Two Cases of Severe Traveler's Falciparum Malaria with Improved Conditions After Administration of Oral Quinines

Umar Zein

ABSTRACT

Traveler's Malaria is a new emerging health problem in the whole world due to (1) increasing mobility of international travelers and (2) recurrence of diseases in areas that was once partially or fully freed from the disease.

We report 2 cases of severe traveler's malaria found in a man from Greece and a man from the Philippines aged 54 years. Both patients were ship captains. They have stayed in Kenya prior to the catching the disease. In the first case, we found acute kidney failure with anuria and lung edema, pneumonia, and a progressive decline in hemoglobin concentration. In the second cases we found reduced consciousness, disorder of liver function with jaundice, disorder of kidney function, bleeding from the upper digestive tract, pneumonia, severe anemia, and signs of DIC (Disseminated Intravascular Coagulation). The second patient was admitted to the ICU (Intensive Care Unit). Peripheral blood smears found ring forms and growing Plasmodium falciparum trophozoits. Both cases were assumed to be resistant to Chloroquine and Fansidar. Both of them were treated with oral Quinine Sulphate (we could hardly find Quinine injection in Medan). With such treatment for seven days, we found significant clinical and laboratory improvements. Asexual parasites were no longer found in the peripheral blood smear. During the hospitalization, both patients required Packed Red Cell (blood) transfusion to overcome the progressive drop in hemoglobin level. With the disappearance of the parasites from the patients' blood, the disorders of the organs mentioned above, gradually became normal. The conditions of the patients also showed satisfactory improvements.

Keywords: *Traveler's Malaria, Plasmodium falciparum, Complication, Quinine Sulphate*

INTRODUCTION

Malaria still creates a problem in both developing and developed countries. This phenomenon is indicated by a still increasing incidence of the disease in recent times. Possible causes are as follows[1]:

1. Increase in malaria parasite resistance to available chemotherapeutical medicines
2. Increase in Anopheles mosquito resistance to currently used insecticides
3. Significant change in climate and ecosystem
4. Increasing number of international travelers

Mosquito-infested areas, such as swamps, have long been associated with a high malaria attack rate. Environments that support long-standing, stagnant water promote mosquito breeding. Currently, endemic areas include parts of the Caribbean, northern South America, Central America, parts of Africa, India, parts of Australia, Southeast Asia, and many Asian Pacific Islands. Malaria also occurs sporadically in non-endemic areas. In many instances, this represents imported, latent disease. Malarial relapses may present months after travelers have returned from the endemic area. These patients have usually been incompletely treated or have taken insufficient chemoprophylaxis.[2]

Malaria import is an emerging problem happening in the whole world. A part of the cause is the increasing mobility of the international travelers and the other is due to reappearance of the disease from past-freed endemic areas. Evidence of malaria in international travelers has significantly increased within the past two decades. East Africa, especially Kenya, is the source of Falciparum malaria infestation in people from America and Switzerland who travelled to the country. In the following part we are report two severe Traveler's Falciparum Malaria cases who were recently treated in a private hospital in Medan, Indonesia.

Division of Tropical Diseases and Infection, Department of Internal Medicine, Faculty of Medicine of The University of North Sumatera/ H. Adam Malik/Dr. Pirngadi Hospital, Medan, North Sumatera, Indonesia

CASE NUMBER ONE

A male, 54-year old, Greek ship captain was admitted to the hospital on March 7th, 2001 with main complaints of fever, weakness, and paleness. The condition has been experienced for a week with a special pattern of up and down fever alternating with normal condition. There was severe headache and shaking chills, nausea, and vomiting. He had stayed in Kenya 3 weeks prior to admission, and consumed Mefloquine Tablets for prophylaxis. On primary physical examination we found the patient to be fully concious, with a blood pressure of 100/70 mmHg, a regular pulse rate of 100x per minute, a respiration rate of 20 per minute and a body temperature 39°C.

During further physical examination we found his conjunctiva to be pale, and no abnormalities in the neck. The patient's heart and lung were within normal limits. His abdomen were within normal limits. His extremities were within normal limits.

Laboratory investigation results were as follows: Hemoglobin level 8.5g%; White Blood Cell (WBC) count: 11,400/mm^3; Blood Sedimentation Rate (BSR): 20 mm/hr; Hematocryte (Ht): 44%; WBC differential count: 3/0/63/30/3/1; Platelet count: 196,000/mm^3; Urinalysis were within normal limits; Blood Sugar: 89 mg%; Liver Function Test: Total Bilirubin level: 1.3 mg/dL; Direct Bilirubin level: 0.54 mg/dL; SGOT: 156 u/dL; SGPT: 128 u/dL; Alkaline Phosphatase: 53 u/dL; Blood Ureum level: 89 mg/dL; Creatinine: 4.2 mg/dL; Peripheral blood smear demonstrated asexual Growing Trophozoites and ring-form of *Plasmodium falciparum*.

Working diagnosis:

Malaria Falciparum with Insufficient Kidney Function.

Treatment:

Bed rest, regular diet, Intravenous fluid drips of Ringer solution 20 drops/minute.

Oral Chloroquine 250 mg tablet with a '4–2–2–2' schedule.

After 2 days treatment, the patient still had fever, coughing and experienced shortness of breath. On physical examination we found wet rales in the lower part of the left lung.

Working diagnosis and further treatment

Severe malaria with Acute Kidney Failure + Pneumonitis (Differential Diagnosis: Acute Pulmonary Edema). The list of medicines added with Cefobid 1 Gr per 12 hours (IV) and Fansidar 3 tablets at once.

On the 5th day of hospitalization the patient suffered from more intense shortness of breath. There was no urine output in 12 hours, and the body temperature 37.6°C. Auscultation of the chest demonstrated more severe wet rales. Blood Ureum: 201 mg/dL, Creatinine: 5.8 mg/dL , WBC: 12,300/mm^2.

The following treatment was added: IV Lasix injection per 8 hours, Essential Amino Acid Solutions (EAS) 2 bottles per day.

On the 6th day: The shortness of breath was reduced, urine output 850 cc per 24 hours, Hemoglobin level: 6.2 g%, Platelet count 48,000/mm^3, WBC: 19,600/mm^3, Ureum: 177 mg/dL, Creatinine: 5.6 mg/dL. Examination of the parasite density gave a figure of 1060 ring forms and 1060 Gametocytes per mm^3 of blood. Chest x-ray showed pneumonia in the lower part of the right lung. From this point, the treatment with Quinine Sulphate 222 tablets was continued with a dosage of 3 tablets 3 times per day for 7 days.

On the 7th day: Hb: 5.8g%. The patient was given 500 cc of Packed Red Cell (PRC) transfusion.

On the 8th day: Hb (post blood transfusion) 10.3gr%. Urine volume: 3180 cc per 24 hours.

On the 10th day, we conducted Ultrasonography (USG) of the kidneys and conducted KUB (Kidney, Ureter, Bladder) X-Ray. The result showed a normal kidney. Urine production was 2100 cc per 24 hours. Chest X-Ray was repeated. The results showed normal lungs. No more fever was found, and the patient's vital signs were within normal limits.

During the laboratory examination we found the following: Ureum 141 mg/dL, Creatinine: 3,6 mg/dL; No ring form malaria was found, but there were 775 of Gametocytes per mm^3 of blood.

On the 12th day, the general condition of the patient had improved. Malaria was negative. Ureum: 75 mg/dL, Creatinine: 2.2 mg/dL. Treatment: Oral multivitamins.

On the 20th day the patient was allowed to go home.

CASE NUMBER TWO

A male, 54-year old, Filipino ship captain was admitted to the hospital on March 7th, 2001 with main complaints of fever, weakness, and jaundice. The condition had been experienced for 5 days. There were trembling chills followed by profuse perspiration and headache. He had stayed in Kenya 3 weeks prior to admission and consumed Mefloquine Tablets for prophylaxis. On primary physical examination we found the patient to be somnolent, with a blood pressure of 90/70 mmHg, a regular pulse rate of 116x per minute, a respiration rate of 20 per minute, and a body temperature of 38.6°C.

During further physical examination we found: jaundice (+). Neck: no any defect found; Thorax: Heart: heart rate 116 per minute, regular beat; intensity was fair, Lungs: found wet rales on both lungs. Abdominal palpation: liver, kidney, and spleen were unpalpable (should be within a normal limit); Extremities: no any sign of abnormality.

Laboratory investigation results: Hb: 5g%; WBC: 12,700/mm^3; Erythrocyte: 1.59 x 10^6; Thrombocyte: 326,000 per mm^3; BSR: 20mm/hrs; Ht: 44%; Blood Ureum: 176mg/dL; Creatinine: 3.3mg/dL; Na: 128meq/dL; K: 4.4meq/dL; Cl 103meq/dL; Total Billirubin: 6.20mg/dL; Direct Billirubin: 2.69mg/dL; SGOT: 84u/dL; SGPT: 57u/dL; Alkaline Phosphatase: 68u/dL; āGT: 159u/dL, HbsAg (negative); Peripheral blood sample: Growing Trophozoites and ring form Plasmodium falciparum were found.

Urinalysis: Protein (+); Sugar (-); Urobillinogen positive, Billirubin (+); Sediment: WBC: 5 to 10 per filed; Erythrocytes>100 per field, and Epithelial cells: 1 to 2 per field.

Blood gas analysis

Blood gas analysis showed: pH: 7.203; pCO_2 mmHg: 26.5 mm.Hg; pO_2: 122.6; BE:-16.1; Bicarbonate: 10.2mmol/dL; Total CO_2: 11.2mmol/dL; Saturated O_2: 97.3%.

Working diagnosis:

1. Severe Malaria Palcifarum with severe anemia
2. Acute Kidney Failure
3. Metabolic Acidosis

Treatment:

Intravenous fluid drips of Ringer Solution 10 drops per minute, injection of Cefobid 1 g per 12 hours intravenously. Fansidar 3 tablets single dose, Chloroquine 250 mg oral tablets with a '4–2–2–2' schedule, Injection of Lasix 1 vial per 12 hours. The patient was admitted to the Intensive Care Unit (ICU).

On the 3rd day, the patient still had a fever, and his blood pressure was 80/50 mmHg. We gave him 200mg of diluted Dopamin in 100 cc of Dextrose 5% solution by intravenous drip with a rate of 5 drops per minute, Quinine Sulphate 3 tablets three times per day FOR 7 days, and 500 cc of PRC transfusion.

On the 4th day, Hb post transfusion: 6.8g%; Parasite count: Ring-form 1290 per mm^3; Gametocyte: 1290 per mm^3; Albumin 2.07g%, Na: 128 meq/dL.; D-Dimer: 1000u/dL. The patient was given NaCl 0.9% 20 drops/minute, 100 cc of Albumin Substitution 25%. The urine output was 1300 cc per 24 hours.

On the 5th day, we conducted a chest x-ray. The reading was within normal limits. USG kidneys readings also gave normal results. Urine protein per 24 hours: 23 mg. The patient vomitted about 100 cc of blood (haematemesis). We added 1 vial of Teranexamic acid injection per 6 hours, 1 vial of Losec Injection per day.

On the 7th day, the upper GI tract bleeding stopped. The general conditions of the patient gradually became normal. The fever disappeared. The amount of urine produced was 2000 cc per 24 hours. Na: 144meq/dL; K: 3.6meq/dL; Cl: 98meq/dL; Hb: 6.6g%; Ht 21.3%. On repeated blood examination for malaria: Ring-form was negative; Gametocytes was 373 per mm^2.

On the 10th day, the patient was transferred from the ICU to the regular ward. Blood ureum: 43; Creatinine 1.1; Thrombocyte: 215,000 per mm^3. Lasix was stopped. Oral multivitamins were given.

On the 14th day, the general condition of the patient improved greatly, the patient's fever absolutely disappeared, but the patient's Hemoglobin concentration still low, 6g%. Another 500 cc PRC transfusion was administered. Peripheral blood examination for malaria found negative of asexual parasite forms.

On the 17th day, the Hb concentration increased to 10.5gr%. Malaria parasites were absent on repeated peripheral blood examination.

On the 20th day of admission, the patient was allowed to go home.

DISCUSSION

Severe malaria always affects a number of organs at once. Therefore, the case requires serious attention and proper follow up.

Treatment options depends on whether the parasite (*P. falciparum*) is or is not susceptible to Chloroquine. This information is available from periodic reports that describe Chloroquine resistance patterns throughout the world. If this information is not available, the infection should be considered as Chloroquine resistant.[3]

The definition of severe malaria itself must be made to include the conditions mentioned below:

Clinical criteria:[4]

1. Cerebral malaria
2. Severe anemia (Hct<15%)
3. Renal failure (no urine or urine out put <400 ml in 24 hours, or 12ml/Kg/24 hours after rehydration, or serum creatinine >3mg%)
4. Pulmonary edema or adult respiratory distress syndrome
5. Hypoglycemia (blood sugar <40mg%)
6. Shock (systolic BP <70 mmHg in adults or <50 mmHg in children ages 1-5 years)

7. Spontaneous bleeding and disseminated intravascular coagulation
8. Repeated convulsions
9. Acidosis (arterial pH <7.25 or plasma HCO3 <15)
10. Macroscopic hemoglobinuria (Black Water Fever)
11. Hyperparasitemia (>5% parasitemia in non-immune-?)
12. Hepatic dysfunction
13. Hyperpyrexia (persistance of rectal temperature >40^{0}C)

In both cases we mentioned above, all of the parameters showed signs and symptoms of severe malaria falciparum with severe anemia, acute kidney failure and pneumonia as a complication.

The second case showed bleeding from the upper gastrointestinal tract (upper digestive tract), thrombocytopenia, and increased D-Dimer. This case showed signs of DIC (Disseminated Intravascular Coagulation). DIC itself was not handled for this case because the bleeding quickly stopped with only hemodynamic interventions.

Acute kidney failure is known to be a killer attributed to the severe malaria. Before the invention of hemodialysis, the death rate attributed to the complication of severe malaria was approximately 10 to 20%.[1]

In both cases we found there were acute kidney failure sign by oliguria, signs of metabolic acidosis, and the elevated level of blood ureum and creatinine. The administration of Lasix via injection and also the intervention to the acidosis condition, monitored continuously via the proper intake & output procedure, the condition of kidney gradually back to normal. Both of the patients did not need any hemodialysis procedure.

It is said in the literature that the proper treatment for severe malaria is the continuous administration of Quinine by intravenous injection or giving of Artemisin or Artesunate or derivatives as the faster alternative to sweep malaria parasite out from blood circulation.[2,3]

We did not give Quinine Infusion nor Artemisin or Artesunate for both cases, because neither medicines were available in Medan. We only gave Quinine Sulfate orally.

There is a strong suspicion that there was resistant to either Chloroquine and Fansidar in both patients we treated. After administration of both medicines there were still clinical fever and in the examination of the peripheral blood there were found malaria parasites in a significant figure after 6th day for the first case and after 4th day of the second. With the administration of Quinine Sulfate, there were a reducing number of parasites and a fully swept out from blood after 2 weeks of treatment.

We decided on blood transfusion with PRC administered to both patients because there was a real tendency of declining Hb concentration during treatment and there were certain haemodynamic disorder monitored.

CONCLUSION

We report 2 cases of Severe Malaria falciparum suffered by 2 foreigners who came from the Philippines and Greece. Both of them were suspected to have resistance to Chloroquine and Fansidar. With oral Quinine Sulfate treatment and proper care to eliminate complications, as well as administration PRC (blood) transfusion, fluid balance, and administration of diuretics to maintain renal function and antibiotics for secondary infections, both patients were cured, clinically and laboratory-wise.

It is recommended that any foreigner who presents with fever or jaundice undergo a proper examination for malaria. This proves that at the moment, the number of malaria cases is increasing. Thus, we recommen not to delay treatment due to a delayed diagnosis. Quinine Sulfate is still the drug of choice for malaria cases, at least in Indonesia.

REFERENCES

1. Ledr K, Weller PF., et al. Epidemiology, pathogenesis, clinical features and diagnose of malaria. CDROM: Up To Date 8,3,2000.
2. Procop GW, Persing DH. Malaria and babesia. In: Wilson WR, Sande MA, Drew WL, et al, editors. Current diagnosis and treatment in infectious diseases. New York: Lange Medical Books/McGraw-Hill Medical Publishinng Division; 2001. p.793–806.
3. Wilairatana P, Looareesuwan S, Walsh DS. Chemotherapy of cerebral malaria. Current recommendations for treatment and prophylaxis. Adis International Limited All rights reserved.CNS Drug 1997;May 7(5):366-80.
4. Looareesuwan S, Chongsuphajaisiddhi T. Malaria. In: Looareesuwan S, Wilairatana P, editors. Clinical tropical medicine I, Department of clinical tropical medicine and hospital for tropical diseases, faculty of tropical medicine. Bangkok, 1994, 1-52.
5. Wilairatana P, et al. Treatment of malaria acute renal failure by hemodialysis. Am.J Trop Med Hyg 1999;60(2):233–7.
6. Miller KD. Treatment of malaria in the united states with a continuous infusion of quinidine gluiconate and exchange transfusion. N Engl J Med 1989;321:65-70.
7. Olliaro P. Artemisin derivatives in the treatment of severe malaria. In the cochrane libray 1998;3. Update Software, Middleway, Oxford OX2 7LG.