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Fatal Cerebral Malaria with Multi-Organ Dysfunction and Oleander Poisoning

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Abstract

Cerebral malaria is a clinical manifestation of the brain during *Plasmodium falciparum* infection, which may lead to fatal outcomes if left unattended or delayed in therapeutic management. It is often accompanied by multi-organ complications such as renal failure, respiratory distress, jaundice, severe anemia etc., further raising the degree of mortality. Over the years, the management of severe and cerebral malaria has improved radically but still the mortality rate in severe malaria is worrysome. An extremely uncommon case is demonstrated here, which is a classical illustration of malarial death due to CM and multi-organ dysfunction; complicated due to an episode of Oleander poisoning amidst. Falciparum malaria can have myriads of clinical presentations which may co-exist with other pathologies which is challenging for the clinicians, therefore, a high degree of suspicion followed by early diagnosis of malaria, may be more frequently pronounced in healthcare settings in malaria endemic areas to improve overall outcome and better management of malaria control programs.

Keywords: *Plasmodium falciparum*; Cerebral malaria; Multi-organ dysfunction; Oleander poisoning

Background

Plasmodium falciparum infection affects almost half of the world population, with around 660,000 human fatalities annually [1]. This clinical scenario is most common in endemic countries Africa and Southeast Asia including the Indian subcontinent. Development of associated organ and metabolic complications is the hallmark of falciparum malaria [2]. While hypoglycemia, severe anemia and metabolic acidosis may be more commonly manifested in children; the major organ complications *viz.* cerebral malaria, jaundice, acute renal failure and acute respiratory distress syndrome etc. are mostly seen in adults although considerable amount of variability in Africa and Southeast Asia including India is acknowledgeable [3,4]. Of these listed WHO defined severe complications, cerebral malaria (CM) is one of the dreaded organ complications of the brain and lack of intervention can lead to fatal outcomes [5,6]. The degree of fatality can be even more and may be predicted [7] but nevertheless, the chance of survival is deemed feeble, with addition of other severe complications of malaria. Over the years, the management of severe and cerebral malaria has improved radically due to early diagnosis and prompt therapeutic intervention and other malaria eradication programs [2]. However, the mortality in severe malaria has remained almost consistent since implementing the management everywhere including the healthcare units in resource limited settings is always a great task; as facilities may not be available or limited at the point of care [8]. Cerebral malaria along with multiple organ complications at times may pose significant challenge for the clinicians with atypical signs and symptoms and similar to other co-morbid disease or pathologies [9,10].

We demonstrate here an uncommon case report of a patient admitted to the intensive care unit due to oleander (Nerium oleander) poisoning and uneventfully recovered without having any neurological deficit; however got readmitted within 24 hours and subsequently died due to cerebral malaria and other organ and metabolic complications. This unique case is reported from the study site Ispat General hospital, a tertiary care industrial hospital at Rourkela, situated in the western part the state of Odisha, India which is a well characterized falciparum endemic region as per several epidemiological, molecular, and hospital based studies [3,11-13].

Case Report

A 50 year old male was admitted to the intensive care unit of with loss of consciousness for 12 hours and having passed scanty and cola colored urine no history of fever (98.40 Fahrenheit) and no convulsion, fever or vomitting. Interestingly, this patient who belonged from a tribal community was admitted for oleander (Nerium oleander) ingestion and poisoning; was treated with temporary pacemaker for heart block with uneventful recovery and discharged from the hospital just 16 hours ago.

On examination, Glasgow coma score was 3/15; temperature 98.4°F, pulse 100/min regular, blood pressure of 90/100 mmHg, respiratory rate 20/min and was moderate to grave icterus. Per abdominal examination revealed hepato-splenomegaly. Chest was clinically clear, heart sounds were normal without any murmur. CNS exam revealed his pupil was equal, reacting to light and eye was conjugate deviation of eye. Detailed cranial nerve examination was not possible due to deep

coma. All deep tendon and superficial reflexes were absent, plantar was flexor. There was no sign of meningeal irritation. Funduscopic examination indicated 1-5 retinal hemorrhages with no papilledema diagnosed. Urine output in 24 hours was measured to be 400 cc dropping down to 20 cc in the next 24 hours.

Rapid Diagnostic test (RDT) was positive for *P. falciparum*, peripheral blood smear showed positive for both *Plasmodium falciparum* asexual and sexual stage of parasite. He was probably was under the incubation period of *P. falciparum* infection while he was being treated for the oleander poisoning as there was no history of fever then. Blood sample for microbiology test showed gross contamination for which any other causes of infection could not be ruled out. HIV, HBsAg, HAV, and HCV tests were negative. Urine sample for microscopic examination revealed presence of pus cells, 10-12 per high power field (HPF) and presence of numerous of red blood cells. There was increase in serum bilirubin (total) 9.3, 6.0 and 4.8 mg/dl indicative of jaundice and hepatic dysfunction. Serum Potassium level was 2.6 indicating severe hypokalemia and he also had severe anemia with hemoglobin 3.8 g% with total leucocyte count of 56,700/cu.mm.

The patient was treated with intravenous artesunate 2.4 mg/kg body weight on 0 hour, 12 hours and 24 hours, 48 hours and 72 hours. Antibiotics (Levofloxacin 750 mg synergistically with Azeteonam 1 g stat followed by 500 mg 8 hourly for suspected uro-sepsis). Patient was given ventillatory support immediately on admission for respiratory distress (PaO_2/FiO2: 181Todd's unit) and was having inadequate O2 saturation in spite of oxygen therapy. Blood transfusion (3 units) was given to the patient; and peritoneal dialysis was done since serum creatinine level increased from 3.8 to 6.5 mg/dl and severe oliguria but since he was on ventilator, it was logistically difficult to be taken to the haemodialysis section. Despite the optimal care and management, the patient's condition deteriorated and he died after 74.5 hr of admission due to CM, acute renal failure, severe anemia, severe hepatic dysfunction, respiratory distress, electrolytic imbalance manifested as hypokalemia and probable urosepsis.

Discussion

Malaria still remains the main killer disease in Southeast Asia next to Africa. If patients have cerebral malaria with multiple organ dysfunctions such as severe anemia, acute renal failure, jaundice, which high-risk indicators, the disease prognosis worsens [8,14] even after ensuring optimal intensive care and life-support systems such as ventilators etc. Typically in cerebral malaria cases, the patient is often presented in hospitals with unrousable coma, with or without convulsions and seizures; and the treatment may be easily complicated due to other co-morbid pathologies affecting the overall outcome [10,15] as in this case was the episode of oleander poisoning. More importantly, the coma can even persist along with other complications till several days, although peripheral parasitaemia may have cleared [2]. Pathogenesis of cerebral malaria is multi-factorial and a dynamic process where the present scientific understanding is argued to be incomplete; though advanced imaging techniques and newer diagnostic tools and biomarkers have started to pave the way forward [16,17]. According to the most established hypotheses, CM usually results due from the sequestration of infected erythrocytes (IEs) which binds to host endothelial receptor leading to microvascular circulatory obstruction and clogging, whereas the decreased deformability of IEs, rosette formation by uninfected RBCs and clumping (via platelets). The inflammatory cytokine release then result in brain endothelial injury leading to tissue hypoxia, increased permeability and dysfunction of the blood-brain-barrier with intracranial hypertension and brain oedema [16,18,19]. The absolute cause of death however, in this case, may apparently be attributed to cerebral malaria along with acute multi-organ failures, however it may not be ruled out that the poisoning episode didn't aggravate his overall clinical condition.

In fatal malaria cases, record of important parasites stage e.g. trophozoites, schizonts, phagocytosis events along with free-floating forms and hyperparasitemia are considered risk factors for severe and fatal malaria [20,21]. Such prognostic indicators usually may indicate the severity at a very early stage leading to prompt therapeutic response and management. In the present case, the microscopic examination confirmed that the patient had P falciparum gametocyte forms besides asexual stages indicating an advanced stage of the infection, suggesting that an early diagnosis of the patient followed by swift therapeutic intervention could have had a favorable outcome [22]. This may be corroborated from earlier reports from the state that shows multi-organ dysfunction in malaria may develop fulminantly within 24-72 hours from the onset of fever, however may be even delayed as well [23]. Nonetheless, the Oleander poisoning episode amidst as a co-morbid condition might have subsided the typical signs and symptoms of falciparum malaria, or the patient probably had asymptomatic falciparum malaria with apparently no clinical signs and the poisoning occurred meanwhile - which aggravated the already sequestered parasites in internal organs leading to manifestation of the severe malaria complications off late.

Collectively, the present report illustrates a classical example of malarial death due to CM and multi-organ dysfunction; complicated amidst by a unique episode of Oleander poisoning. Falciparum malaria can have myriads of presentations which can co-exist with other pathological conditions, therefore a high degree of suspicion and ruling out malaria by early diagnosis may ensure better outcome in endemic areas [2,24].

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