A Severe Case of Falciparum Malaria, 10 Years After Malaria Eradication: A Case Report

Shadan Jabbar Abdullah, Darya Saeed Abdulateef, Heshu Sulaiman Rahman, Safeen Othman Mahmood, Vyan Nasih Mustafa, Rezhin Omer Ahmed, and Rawand Aso Ahmed

Malaria is a major mosquito-borne public health problem especially in tropical countries. The authors report a malaria infection in a 31-year-old man who had returned from East Africa with developed fever and rigor. Because of his thrombocytopenia, decreased hemoglobin, elevated liver enzymes, and splenomegaly, and because of failure to question about recent travel history, he was initially referred to the hematological hospital and medical staff suspected a hematological problem, so he was investigated for bone marrow aspirate and biopsy. As he progressively deteriorated, and after retaking history, his relatives eventually came to mention their travel to Africa. Blood samples were sent to detect malarial parasites, but the results were negative. When an internist was consulted, the patient was drowsy with low oxygen saturation (SpO2), so he was intubated and put on continuous positive airway pressure (CPAP). The internist suggested empirical anti-malarial treatment, which improved the clinical and hematological conditions of the patient. However, the repeated thin blood film showed falciparum malaria ring-shaped trophozoites. The patient persisted with the same treatment for 1 week until his condition improved gradually and completely stabilized, and then he was discharged. Presentation of this case of malaria is crucial to outpatient clinics’ proper referral of cases, as is encouraging the physician to think of malaria as a cause of fever and rigor even in countries with eradicated malaria and to insist on mentioning travel history. It is also imperative, in the case of sustaining fever with further deterioration of the patient after proper antibiotic use, to start empirical anti-malarial treatment immediately.

Keywords: Malaria, Plasmodium falciparum, hospitalization, travel history, imported case, Iraq

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine transaminase; Anti-PR3, Anti-Proteinase-3 Antibody; ANCA, Anti-neutrophil Cytoplasmic Antibody; AST, Aspartate transaminase; BP, Blood Pressure; CBC, Complete Blood Count; CCHF, Crimean-Congo Hemorrhagic Fever; CMV, Cytomegalovirus; CPAP, Continuous Positive Airway Pressure; CRP, C-reactive protein; CV, Cardiovascular; CXR, Chest X-ray; EBV, Epstein-Barr Virus; ECG, Electrocardiogram; ESR, Erythrocyte Sedimentation Rate; GCS, Glasgow Coma Scale; GUE, General Urine Examination; Hb, Hemoglobin; ICU, Intensive Care Unit; IgG, Immunoglobulin G; IgM, Immunoglobulin M; INR, International Normalized Ratio; IU, International Unit; IV, Intra-venous; LDH, Lactase Dehydrogenase; LN, Lymph Node; LOC, Loss of Consciousness; LP, Lumbar Puncture; MPO, Myeloperoxidase; PANCA, Perinuclear Anti-neutrophil Cytoplasmic Antibody; PT, Prothrombin Time; PTT, Partial Thromboplastin Time; RBC, Red Blood Cell; RBS, Random Blood Sugar; RR, Respiratory Rate; SpO2, Oxygen saturation; TSB, Total Serum Bilirubin; TTP, Thrombotic Thrombocytopenic Purpura; Uls, Ultrasound; WBC, White Blood Cells; WHO, World Health Organization.

Copyright © 2021
BACKGROUND

Malaria is a life-threatening disease that is transmitted to humans mostly via bites of a female *Anopheles* mosquito, which carry *Plasmodium* parasites [1]. In 2018, more than 400,000 deaths were reported from malaria worldwide [1]. It occurs mostly in areas where the mosquito has a longer life span, such as Africa. Climatic effects like humidity, rainfall, and temperature all have a role in the transmission of this disease. It mostly affects young children, especially in African Regions (where WHO accounted for 93% of all malaria cases in 2018 [1,2]) and other malaria-endemic regions like the Southeast Asia and Western Mediterranean Regions (where immunity was at least partially developed). Meanwhile, in a non-endemic area, all ages of individuals are vulnerable to a malarial infection. This is especially true for those who are migrating to endemic areas, including frequent travelers and refugees [1].

A major outbreak in Iraq occurred in the 1960s when 11,878 cases were recorded by 1965. The second major outbreak in Iraq was in 1995, when the reported cases reached 39,000. Malaria can be prevented in any country with proper prevention planning and action. In this regard, in 2009 the Iraqi Ministry of Health announced that Iraq was free of malaria after a long battle with the disease [3]. However, since then, a few cases are recorded every year in some Iraqi cities [4-6]. However, to the best of our knowledge, none of them were reported in Sulaimaniyah city, Kurdistan region, Northern Iraq.

Malaria infection is curable, but if it is not diagnosed early it may lead to severe disease with a high rate of complications, such as multi-organ failure or even death. Fever and associated rigor and headache are among the early symptoms of malaria infection. These may be very mild, making it quite difficult to differentiate from other less severe infectious diseases that present with fever. Travel history is a very important factor to be considered for diagnosis, especially in cases of fever and rigor, as conversion to more severe disease mostly occurs when the patient did not disclose, or has denied, traveling to an endemic area in the stated travel history. This could lead to delay in the diagnosis and treatment of the disease [1,7]. Five species of *Plasmodium* parasite affect humans; among them, *P. falciparum* and *P. vivax* are the most life-threatening species [1]. A high rate of morbidity and mortality were recorded with *P. falciparum* infection [8]. In severe cases, intravenous administration of the anti-malarial drug is a critical part of disease management [9,10].

CASE PRESENTATION

A 31-year-old male visited Shorsh Hospital (in Sulaymaniyah, Iraq) Outpatient Clinic on September 6, 2019, complained of fever and rigor for two consecutive days. After clinical examination, some laboratory investigations (Table 1), and without questioning about travel history, the physician referred him to Hiwa Hematology/Oncology Hospital for further investigations and confirmation of the causes of his thrombocytopenia.

Once the patient had been admitted to Hiwa Hematology/Oncology Hospital on September 7, 2019, he complained of malaise, intermittent fever, and rigor with sweating, headache, and dizziness. Moreover, nausea without vomiting, anorexia, and weight loss of 5.0 kg in 10 days were reported by the patient.

On clinical examination by an expert clinician, yellow discoloration of the skin and sclera were noted, but there was no itching, skin rash, or abdominal pain, and bowel motion and urination were reported to be normal. On September 8, 2019, the laboratory tests were repeated, and the results of some tests had fluctuated drastically (Table 2). Chest X-ray (CXR) and Ultrasound (Uls) of the neck and axilla were normal. However, abdominal Uls revealed splenomegaly with a long axis of 17.2 cm.

His blood film appeared normochromic and normocytic with mature cells but a moderately reduced number of thrombocytes. On the same day, he received the following treatments: 500 ml of glucose saline infusion, Piperacillin/Tazobactum (4.5 g vial, four times daily intravenously (IV)), omeprazole (40 mg vial, daily by IV infusion), and paracetamol bottle (100 mg, IV infusion, three times daily).

On September 9, 2019, his hemoglobin (Hb), White Blood Cell (WBC), and platelet counts were 10.9 g/dl, 6.6 x10^9/L, and 19 x10^9/L, respectively. The next day, the values of Hb, WBC, platelets, and lymphocytes were 9.2 g/dl, 4.6 x10^9/L, 14 x10^9/L, and 26%, respectively. However, his albumin (3.4 g/dl), Alanine aminotransferase (ALT) (48 IU/L), and Aspartate aminotransferase (AST)
(46.7 IU/L) were normal, while his C-Reactive Protein (CRP) was elevated to 196.7 mg/L. Other tests that came back normal were serum electrolytes, coagulation profiles including international normalized ratio (INR) (1.3), prothrombin time (PT) (16.4 seconds), and partial thromboplastin time (PTT) (33.7 seconds). Negative blood cultures were also recorded.

Similarly, his anti-proteinase-3 (anti-PR3) antibody or antineutrophil cytoplasmic antibody (cANCA), myeloperoxidase antibody (anti-MPO) or perinuclear anti-neutrophil cytoplasmic antibodies (PANCA), and anti-nuclear antibody (ANA) tests, as well as anti-double strands DNA IgG and IgM and rheumatoid factor tests were negative, so he continued the same treatment regimen.

The next day, he was transfused with a single donor unit of platelets (300 ml) because his platelet count was < 20 x10⁹/L. Due to his persistent fever, the new antibiotics (meropenem vial (1000 mg, IV infusion, three times daily) and vancomycin vial (1000 mg, twice daily intravenously), and dexamethasone (8 mg ampule, twice daily)) were prescribed. Upon neurological consultation and examination, he did not present any meningeal or focal neurological signs; he had normal brain computerized tomography (CT) with IV contrast. Lumbar puncture (LP) was avoided due to his thrombocytopenia. Thus, carrying on the using of the same prescribed treatment of meropenem and vancomycin vials was recommended. Simultaneously, the consultation of an expert clinician with qualified internal medicine was suggested to determine the main cause(s) of the patient’s fever.

On his third day of admission at Hiwa Hematology/Oncology Hospital (September 10, 2019), he received another 300 ml of platelets. The case history was retaken, and several questions were asked of him and his brother regarding recent travel history. His brother declared that the patient had a travel history of 16 days to Africa, specifically Mozambique, from August 14 to September 1, 2019). His condition started three days after returning to Iraq.

We discovered that he traveled illegally with his family (his wife and two children) and wanted to pass borders to travel abroad and reach European countries. In Africa, they were captured and separated from each other, and he was jailed for six days in a very dirty room. The room and its equipment were shared with other prisoners, and he was drinking unclean water. Then, his brother stated that the patient had a history of mosquito bites and received a yellow fever vaccine in Mozambique.

With this new information, a blood sample was collected from him and sent for thin and thick blood film preparation to be stained with Gimesa (described by Daice and Lewis [11]) for malaria and leishmaniasis detection. Upon examination of the slides, no parasites were seen, which might be due to the poor slide preparation and too much debris, which might in turn be due to the old blood sample and RBC hemolysis. Hence, the fluorescent microscopy technique was recommended. The patient’s history of yellow fever vaccine, without detection of the malaria parasite, made the physician consider an allergy.

### Table 1. Shows initial laboratory tests of a 31-year-old male patient suspected with malaria infection.

| Sample and/or Test      | Result            | Normal Range      |
|-------------------------|-------------------|-------------------|
| **Blood**               |                   |                   |
| Random Blood Sugar (RBS)| 134 mg/dl         | 70-110 mg/dl      |
| White Blood Cells (WBCs)| 8.6 *10⁹/L        | 3.5-10 *10⁹/L     |
| Lymphocytes             | 9.6%              | 15-50%            |
| Thrombocytes            | 58, 54, and 42 *10⁹/L on three test samples | 100-400 *10⁹/L |
| Granulocytes            | 86.6%             | 35-80%            |
| Mid-range absolute count (MID) | 3.8% | 2-15%            |
| Red Blood Cell (RBC)    | 5.17 *10¹²/L      | 3.5-5.5*10¹²/L    |
| Hemoglobin (Hb)         | 13.6 g/dl         | 11.5-16.5 g/dl    |
| **Serum Electrolyte**  |                   |                   |
| Sodium (Na⁺)            | 136.8 mmol/L      | 136-145 mmol/L    |
| Potassium (K⁺)          | 3.7 mmol/L        | 3.5-5.1 mmol/L    |
| Chloride (Cl⁻)          | 107.3 mmol/L      | 98-107 mmol/L     |
| **Urine**               |                   |                   |
| Urobilinogen            | Positive          | Negative          |
| Protein                 | Positive          | Negative          |
Because of his deterioration, the antibiotics were replaced with Tigecycline vial (50 mg, IV) and Ribavirin (200 mg, capsule). An antiviral medication was added to his treatment due to suspicion of viral hemorrhagic fever. However, no health improvement was seen, and the fever did not subside. His thrombocytes and Hb level decreased progressively, while liver enzymes were elevated. Because of decreased platelet and Hb, with elevated liver enzymes, splenomegaly, and with failure to detect parasites on the blood film, the hematological problem was among the main differential diagnoses, while his bone marrow aspirate and biopsy investigations showed to the yellow fever vaccine as one of the main differential diagnoses.

On September 11, 2019, his Hb (8.5 g/dl) and thrombocytes (21 x10^9/L) decreased significantly, despite two consecutive days of platelet transfusion. Another 300 ml unit of platelets was prepared and transfused. His WBC (5.3 x 10^9/L), lymphocytes, renal function tests, serum electrolytes, amylase, lipase, and ALT were normal. His AST was 64 IU/L with greatly elevated CRP (316 mg/L), and LDH (619 IU/L). Tests for Brucella IgG and IgM were negative. Abdominal Ultrasound was normal except an enlarged spleen (long axis of 18 cm).
normal active marrow.

On September 12, 2019, the patient’s health condition badly deteriorated. The oxygen saturation (SpO₂) of 85% on room air, blood pressure (BP) of 100/40 mmHg, body temperature (Temp) of 38.2°C, and random blood sugar (RBS) of 105 mg/dl were recorded.

The consultation of internal medicine was performed at Shar Hospital. The patient had a decreased level of consciousness (LOC) and was dyspneic.

**GENERAL EXAMINATION**

The patient was drowsy with a Glasgow coma scale (GCS) of seven (7/15), and he experienced gaze palsy and decorticated posture. He was febrile, sweaty, tachypneic (respiration rate (RR) of ten cycles/min), pale, and jaundiced with no goiter, no palpable lymph nodes (LNs), and no positive peripheral pulses.

Other examinations included the following:

- **Neurological**: positive meningeal signs (neck stiffness and Kernig’s sign)
- **Chest**: good air entry, no added sound
- **Abdomen**: guarding, palpable spleen (three fingers below costal margin), positive bowel sound
- **Precordium**: no significant findings
- **Skin**: no rash

Consequently, we requested to refer the patient into Shar Hospital to be admitted to the Intensive Care Unit (ICU). In the ICU, the patient was intubated and put on an invasive ventilator. The next day, he was extubated and put on CPAP, his SpO₂ was 91%–100% on CPAP, pulse rate was 93–107 beats per minute (bpm), RR was 10–17 CPM, and BP was 110/60 mmHg. Body temperature was around 37.3–38.3°C and RBS ranging from 173–308 mg/dl. His Hb was 7.6 g/dl, whereas his RBS, serum electrolytes, renal enzymes, and coagulation studies were normal. Liver enzymes were also normal, apart from a low albumin level (3.1 g/dl). The same day, his Hb (8.6 g/dl) and platelets (60 x 10⁹/L) followed, by 60 mg daily for five consecutive days (September 13th to the 18th). He also received a Primaquine tablet (30 mg) as an empirical treatment for other types of malaria, and he continued Ribavirin tablet (200 mg) accompanied by antibiotic and IV fluid administration. The same day, his Hb (8.6 g/dl) and platelets (60 x 10⁹/L) began to increase with WBC (5.7 x 10⁹/L).

Finally, on September 14, 2019, the result of the second thin blood film was positive for a malarial parasite (ring-shaped trophozoites) with rouleaux phenomenon which is indicative of inflammation (Figure 1), and the anti-malarial drugs were continued. The result was confirmed after five days by the Central Public Health Lab directorate of Iraq, and the case was recorded. On September 15, 2019, his platelets became 95 x 10⁹/L, and Hb was 8.1 g/dl, whereas his RBS, serum electrolytes, renal enzymes, and coagulation studies were normal. Liver enzymes were also normal, apart from a low albumin level (3.1 g/dl). The next day, his Hb elevated to 9.1 g/dl with platelets to 122 x 10⁹/L, while he had normal RBS, serum electrolytes, renal enzymes, and electrocardiogram (ECG).

On September 18, 2019, there was a decreasing Alkaline phosphatase (ALP) to 76 IU/L and decreasing both ALT and AST toward the normal range, with slightly decreased spleen size to a long axis of 15 cm on abdominal Ultras. The next day, on September 19, 2019, further improvement in Hb (11.4 g/dl) and platelets (170 x 10⁹/L) were documented, which drove us to discharge the patient that day.

Two days after his discharge (17 days from his initial symptoms), the patient came back to follow up on his condition, and we realized that all his symptoms were resolved except headache. On examination, he was pale, without jaundice, and with palpable spleen one finger below the costal margin. He had normal vital signs, such as BP of 90/60 mmHg, body temp of 36.5°C, and RBS of 125 mg/dl. His Hb on follow-up visit was 11.2 g/dl, while serum electrolytes and
renal and liver enzymes were normal with a total serum bilirubin (TSB) of 0.6 mg/dl.

**DISCUSSION**

Malarial eradication is an important international goal, and many countries are making great efforts to be classified as malaria-free nations and receive WHO certificates. Such classifications are not only health-related but also may affect the economic and tourism status of the country. Therefore, malarial eradication may positively affect the country’s reputation [12].

In the last few years, Iraq has had a more complicated humanitarian situation due to ongoing conflicts and displacements of approximately 3.2 million people in the country, but it was still considered among the countries that are free of malaria. Iraq started a malarial eradication campaign in 1957 to successfully achieve malarial elimination [13]. During the Gulf war in 1991, three autonomous governorates (Sulaymaniyah, Erbil, and Duhok) of Iraq had once again been affected by, and experienced a serious epidemic of, *P. vivax*. It transmitted rapidly to other cities (especially Ninawa and Tamim) and reached 49,840 cases in 1995. Simultaneously, the National Malaria Program started to detect the infected cases, control the transmission of the disease, and introduce free treatment (chloroquine/proguanil antimalarial regimen) for infected people. Proper environmental management systems and vector control were applied at that time to reduce the rate of the disease until 1999, when only 4,134 cases remained [13,14].

Similarly, the prevalence of malaria infection in Iraq was 47,395 cases from 1970–1975, which had declined to 20,191 cases from 1977–1984 [14]. The last two indigenous malaria cases in Iraq were reported in 2008. Finally, in 2009, Iraq officially declared that the country was free from the disease, and the infection was not considered as a heavy burden on the society anymore [3,15].

Vector control is one of the most important factors in this disease’s control and management. However, a recent entomological study conducted in Diyala province, Iraq, revealed that mosquito species (*Anopheles*, *Anopheline*, and *Culex*) that can play a role as malarial vectors are increased in the province. The presence of these mosquito species puts people at great risk, especially in a hot and humid climate, which provides a suitable environment for larvae to develop. Thus, this issue needs the authority to conduct further research and investigation to discover the mosquito’s source and find a proper way to eradicate the mosquito species to protect citizens from the disease of malaria [16].

According to the WHO report, many of the neighboring countries of Iraq (including the Islamic Republic of Iran, Turkey, and Syria) are continuing efforts to eliminate malaria. Regarding the Islamic Republic of Iran, it is considered one of the malaria-endemic countries of the Eastern Mediterranean Region, as there were 89 locally-transmitted cases in 2017 [17], and in 2018 there were 625 reported imported cases of malaria, only two out of those 625 cases were introduced and not indigenous. The majority of reported cases were *P. vivax*, which was detected in Afghan nationals, while the minority was *P. falciparum* cases. Iran declared that their large, shared border area with Pakistan is a source of malaria. In 2019, they updated the treatment guideline and provided Mefloquine for travelers to malaria-endemic countries [18]. Thus, our research is in agreement with Iranian authority suggestions that unregistered foreign seasonal workers,

**Figure 1.** Shows ring form trophozoites of *P. falciparum* in the stained thin smear of the patient’s blood sample (Yellow arrows), with rouleaux phenomenon (Red arrows). High power field ($\times$100).
A severe case of Plasmodium falciparum malaria in Iraq

Abdullah et al.

May have fatal consequences. Before receiving the positive result on blood film for the parasite, SJAA is an internist who decided and started empirical anti-malarial treatment. SJAA, VNM, and RAA are the clinicians who dealt with, monitor, and manage the case in the internal medicine ward and ICU. ROA is the clinician that monitors and manages the hematological issues of the patient. All authors read and approved the final draft of the manuscript before submission.

Acknowledgment: We acknowledge all the staff at the hematology ward of Hiwa Hematology/Oncology Hospital, and we have gratitude to all staff at the internal medicine ward of Shar Hospital.

Ethical approval and consent to participate: Ethical approval from the College of Medicine, University of Sulaimani ethical committee was taken under approval number of 144, on 16-8-2020.

Consent for publication: Consent was granted by the patient for the publication of this case report.

REFERENCES

1. Malaria. https://www.who.int/en/news-room/fact-sheets/detail/malaria (accessed 22 May 2020).
2. World malaria report 2019. https://www.who.int/publications-detail/world-malaria-report-2019 (accessed 22 May 2020).
3. WHO EMRO | Iraq free of malaria… a new success and upcoming challenge | 2011 | Iraq press releases. http://www.emro.who.int/iraq-press-releases/2011/iraq-free-of-malaria-a-new-success-and-upcoming-challenge.html (accessed 23 May 2020).
4. Saheb EJ. The prevalence of parasitic protozoan diseases in Iraq, 2016. Karbala Int J Mod Sci. 2018;4(1):21–5.
5. Schlagenhauf P. Malaria in Iraq—the pitfalls of Plasmodium vivax prophylaxis. Lancet Infect Dis. 2003 Aug;3(8):460.
6. Mosa IS, Ghazi Mahdi S, Saheb EJ, et al. An Epidemiology Study of Some Protozoan Parasitic Diseases in Iraq from 2011 Till 2015. J Al-Nahrain Univ. 2017;20(3):115–20.
7. Boggild AK, Page AV, Keystone JS, Morris AM, Liles WC. Delay in diagnosis: malaria in a returning traveller. CMAJ. 2009 May;180(11):1129–31.
8. Arends JE, Oosterheert JJ, Kraaij-Dirkzwager MM, Kaan GA, Fanoy EB, Haas PJ, et al. Two cases of Plasmodium falciparum malaria in the Netherlands without recent travel to a malaria-endemic country. Am J Trop Med Hyg. 2013 Sep;89(3):527–30.
9. Arcelia F, Asymida F, Lubis NF, Pasaribu AP. Severe falciparum malaria: A case report. IOP Conf Ser Earth Environ Sci. 2018;125:012021.
10. Sikora SA, Poespoprodjo JR, Kenangalem E, Lampah DA, Sugianto P, Laksono IS, et al. Intravenous artesunate plus oral dihydroartemisinin-piperaquine or intravenous quinine plus oral quinine for optimum treatment of severe malaria: lesson learnt from a field hospital in Timika, Papua, Indonesia. Malar J. 2019 Dec;18(1):448.
11. Bain BJ, Bates I, Laffan MA. Dacie and Lewis Practical Haematology, supplementary Techniques Including Blood films, and confirmed the presence of the parasite. SJA is an internist who decided and started empirical anti-malarial treatment. SJAA, VNM, and RAA are the clinicians who dealt with, monitor, and manage the case in the internal medicine ward and ICU. ROA is the clinician that monitors and manages the hematological issues of the patient. All authors read and approved the final draft of the manuscript before submission.
Abdullah et al.: A severe case of falciparum malaria in Iraq

Parasite Diagnosis. 12th ed. Elsevier; 2017. https://doi.org/10.1016/C2014-0-01046-5.

12. Hemami MR, Sari AA, Raeisi A, Vatandoost H, Majdzadeh R. Malaria elimination in Iran, importance and challenges. Int J Prev Med. 2013 Jan;4(1):88–94. [cited 2020 Sep 20].

13. Shamo FJ. Malaria in Iraq [Malaria in Iraq]. Med Parazitol (Mosk). 2001 Jan-Mar;1(1):46–7.

14. Salam A. The distribution of malaria in Rabiea region in Northern Iraq. Medical Journal of Babylon. 2004;1(3-4).

15. Murray CJ, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014 Sep;384(9947):1005–70.

16. Hasson RH. Mosquitos’ species of Diyala province, Iraq. Int J Environ Agric Biotechnol. 2017;2(4):2121–6.

17. Vatandoost H, Raeesi A, Saghafiipour A, Nikpour F, Nejati J. Malaria situation in Iran: 2002-2017. Malar J. 2019 Jun;18(1):200.

18. Cross-border collaboration on malaria between countries of the WHO Eastern Mediterranean and European regions. Report of the Biregional Coordination Meeting Dushanbe, Tajikistan. 2020. http://apps.who.int/bookorders. (accessed 20 Sep 2020).

19. Hadi AM. The role of mosquito in the transfer of blood protozoa in Baghdad, Iraq. Int J Mosq Res. 2019;6:19–25. [cited 2020 Sep 20] Available from: http://www.diptera-journal.com/archives/2019/6/1/A/5-6-3