Case Report: Fatal Plasmodium Knowlesi Malaria Following an Atypical Clinical Presentation and Delayed Diagnosis

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INTRODUCTION

Plasmodium knowlesi is now recognized as a common cause of malaria in Sabah and Sarawak, with cases also reported in peninsular Malaysia (1-4). The parasite's 24 hour replication cycle, as compared to 48 or 72 hours for the other human malaria species, can lead to rapid increases in parasitemia and consequent complications, and case fatality rates of up to 11% have been reported [1,2]. However, mortality rates have been shown to be low with the use of intravenous artesunate and tertiary hospital referral for all severe malaria, with no deaths occurring in a prospective study at Queen Elizabeth Hospital in Kota Kinabalu involving 295 patients with malaria[3]. This included 38 of 130 (29%), 13 of 122 (11%) and 7 of 43 (16%) of those with *P. knowlesi, P. falciparum* and *P. vivax* respectively having severe disease [3]. Malaria deaths in Sabah are therefore largely preventable, provided the diagnosis is made early and appropriate treatment instituted. However, the marked decrease in the incidence of malaria as a result of successful malaria control policies over the last decade has resulted in doctors being unfamiliar with atypical clinical presentations of this disease. This case describes a patient who presented with non-specific symptoms of malaria, leading to delayed diagnosis and hospital presentation.

CASE REPORT

A 71-year-old female with a history of hypertension and peptic ulcer disease was admitted to Keningau Hospital in April 2012 with a 5 day history of fever associated with chills and rigors, abdominal pain, myalgia and arthralgia. She lived in Ranau and had stayed overnight at her palm oil and rubber plantation in the forest fringe 10 days prior to becoming unwell. On day 3 of her illness she had attended a government health clinic complaining of abdominal pain and dizziness, and was treated for gastritis with magnesium trisilicate syrup. A history of fever was not obtained and no temperature was recorded. The following day she presented to a private clinic with similar complaints, and had her antihypertensive medications adjusted. No blood film for malaria parasites was taken on either occasion. Her symptoms continued and she was brought to hospital on the 5th day of illness.

On admission she was alert but jaundiced and tachypnoeic with a respiratory rate of 38 breaths per minute, and the oxygen saturation was 98% on room air. The blood pressure was 127/87 mmHg, pulse rate was 111 beats per minute, and temperature was 37.8°C. She had hepatomegaly with a span of 17cm, and bilateral lower zone crepitations were heard on respiratory examination. Chest radiograph was normal. The patient had markedly deranged haematological and biochemical parameters on admission, summarised in Table I. Blood smear for malaria parasites (BSMP) was reported as *P.malariae* with a parasite count of 120,000 parasites/µL.

Oxygen and 2 liters of intravenous fluids were given, and the patient was commenced on intravenous artesunate, oral doxycycline and intravenous ceftriaxone within 2 hours of presentation. However, her condition deteriorated rapidly, with oxygen saturation decreasing to 70% on 15 litres of oxygen, and blood pressure dropping to 80/50 mmHg. She was intubated, transferred to the intensive care unit and commenced on dopamine, dobutamine and noradrenaline. Chest radiograph post intubation showed bilateral diffuse heterogenous opacities, and she died 18 hours after presentation to hospital from respiratory arrest, with a diagnosis of severe malaria complicated by acute kidney injury, hyperbilirubinemia, hypoglycaemia, acute respiratory distress syndrome and metabolic acidosis. Nested PCR from the DNA extract of her blood film using previously published methods confirmed *P. knowlesi* monoinfection [1,2,4], and blood cultures done on admission were negative.

DISCUSSION

P.knowlesi is a common cause of severe malaria in Sabah [1, 3], and although we have recently reported low mortality rates with adherence to strict treatment and referral guidelines [3], this case illustrates that fatalities may occur if diagnoses are delayed. Clinicians must therefore be familiar with the presenting features of knowlesi malaria including non-specific manifestations, the demographic characteristics of the patients most likely to be affected, and the risk factors for severe disease.

The clinical presentation of knowlesi malaria is similar to that of the other human malarias. Fever and rigors occur in nearly all patients, and non-specific symptoms include headache, myalgia, arthralgia and cough [1,2,3]. Gastrointestinal symptoms have been reported in over 30% of all patients with knowlesi malaria, and 100% of fatal cases

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Table I: Summary of laboratory features of patient, on admission

Laboratory Parameters	Results
Hemoglobin, g/dL (females 12.0-16.0, males 13.5-17.5)	14.1
White blood cells, x 10^3 cells/μL (4.5-11)	13.3
Platelet, x 10^3 cells/μL (150-450)	53
Serum creatinine, mmol/L (63-133)	662
Serum urea, mmol/L (1.0–8.3)	36.3
Total serum bilirubin, mmol/L (<17)	108.9
Serum aspartate aminotransferase, U/L (<37)	322.1
Serum alanine aminotransferase concentration, U/L (<40)	145.5
Serum albumin, g/L (35-60)	24
Serum bicarbonate, mmol/L (18-23)	4.2
Random plasma glucose, mmol/L	2.4
Blood cultures	Negative
PaO2:FiO2 (in ICU)	86
Initial microscopic diagnosis	*P.malariae 120,000 parasites/μL.*
Nested PCR result	*P. knowlesi*

[2,3,4]; among patients with falciparum malaria, gastroscopy findings have demonstrated a high incidence of gastritis [5]. Knowlesi malaria disproportionately affects older people compared to other malaria species, and these patients are therefore more likely to have co-morbidities [3] which may distract clinicians from considering malaria as a possible diagnosis. More importantly, increasing age is associated with an increased risk of severe disease [1, 3], and early diagnosis and commencement of treatment in older patients is therefore imperative.

The case also highlights the need to monitor the respiratory status of the patient even after the institution of anti-malarial therapy, as acute respiratory distress with hypoxemia can develop even with a decreasing parasite count [1]. This may be more important in severe knowlesi malaria where pulmonary complications appear to be common [1,2].

In our 71-year-old patient the diagnosis of malaria was not considered despite attendance at two health care facilities, possibly because abdominal pain was reported as the predominant symptom. A blood film was not taken on either occasion, leading to delayed diagnosis and treatment, with an ultimately fatal outcome. Given the implications of delayed diagnosis and treatment, clinicians seeing patients and returning travellers from Malaysia must be alert to the possibility of knowlesi malaria, particularly if a history reveals recent activities in or near forested areas. A blood film should be requested on any patient with a fever or reporting a history of fever, including those with atypical features such as abdominal pain.

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