Severe Subconjunctival Hemorrhage: An Uncommon Ocular Manifestation of Malaria Induced by Antimalarial Drug - A Case Report

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Abstract:

Malaria is a major public health issue in many parts of the world, particularly in sub-Saharan Africa, where it accounts for a significant burden of morbidity and mortality. In Sudan, the disease is endemic and poses a serious health risk to the population. We present a case of severe malaria caused by *Plasmodium falciparum* in an 18-year-old male who presented with fever and headache. Despite initial treatment with antibiotics and antimalarials, the patient's condition deteriorated, and he developed severe anemia and subconjunctival hemorrhage. This case highlights the importance of early and accurate diagnosis, prompt treatment, and ongoing monitoring of patients with malaria to prevent the development of severe complications. It also underscores the need for increased efforts to control and eradicate malaria in endemic regions, including improved access to effective antimalarial drugs and the development of effective prevention strategies. Un-

derstanding the clinical presentation and management of severe malaria is critical for reducing the burden of this deadly disease in affected populations.

Key words:

Malaria, *Plasmodium falciparum* , ocular manifestations, Sudan

Introduction

Malaria is a global public health threat, particularly in tropical and sub-tropical countries [1]. The majority of malaria episodes reported annually worldwide are from the Sub-Saharan African countries including Sudan [1,2]. Unfortunately, Sudan suffers from several infectious diseases with overlapping symptoms creating additional challenges in the case definition and management [3–6]. This delay in identifying the cases, reporting, and management is contributing to the increase of malaria burden [7–9]. In Sudan, the national malaria treatment guidelines recommend using Artesunate/Lumefantrine as a first-line treatment for uncomplicated falciparum malaria, and Artesunate or Quinine for treating the severe infections [10]. This case report presents a severe subconjunctival hemorrhage due to severe consecutive vomiting that was induced by the intake of artemether/lumefantrine for malaria treatment.

Case presentation:

A18-years-old male, from Khartoum state, presented to the outpatient clinic on August 19$^{\text{th}}$ 2020 with fever and headache for 10 days during which he received cefixime 400 mg orally once a day (OD). Two days later, fever attacks continued progressively and the patient was further investigated for malaria infection which turned to be negative for malaria parasites using rapid diagnostic test. The patient did not show any improvement. On the initial clinical examination, he looked pale, fatigued, and not jaundiced or cyanosed. He was febrile (axillary Temp 39°C) and restless. His pulse rate was 130/min with normal volume and character. His respiratory rate was 18/min, and his blood pressure was 120/80 mmHg. The patient was not suffering from any chronic illness and had he is not addicted to drugs or any hypnoid or had any prolonged febrile illness over the last year. Clinical investigations of heart and abdomen were normal. The hematological investigation revealed severe anemia (Hb 7.1 gm/dl). Microscopic examination of thick and thin blood smears, performed at the day of admission was positive for *P. falciparum* . DNA from the blood was isolated and the 18S RNA region was amplified for detection of *P. falciparum* using the previously protocol [5]. The result confirmed a current infection with *P. falciparum* .

It is noteworthy that the patient had recently traveled from Khartoum state to El-Gezira state, an area known for a high transmission rate of malaria. [5]. The patient was not successfully treated with the initial malaria treatment artemether 80mg/lumefantrine 480mg (Comether®). Following the intake of the treatment, the patient suffered from a severe vomiting. After 4 days i.e., 19$^{\text{th}}$ of August, the patient was admitted to the medical health center for further examination. More importantly, he showed up with extraordinary reddish eyes indicating severe subconjunctival hemorrhage (Figure 1A).

Further health concerns were considered and investigated accordingly, and the patient tested negative for COVID-19, HBsAg, Anti-HCV, HIV-1 and HIV-2. Also, IgM antibodies for dengue virus, Rift valley fever and yellow fever virus were not detected. The ECG, ultrasonography of abdomen, and Chest X-ray were normal and no abnormality of the head CT scan. Urine analysis showed mild hematuria and microscopic examination of malaria infection was positive for *P. falciparum* . Considering the recent medical treatment, the patient was administered artesunate injections for 4 consecutive days (2.4 mg/kg, supplied with 12 mL of sterile 0.3 M pH 8.0 sodium phosphate buffer).

After the successful treatment course of artesunate, the patient was further investigated for the presence of malaria parasite, both microscopically and PCR assay. Both tests were negative, indicating a complete clearance of the parasite while the subconjunctival hemorrhage was still present. The patient's blood pressure was 120/80 mmHg, pulse rate 110 beats/min, regular and respiratory rate was 18 breaths/min. Ophthalmic examination of the patient showed a visual acuity of 6/18 in both eyes with history of poor vision and family

history of hypertension and diabetes mellitus type 1. Local examinations of the lid, cornea, iris, lens and fundus of both eyes were normal.

After 30 days of follow up, the patient became healthy with normal hematological parameters including Hb 12.1 gm/dl, total leukocyte count was 5800/mm3 and platelet count 175000/mm3. C-reactive protein (CRP) was <6 mg/dL. The patient recovered his normal vision and the subconjunctival hemorrhage was completely absorbed (Figure 1B).

Discussion:

Malaria remains a significant public health issue [11], and complications associated with the disease can be severe and potentially life-threatening [12]. This case report highlights the challenges of diagnosing and treating malaria in a young, previously healthy male who presented with fever, headache, and progressive illness. The patient was firstly given a wrong medication i.e cefixime, and thus the symptoms did not improve, and further investigation revealed severe anemia, low platelets, and ultimately a positive diagnosis of *P. falciparum*malaria through microscopic examination of blood smears and PCR testing. Importantly, the patient had recently traveled to an area known for high malaria transmission, underscoring the need for providers to consider travel history and geographic risk factors in the evaluation of febrile illness [12,13].

The patient's subconjunctival hemorrhage was an unexpected complication, which may have been related to the malaria infection, the prior treatment with artemether/lumefantrine, or some other underlying factor. The negative test results for other infectious diseases and imaging procedures, such as head CT scan, echocardiography, ECG, and chest X-ray, suggest that the subconjunctival hemorrhage is unlikely to have resulted from any other identifiable underlying cause. Nonetheless, this case report underscores the importance of careful monitoring and follow-up of patients who present with malaria, as well as the need for further research into the full range of potential complications associated with this disease. The subconjunctival hemorrhage usually occurs when a tiny blood vessel underneath the conjunctiva breaks and often occurs without any obvious trauma to the eye. The main causes of the subconjunctival hemorrhage are not always known. However, trauma, violent coughing and sneezing, straining, or severe vomiting can lead to the break of the small blood vessels underneath the conjunctiva [14].

Ophthalmic changes due to malaria infection were mainly attributed to retinal hemorrhage which were frequently observed in *P. falciparum* infection, particularly with cerebral malaria in children; but uncommon in non-cerebral malaria [14]. Malarial retinopathy includes various retinal changes and signs including retinal whitening, vessel changes, retinal hemorrhages and papilledema [15]. The visual defects are usually reversible with complete recovery after treatment; but may rarely be irreversible [16]. Retinal hemorrhage is usually absorbed spontaneously over the period of one to four weeks without retinal sequelae and visual defect improved completely after successful treatment of malaria [17]. Few cases have been reported with irreversible visual defects [16]. While presented here in this case, subconjunctival hemorrhage was observed to be mainly induced by the vomiting which was initiated by the drug artemether/lumefantrine. This suggestion was also supported by the normal retinal investigation which excluded the red blood cells sequestration phenomena that induced the retinal hemorrhage signs, and also the stopping of the vomiting episodes after discontinuing the drug.

Pharmacovigilance studies (PV) were known to be the formal way of investigating treatment outcomes in patients and further follow up without severe adverse events [18].

It is worth mentioning that PV studies confirmed the effectiveness of artemether/lumefantrine in Sudan [19]. However, no any adverse events were noted, meanwhile, supporting the assumption of drug quality which was provided by the WHO [20]. The current case supports the assumption of the physiological outcomes of the currently used drug, since the internationally recommended dose of artemether/lumefantrine for patients (weight > 34 kg) is 40 mg artemether and 240 mg lumefantrine. Sudan malaria treatment protocol is based on the use of the higher recommended dose (80 mg artemether and 480 mg lumefantrine) [20].

One area in which this case report provides useful insights is in the inability of the initial treatment with

artemether/lumefantrine to clear the patient's malaria infection highlights the importance of following established protocols for managing falciparum malaria. The use of artesunate injections for four consecutive days, in accordance with WHO guidelines, was able to clear the patient's infection, while providing a safer and more effective alternative to the initial treatment used.

Declarations

Ethics approval and consent to participate

Written, informed consent to publish history, findings, and images for educational purposes were obtained from the patients.

Consent for publication

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not Applicable.

Authors' contributions

NSM, AEA, AA, EES and AMM case management and follow up, EES, AA, NSM and RR, conducted ophthalmic examination and reports, NSM performed the molecular examination, AA , NSM, EES and HS data interpretation drafted the manuscript. All authors reviewed, edited, and approved the final manuscript.

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Key clinical message:

This case highlights the importance of considering travel history and geographic risk factors in the evaluation of febrile illness. It also emphasizes the need for appropriate antimalarial treatment protocols, as well as the potential for unusual complications such as subconjunctival hemorrhage, which should be closely monitored and further investigated in patients with malaria.

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Figure Legend:

Figure 1: A; Subconjunctival hemorrhage in a malaria patient following artemether/lumefantrine intake which led to severe consecutive vomiting. **B;** resolving of the subconjunctival hemorrhage after successful treatment with artesunate.

A

B