MISDIAGNOSIS OF *PLASMODIUM FALCIPARUM* MALARIA AS HEMORRHAGIC FEVER WITH RENAL SYNDROME: A CASE REPORT

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Abstract. Malaria is an infectious disease caused by human *Plasmodium* spp, transmitted through bites of infected female Anopheline mosquitoes. Malaria remains one of the major health problems in tropical and sub-tropical countries and, although the number of new annual cases of malaria is decreasing, global warming threatens to spread malaria over a wider region of the world. In China and elsewhere, misdiagnosis of falciparum malaria can lead to mortality. Traditional diagnosis is based on clinical symptoms, but current practice requires both clinical symptoms and detection of malaria parasites in blood using microscopy, rapid immunological diagnostic tests and/or PCR-based detection methods, which significantly improve specificity and accuracy of diagnosis. The case report describes an individual with imported falciparum malaria who presented negative blood smears for malaria parasites and an absence in the medical record of recent history of travel in malaria-endemic areas prior to admission to the Infectious Diseases Second Affiliated Hospital, Air-force Military Medical University, Xi'an, PR China. The patient unfortunately expired from multiple organ failure despite treatment with artemisinin. This case report highlights the need for a thorough record of travel through regions with life-threatening infectious diseases and implementation of more precise detection methods of infectious agents such as *P. falciparum* where delay in drug treatment can lead to fatal consequences.

Keywords: *Plasmodium falciparum*, malaria, misdiagnosis

INTRODUCTION

Malaria is caused by parasites of genus *Plasmodium*, of which *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax* are well-known human parasites, and only more recently has monkey *P. knowlesi* been added to the list (Thaha *et al*, 2008). The parasite is transmitted to humans through bites of infected female Anopheline mosquitoes (Boissiere *et al*, 2012). Approximately 80% of malaria cases are caused by *P. falciparum*, which is endemic in tropical and sub-tropical regions, with *P. vivax* being the second most common species and *P. knowlesi*, *P. malariae* and *P. ovale* responsible for a relatively small proportion of malaria cases (Hong *et al*, 2012). *P. falciparum* is the most virulent of the five species, and if untreated can cause fatal cerebral malaria.

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Accurate diagnosis of the disease and identification of the causative *Plasmodium* spp are essential for prescribing the proper antimalarial drugs to the infected individuals (Phiri *et al*, 2016). Currently, clinical diagnosis of malaria is mainly based on symptoms with one or more of the following clinical features indicative of the severe form of the disease: coma (cerebral malaria), severe anemia, renal failure, pulmonary edema, hypoglycemia, shock, disseminated intravascular coagulation, repeated generalized convulsions, acidosis (pH <7.25), macroscopic hemoglobinuria, hyper-parasitemia (>5% infected red blood cells), or jaundice (Eleonore *et al*, 2020). However, reliance solely on clinical presentations for diagnosis of malaria is known to be inaccurate (Loomans *et al*, 2019). Consequently, confirmation through use of malaria parasite-based diagnostic tests is necessary, such as microscopic examination of blood smear, rapid immunological diagnostic tests, and parasite genome identification through PCR or isothermal amplification techniques (Baird *et al*, 2016).

Imported malaria poses a challenging diagnostic problem in areas of the world where the disease is non-endemic (Lai *et al*, 2016). In China, incidence of malaria infection and transmission has been decreasing since the initiation of a national malaria eradication program (Diouf *et al*, 2014), but among returning overseas workers, malaria fatality rate is on the rise due to a combination of delay in seeking medical attention and misdiagnosis (Lai *et al*, 2016).

CASE REPORT

A male 30 years of age with no previous disease history presented to the emergency room of Shaan Xi Provincial People's Hospital on 15 November 2012. The subject had been living for six months in South Sudan, Africa and 12 days subsequent to his return, he had a fever of 38.6°C with negative standard laboratory results. Although malaria was suspected, thick film blood smear proved negative for presence of malaria parasites. Consequently, the patient was discharged as having an upper respiratory tract infection. However, after two days of sustained fever (39.8°C) accompanied by abdominal pain, headache and lumbago, the patient was admitted to the same hospital and, in view of his two weeks residence in Xi'an where there is a high prevalence of rodent-borne infection (Ajayi *et al*, 2014) and taking into consideration clinical manifestation and outdoor activities, the patient was provisionally diagnosed with hemorrhagic fever with renal syndrome (HFRS).

On the following day, laboratory tests results showed white blood cell count of 10.5×10^9/l, 56.4% neutrophils, platelet count of 35×10^9/l, and hemoglobin level of 11.9 g/l. Liver function tests revealed aspartate transaminase (AST) and alanine transaminase (ALT) serum concentration of 1,598 and 1,049 U/l respectively. However, renal function tests were normal. Lactate dehydrogenase (LDH) level was 3,465 U/l. Hepatitis B surface antigen and anti-hepatitis C virus antibody were negative. IgM assayed using immunofluorescence and IgG using enzyme-linked immunosorbent assay were in normal range. Blood film for malarial parasites was again negative. Abdominal ultrasound and computerized tomography (CT) demonstrated morphologically normal kidneys with no ureteral dilation, with perineal free

liquid (Fig 1). The patient was treated for HFRS for six days with combination of antibiotics together with balanced salt solution.

On the seventh day, the patient was transferred to The Second Affiliaterd Hospital, Air Force Medicial University for more expert management. The patient then presented severe febrile illness in association with worsening jaundice and diminished consciousness. He had complete lethargy with normotensive blood pressure (120/80 mm/Hg), but further clinical examination revealed tachycardia and severe jaundice. In addition, peripheral oxygen saturation was 87%. Based on his travel history and clinical characteristics, malaria was suspected. Laboratory tests now showed AST and ALT level of 4,540 and 1,630 U/l respectively, white blood cell count of 25.95×10^9/l, 68% neutrophils, platelet count of 195×10^9/l, hemoglobin level of 7.3 g/l, serum creatinine of 319 mM, blood urea nitrogen (BUN) of 23.84 mM, and other routine laboratory values were within normal range. The patient was oliguric with urine volume <20-30 ml/hour, with urine proteinuria and microscopic hematuria. A repeat malaria parasite smear now revealed presence of *P. falciparum* (Fig 2). Six hours after admission, his mental condition deteriorated (from mild confusion to severe delirium, then coma) and progressive multiorgan failure was observed while undergoing artemether treatment (80 mg intramuscular injection of artemether once a day for five days). Then, red frothy expectoration was expelled from patient's oral airway; the patient became hypotensive (70/50 mm Hg), and, despite prompt mechanical ventilation and application of cardiac resuscitation, the patient expired.

DISCUSSION

Delayed diagnosis and treatment of malaria can result in serious complications and poor prognosis (Amet *et al*, 2013). Details from medical examination, the characteristic cyclic fever and a history of residency in a malaria endemic area can help identify malaria (Kain *et al*, 1998), but this is prone to misdiagnosis when

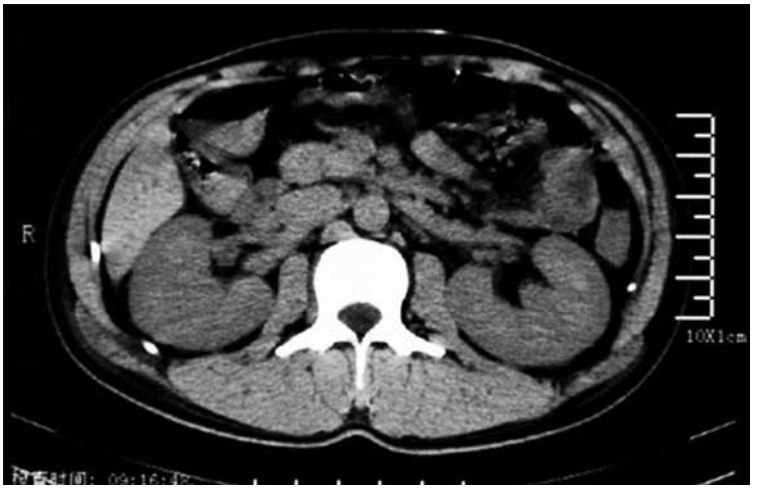

Fig 1-Abdominal CT scan of patient showing edema of kidney.

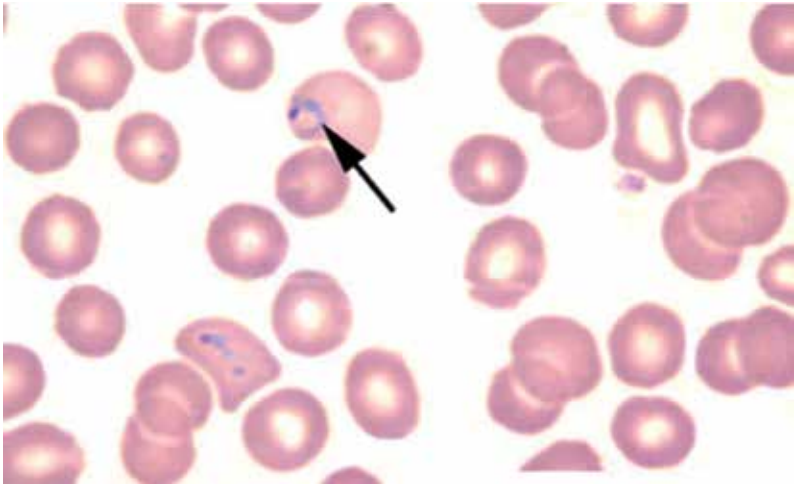

Fig 2-Peripheral thin blood smear showing intra-erythrocytic *Plasmodium falciparum* ring stage (arrow).

symptoms are not typical. Peripheral blood smear (thin and thick) is the gold standard for diagnosing malaria (Mehta and Das, 2006).

The case patient did not present a positive thin blood film for *P. falciparum* until Day 15 following admission. The patient was misdiagnosed as having HFRS and the history of recent travel in a malaria-endemic country was not brought to the attention of the attending physician. A long duration between exposure and positive blood film examination has been documented (Choi *et al*, 2016). In addition, the occurrence of diffuse intravascular coagulation and thrombocytopenia from small blood vessels obstruction caused by binding of mature *P. falciparum*-infected red blood cells to endothelial walls can lead to ischemic hypoxia, high-expression of transaminases and bilirubin, indicative of liver dysfunction, acute renal failure, pulmonary edema and eventually death (Asare *et al*, 2020). The patient's clinical manifestations were complex and atypical, which increased the possibility of not being alerted to the possibility of malaria, resulting in a rapid deterioration in the patient's condition.

With increase in overseas travel and wider spread of malaria-endemic areas into more temperate regions across the globe, physicians should be more alert to imported falciparum malaria and improve their ability to diagnose this potentially lethal infection by obtaining a detailed history of recent travels, particular in countries where malaria is endemic. More accurate and sensitive diagnosis strategy should be initiated beyond physical examination, laboratory tests, blood film scrutiny and obtaining a detailed travel history.

CONFLICTS OF INTEREST

The authors declare no conflicts of interests.

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