmed knowlesi malaria had severe disease by WHO criteria, and six (27%) of them died (William *et al.*, 2011). Since then, there has been a few case series reported in peninsular Malaysia. Lee

et al. reported seven cases of *P. knowlesi* infection in Klang Valley (Lee *et al.*, 2010). Azira *et al.* also reported a few cases of *P. knowlesi* occurring the in the same state as our case (Azira *et al.*, 2012). However the cases involve milder presentations of *P. knowlesi* infection.

This patient's presentation mimics the fatal cases described in Sarawak (Cox-Singh *et al.*, 2008) and Sabah (William *et al.*, 2011). All the cases were diagnosed within seven days of onset of symptoms. The clinical features include abdominal pain, thrombocytopenia, renal impairment and jaundice. The difference is that the parasitaemia in this patient (4800 parasites / µl blood) was not as high as the reported fatal cases in Kuching which ranged from 75,000 – 204,800 parasites/µl blood (Cox-Singh *et al.*, 2008).

Severe malaria represents a medical emergency because it may rapidly progress to complications and death without prompt and appropriate treatment. Clinical deterioration usually appears 3–7 days after onset of fever which was seen in this patient. Complications involve the nervous, respiratory, renal, and hematopoietic systems (Trampuz *et al.*, 2003; Rajahram *et al.*, 2012). Treatment regime for *Plasmodium vivax* and *Plasmodium ovale* infections include chloroquine and primaquine. For the treatment of *P. malariae* and *P. knowlesi*, the treatment regime is similar to *P. vivax* and *P. ovale* infections but without primaquine. However, for severe and complicated *P. knowlesi* infection, the recommended treatment is similar to *Plasmodium falciparum* treatment regime (Soo, 2005). In this case, the patient was treated for severe infection even though *P. knowlesi* usually only causes mild to moderate infection.

The usual treatment for severe malaria is IV Artesunate. Artesunate is the drug which is available and widely used. WHO had strongly suggested an intravenous artesunate as a first line treatment for severe malaria. It was shown to significantly reduce the risk of death from severe malaria compared to intravenous quinine (Artemether Quinine Meta-analysis Study Group, 2001). A recent case series in Sabah has shown that with early referral and institution of IV artesunate, patients responded well and have good prognosis (Barber *et al.*, 2013). This patient was successfully treated with the regime as for severe malaria infection.

This patient could be mistaken as having dengue fever on presentation with the history of fever, abdominal pain, petechiae rash and having low platelet level. The similarity in the clinical presentation of *P. knowlesi* and dengue fever was highlighted by previous case series (Azira *et al.*, 2012). Even though dengue is more endemic than malaria in this area, routine blood film for malarial parasites is still being done since it is a differential diagnosis in any patient presenting with fever. Prompt awareness by clinicians is important not only for patient that stays in this area but also to any patient that travel to areas where malaria is still endemic.

Another issue is that differentiation between *P. knowlesi* and *P. malariae* is through PCR assays. At the time the case was seen, the PCR assay was done in the Institute of Medical Research in Kuala Lumpur resulting in the delay of the diagnosis by two months. Since then PCR is also done in the Public Health Laboratories of the states and is released much earlier. The research for the development of rapid and cost-effective diagnostic test for *P. knowlesi* is currently ongoing. In Sabah, a recent prospective study was done to evaluate the sensitivity of a pan-Plasmodium lactate dehydrogenase (pLDH)-*P. falciparum* histidine-rich protein 2 (PfHRP2) RDT (First Response) and a pan-Plasmodium aldolase-PfHRP2 RDT (ParaHIT). In *P. knowlesi* malaria, the sensitivity of the pLDH component of the pLDH-PfHRP2 RDT was 74% (95/129; 95% confidence interval [CI], 65 to 80%), however, its sensitivity was shown to be better in severe cases reaching up to 95% (36/38; 95% CI, 83 to 99). The aldolase component of the aldolase-PfHRP2 RDT performed poorly in *P. knowlesi* cases. Thus, this study concluded that neither the pLDH- nor aldolase-based RDT demonstrated sufficiently high overall sensitivity for the diagnosis of *P. knowlesi* (Barber *et al.*., 2013).

In conclusion, *P. knowlesi* infection should not be regarded as a rare human infection especially in the South-east Asian region. Prompt recognition of the infection and appropriate management is vital to prevent fatal outcome as illustrated in this case.

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