LIFE-THREATENING PLASMODIUM FALCIPARUM MALARIA IN PATIENT AFTER VISITING ANGOLA-CASE REPORT

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TEŠKA FORMA PLAZMODIJUM FALCIPARUM MALARIJE KOD BOLESNIKA KOJI JE BORAVIO U ANGOLI-PRIKAZ SLUČAJA

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ABSTRACT

Malaria is a potentially life-threatening disease, especially when complicated by a septic shock. It is caused by infection of erythrocytes with protozoan parasites of the genus Plasmodium that are inoculated into the humans by a feeding female anopheline mosquito. Of the four Plasmodia species, infection with Plasmodium (P.) falciparum is oftenassociated with different types of complications and significant mortality. Most imported cases of malaria are not in tourists but in immigrants and their children who have returned to the country of their family's origin to visitfriends and relatives (so-called VFR travelers) and have forgone chemoprophylaxis.

We described a case of a 52 year old patient who came from Angola, an African country with endemic malaria before the occurrence of the first symptoms of the disease. The first symptoms were not recognized by the presence of nonspecific symptoms. Very soon the patient was gone under the hemodynamic unstability that eas followed by shock and high percentage parasitemia of 25%. A global health disorder was developedaccompanied withhemodynamic instability and cerebral dysfunction. He performs pulmonary ventilation disorder and renal failure. Only data from social epidemiological survey of travel to the African country, was sufficient to cast doubt on malaria. The diagnosis was conducted using the standard method - peripheral blood smear. After turning antimalarial drugs, improvement of health status with complete recovery within 10 days was noticed. The only consequence of the disease is persistent hypertension that is sensitive to standard antihypertensive therapy.

Keywords: *P.falciparum malaria, cerebral dysfunction, antimalarial drugs, chemoprophylaxis*

SAŽETAK

Malarija je jedna odnajtežih zaraznih bolesti,posebno ako se komplikuje septičnimšokom.Karakteriše se ponavljanim napadima groznice zbog sinhronizovanog raspadanjaeritrocita, zaraženihjednom ili više vrsta parazita iz rodaPlasmodium. Od četirivrsteroda Plasmodium, infekcijaP. falciparum je često povezana sa različitim komplikacijama i značajnim smrtnim ishodom. Većina importovanih slučajeva malarije nisu turisti, većimigranati ili radnici koji rade u endemskim područjima supsaharske Afrike,koji nisu koristili lekove za hemoprofilaksu.

U ovom radu prikazan je slučaj bolesnika, starosti 52 godine sa teškom kliničkom slikom malarije koji je doputovao iz Angole,gde je malarija endemska bolest.Prvi simptomi bolesti u vidu tempereture i groznice nisu bili pravovremeno prepoznati, tako da u daljoj evoluciji bolesti razvija se hemodinamska nestabilanost , šokno stanje sa multiorganskom insuficijecijomi visokim procentom parazitemije od 25%.Dolazi do razvoja respiratorne i bubrežneinsuficijencije sa razvojem DIK-a uz poremećaj stanja svesti. Podaciiz socio-epidemiološe anamneze o putovanju u afričke zemlje, su ukazali na sumnju na malariju. Dijagnoza je potvrđenaperifernimkrvnimrazmazom kao standardnommetodom. Nakon uključivanja antimalaričnе terapije, uz intenzivnu potpornu terapijuusledilo je poboljšanje zdravstvenog stanja sa potpunim oporavkom u roku od 10 dana. Kao posledica bolesti registrovana je hipertenzija, koja je lečena standardnom antihipertenzivnom terapijom.

Ključne reči: *P. falciparum malaria, cerebralna disfunkcija, antimalarici, hemoprofilaksa*

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INTRODUCTION

Malaria is an important cause of illness in children and adults, especially in malaria's endemic areas. It is caused by infection of erythrocytes with protozoan parasites of the genus Plasmodium that are inoculated into the humans by a feeding female anopheline mosquito. In non endemic areas, this clinical entity is rare and locally acquired infections. Reports from the National Vector Borne Disease Control Programme (NVBDCP) have indicated that around 1.8 million cases of malaria and 1,000 malaria-related deaths occur annually in the country (1). However, the World Health Organization (WHO) estimates that there are about 20 million cases of malaria and 15,000 deaths annually in India. (2)

The signs and symptoms of malaria are nonspecific. Malaria is clinically suspected mostly on the basis of fever or a history of fever. Diagnosis based on clinical features alone has very low specificity and results in over-treatment. Other possible causes of fever and the need for alternative or additional treatment must always be carefully considered. Clinical suspicion of malaria should be confirmed with a parasitological diagnosis.

Of the four Plasmodia's species, infection withPlasmodium (P.) falciparum is oftenassociated with different types of complications and significant mortality. Most imported cases of malaria are not in tourists but in immigrants and their children who have returned to the country of their family's origin to visit friends and relatives (so-called VFR travelers) and have forgone chemoprophylaxis. (3-6)

Malaria is clinically suspected mostly on the basis of fever or a history of fever. Diagnosis based on clinical features alone has very low specificity and results in over-treatment. Clinical suspicion of malaria should be confirmed with a parasitological diagnosis.

The primary objective of antimalarial treatment in severe malaria is to prevent death, but prevention of neurological deficit is also an important objective in treating cerebral malaria. Most of the countries where *P. falciparum* isn't endemic have progressively updated treatment policies from the artemisinin based combination therapies (ACTs); this is the best current treatment for severe form of disease complicated especially for cerebral dysfunction.

CASE REPORT

A previously healthy 52-year-old caucasian man was admitted to the Department of infectious and tropical disease in the Clinical center of Kragujevac, Serbia, due to high fever (39°C), shivering and confusion. Epidemiologically, he left Angola two months before the onset of the first signs of disease. During his two-years' staying in this African country, he used chemo-prophylaxis against malaria, although a disease was endemic in most of the African countries. Specific chemo-prophylaxis was not conductedlast six months before onset of the disease. After the first signs and symptoms were registered, the patient was unsuccessfully treated by macrolide 500 mg daily and aminoglycoside antibiotics. Very soon, reduced exercise tolerance that followed sweating and high fever was noticed.

Laboratory evaluation revealed the white blood cells of 10.4 x 10^9/L , with neutrophils (85.5%), red blood cells of 2.39 x10^{12}/L, hemoglobin of 74 μmol/L, lactate dehydrogenase of 2446 U/L), indicative of ongoing hemolysis. Procalcitonin and C-reactive protein (CRP) were markedly elevated (7.77 μg/L and 99.7 mg/dL, respectively) and the patient showed severe thrombocytopenia (thrombocytes' value of 7x10^9/L) with signs of petechial haemorrhage . In blood analysis, there was a sign of fibrinolysis (D dimer was 15 687). Other blood tests were normal.

The X-ray chest radiograph on admission (PA view) was normal.

The P. falciparum parasites were detected using microscopical examination of a thick blood film and parasitemia of 25% of parasites's infected erythrocytes was noticed.

The somnolence with generalized convulsions were developed several hours after the admission and the patient was admitted in Intensive Care Unit (ICU) of the Clinic. The cerebrospinal fluid (CSF) contained 300 mg per deciliter of protein and 3 100 mg per deciliter of glucose. After he had been admitted in ICU, severe respiratory failure has been detected. The patient was undergone invasive mechanical ventilation with 10 l by minute of pure oxygen therapy. Laboratory findings that suggested on acute respiratory failure were saturation under 86%, oxygen partial pressure of 6.2 kPa and carbon partial pressure of 4.8 kPa. The X-ray chest radiograph after diagnosed respiratory failure showed diffuse emphasized of the lung parenchyma and hila. A mechanical ventilation was immediately initiated under analgesia and sedation with propofol and sufentanil. The patient was breathing spontaneously by means of pressure support of 15 to 20 mmHg and a positive endexspiratory pressure of 5 mmHg. The shock was treated with fluid resuscitation according to the concept of early goal directed therapy.

In the ICU, a central venous catheter was inserted into the right jugular vein and a catheter for pulse contour analysis and continuous hemodynamic measurement was placed into the left femoral artery. A computed tomography (CT) scan of the brain showed no signs of bleeding, ischemia or edema. Due to increased myoglobin levels, increased blood urea nitrogen (value of 49,7 mmol per liter) and creatinine (value of510 μmol per liter), the subsequently developed renal failure, renal replacement therapy was initiated via continuous venovenous hemodiafiltration (CVVHDF).

The drug mefloquine was orally administered in association with artemisinin in dose of 80 mg twice daily. The next day, the parasite load of 25% on admission decreased to 20%. The parasite load decreased to 15% the next day. The extremely high scores (Acute Physiology and Chronic Health Evaluation II, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment) on the day of

the shock improved gradually within thefifth day of orally administered antimalarial drugs. Mechanical ventilation was discontinued on day 7, and continuous dialysis was replaced by intermittent dialysis.The following day the hemodynamic status of the patient stabilized with a raise of SBP to 180 mmHg respectively and the heart rate was 90 beats/min. Laboratory data showed increased thrombocytes ($51x10^9$/L), decreased D-dimer (4854), and improved parameters of renal function.At the time of discharge (after 10 days of hospitalization), renal function had been resumed and thus there was no need for further dialysis. As a consequence of P. falciparum malaria, mild hypertension was registered that was sensitive on standard antihypertensive medications.

DISCUSSION

The consequences of infection with *P. falciparum* range from asymptomatic parasitemia to severe and often fatal malaria. Repeated malaria infections lead to gradual acquisition of immunity in regions where it is endemic, but the mechanisms of antimalarial immunity remain poorly understood. In addition, the reasons why some infections progress from asymptomatic parasitemia to uncomplicated febrile illness and others to severe clinical manifestations are unclear (7).

We described an unusual case of a patient with malaria in which high parasitemia resulted in a positive thick blood film. Many clinical examinations as well as clinical records described the cases ofmalaria with parasitemia being 1.8% to 10% (8, 9). There is no consensus on what constitutes 'hyperparasitaemia'.Hyperparasitaemia in itself does not necessarily have major prognostic significance in semi-immune individuals (individuals living in an endemic area and exposed to malaria several times). The individuals with some antimalaria immunity can often tolerate high parasite counts without severe effects. However, in non-immune travellers, the parasitaemia is often an indicator of potentially severe disease (9), and levels as low as 2% may be considered in some cases as the prelude to severe disease. In our case report a parasitemia amounted to 25%, which is different from many other clinical presentations. At the time of presentation in our emergency room, the patient suffered from severe malaria. He was severely confused and during the first hours his hemodynamic and respiratory status became deteriorated. Despite of his unstable status, the patient showed biochemical features indicating a poor prognosis, amongst others a very high parasite load, respiratory and renal failure as well as disturbance of consciousness.

Procalcitonin, which was found to be pathological during or even prior to sepsis, was extremely high on admission in the ICU. After several hours from admissionthe patient developed a shock. The frequency of shock on admission to a hospital in patients with severe malaria is 7.7% , and is up to 21.5% in hospitals with ICUs, that are specialized in the treatment of infectious diseases (10).

The first symptoms of malaria (most often fever, chills, sweats, headaches, muscle pains, nausea, and vomiting) are often not specific and are also found in other diseases (such as influenza and other common viral infections). Likewise, the physical findings are often not specific (elevated temperature, perspiration, tiredness). These are the reasons why the disease in this patient did not initially recognized. The therapy, thus, was not administered properly in the beginning of the disease. Furthermore, the most important information of relevance for the diagnosis of malaria is the history of travelling to the African country where the malaria is epidemic disease. The social epidemiological survey from the disease's history shows a critical risk factor for the disease. In severe malaria (caused by P. falciparum in our case), clinical findings (confusion, coma, neurologic focal signs, severe anemia, respiratory difficulties) are more striking and may increase the suspicion index for malaria. Therefore the first diagnostic procedure for detection of malaria was done - a thick blood film examination.

The primary objective of antimalarial treatment in severe malaria is to prevent death. In treating cerebral malaria, prevention of neurological deficit is also an important objective. The cause of death in severe P. falciparum malaria is often multi-factorial, but shock is one of the leading causes, a fact that forces us to adapt a quick and sophisticated treatment approach towards the critically ill patient.

Unrousable coma may persist for up to 72 h in children and longer in adults. Long-term neurological sequelae of cerebral malaria have been reported in African children and also in non-immune travellers. Patients who are unconscious should be nursed in the appropriate position, their stomach drained with a nasogastric tube with an endotracheal tube inserted. Regular neurological observations should be recorded. Mechanical ventilation may be necessary to reduce intracranial pressure.

A relationship between the cardiac event and the parasite challenge and/or its treatment seems probable, especially because of the chronology of the event and the absence of an alternative explanation. Thecardiac complications are extremely rare in malaria. To date, myocardial infarction during or after naturally acquired *P. falciparum* infection has not been reported, neither in hundreds of millions of endemic cases, nor in hundreds of thousands military troops that were temporarily deployed to endemic areas. In our case, only cardiovascular complications that raised from malaria was hypertension that was sensitive on standard antihypertensive therapy.

CONCLUSION

Severe imported malaria still carries a relatively high mortality rate, even when treated under optimal conditions in a highly experienced ICU. Although WHO criteria are not all relevant to imported malaria in adults, the presence in the emergency room of any degree of neurologic,

acid-base, circulatory, or pulmonary failure should lead to ICU admission. Bacterial coinfection is not infrequent and may contribute to death. Finally, it should be kept in mind that most of our patients did not take appropriate malaria chemoprophylaxis. Thus, the best way to reduce the number of deaths caused by imported malaria is to improve the quality of prevention.

Every febrile patient with a history of travel to the regions where malaria is endemic (tropical regions for the world, southeast regions for our country) should raise the suspicion of malaria.

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