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Atypical presentation of falciparum malaria in a returning traveler: a diagnostic dilemma

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ABSTRACT

Falciparum malaria, caused by *Plasmodium falciparum,* is a significant global health concern, especially in tropical regions. This case report details an atypical presentation of falciparum malaria in a 32-year-old male who returned to India after traveling to South Africa. The patient presented with a two-month history of high-grade fever, severe anemia, jaundice, easy fatigability, and significant weight loss. Initial laboratory investigations revealed severe anemia, thrombocytopenia, elevated inflammatory markers, and splenomegaly, but peripheral blood smears were negative for malaria parasites. Despite initial challenges in diagnosis, bone marrow aspiration confirmed the presence of *P. falciparum.* The patient was treated with artemether/lumefantrine, resulting in clinical and hematological improvement. This case highlights the importance of considering malaria in patients with unexplained anemia and splenomegaly, especially those with recent travel to endemic areas, even when initial diagnostic tests are negative. It underscores the value of comprehensive diagnostic approaches, including bone marrow examination, in atypical cases. This report contributes to the understanding of malaria's varied clinical presentations and reinforces the need for awareness and timely intervention to prevent complications.

Keywords: *Plasmodium falciparum,* malaria, travel-related illness, severe anemia, spleenomegaly

INTRODUCTION

Malaria remains one of the world's most significant public health challenges, with *Plasmodium falciparum* being the most deadly species of the malaria parasites. *P. falciparum* malaria is responsible for the majority of malaria-related deaths globally, particularly affecting regions in sub-Saharan Africa, Southeast Asia, and parts of South America [1]. The transmission of malaria occurs through the bite of an infected female Anopheles mosquito, which introduces the parasites into the human bloodstream. Once inside the host, the parasites undergo rapid multiplication within red blood cells, leading to symptoms such as high-grade fever, chills, anemia, and, in severe cases, organ dysfunction and death [2].

Despite significant progress in reducing malaria incidence and mortality through prevention and treatment strategies, the disease continues to impose a heavy burden on endemic regions. In non-endemic countries like India, cases of *P. falciparum* malaria are often imported by travelers returning from endemic areas, which poses unique diagnostic and management challenges [3]. The disease can present with a wide range of symptoms, sometimes mimicking other tropical and infectious diseases, making early and accurate diagnosis crucial for effective treatment and prevention of complications [4].

The case presented here is of a 32-year-old male who returned to India after traveling to South Africa, where malaria is endemic. He presented with atypical symptoms, including severe anemia, fa-

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tigue, and significant weight loss, which are not immediately suggestive of malaria. Initial diagnostic tests, including peripheral blood smears, failed to detect the presence of malaria parasites.

However, further investigation through bone marrow aspiration confirmed the diagnosis of falciparum malaria. This case underscores the need for healthcare providers to maintain a high index of suspicion for malaria in patients with recent travel history to endemic areas, even in the absence of classical symptoms or initial negative diagnostic tests.

Comprehensive diagnostic approaches, including advanced techniques such as bone marrow examination, can be pivotal in identifying malaria in atypical presentations.

Prompt initiation of appropriate antimalarial therapy, as demonstrated in this case with artemether/lumefantrine, is essential to ensure favorable patient outcomes.

This report highlights the importance of recognizing the diverse clinical manifestations of falciparum malaria and the role of thorough diagnostic investigations in guiding effective treatment strategies.

CASE DETAILS

A 32-year-old male presented with a two-month history of high-grade fever occurring 2-3 times daily, along with easy fatigability, jaundice (which resolved after taking native medication), and significant weight loss of 8 kg in one month.

The patient had recently traveled to South Africa from February to March 2024, returning to India on March 15th, 2024. Initial investigations on April 2nd revealed a hemoglobin level of 14 g/dL.

However, subsequent tests on May 29th showed a significant drop in hemoglobin to 7.3 g/dL, a total leukocyte count [TLC) of 4710/mm³, and platelets at 1.05 lakh/mm³.

Liver function tests showed mild elevation in bilirubin levels, and the lipid profile indicated a low total cholesterol of 83 mg/dL with an HDL of 8 mg/dL. An ultrasound of the abdomen revealed splenomegaly measuring 15 cm.

Further investigations on June 1st showed worsening anemia with hemoglobin at 6.8 g/dL, platelets reduced to 17.7 lakh/mm³, and a TLC of 5610/mm³. A peripheral smear showed normocytic normochromic anemia, and tests for malaria parasite and microfilaria were negative.

Other laboratory findings included a corrected reticulocyte count of 2%, LDH at 373 U/L, ferritin elevated at 921 ng/mL, and a C-reactive protein level of 47.2 mg/L. Stool routine, direct Coombs test, and serology for infectious diseases were negative, ruling out other common causes of anemia and jaundice.

On June 3rd, following a transfusion of one unit of packed red blood cells, the patient's hemoglobin slightly improved to 7.2 g/dL. A bone marrow aspiration was performed and revealed positivity for *Plasmodium falciparum*, along with erythroid hyperplasia and micronormoblastic maturation.

Bone marrow biopsy confirmed these findings, showing normocellular marrow with erythroid hyperplasia. Based on these results, a diagnosis of falciparum malaria was made, despite the atypical presentation and initial negative peripheral smears. The patient was promptly started on a full course of artemether/lumefantrine (80/480 mg), an artemisinin-based combination therapy. The treatment led to a significant improvement in symptoms and laboratory parameters, highlighting the importance of considering malaria in patients with atypical presentations, especially those with recent travel to endemic areas.

DISCUSSION

This case report highlights an atypical presentation of *Plasmodium falciparum* malaria, characterized primarily by severe hematological abnormalities such as anemia and splenomegaly, rather than the classical acute febrile illness typically associated with malaria.

The patient's travel history to South Africa, a region endemic for malaria, played a critical role in considering malaria as a differential diagnosis despite initial negative results from peripheral blood smears.

This study gives the importance of taking a comprehensive travel history in patients presenting with unexplained hematological symptoms, particularly when they have returned from areas known for high malaria transmission [4].

The initial blood tests for malaria failed likely due to low parasitemia or sequestration of Plasmodium falciparum in the microvasculature of organs like the spleen, liver, and bone marrow, which often leads to false-negative results in peripheral blood smears.

Falciparum malaria is known for its ability to sequester infected red blood cells, reducing their detection in peripheral circulation, especially at low parasitemia levels.

In such cases, bone marrow aspiration can be a valuable alternative diagnostic tool, as it may detect malaria parasites when peripheral smears are inconclusive, providing a more definitive diagnosis [5].

In our case, the failure of peripheral smears to detect malaria parasites may be attributed to low

parasitemia or sequestration of parasites in microvasculature, which is not uncommon in falciparum malaria [6]. Bone marrow aspiration, though not routinely used for diagnosing malaria, proved to be an invaluable diagnostic tool in this scenario.

Bone marrow examination can reveal the presence of malaria parasites, particularly in cases where peripheral blood smears are inconclusive [7]. The bone marrow findings of erythroid hyperplasia with micronormoblastic maturation observed in this patient align with the body's compensatory response to hemolytic anemia and the increased turnover of red blood cells typical in malaria infection.

This observation is supported by literature indicating that bone marrow examination can aid in the diagnosis of malaria in patients with atypical presentations or negative peripheral smears [8].

The successful management of this case with artemether/lumefantrine highlights the efficacy of artemisinin-based combination therapies [ACTs] in treating falciparum malaria, even in cases with severe hematological manifestations [9,10]. ACTs remain the cornerstone of malaria treatment due to their rapid action and ability to clear parasites effectively, reducing the risk of severe complications and transmission.

Artemether, in combination with lumefantrine, is specifically recommended for its high efficacy against *P. falciparum* and its ability to reduce gametocyte carriage, thus lowering transmission potential [11].

This case explains the necessity for clinicians to maintain a high index of suspicion for malaria in travelers presenting with atypical symptoms such as unexplained anemia, jaundice, and splenomegaly, particularly when initial diagnostic tests are negative. The use of bone marrow aspiration in this context provides a compelling example of how alternative diagnostic methods can be employed to identify infections that might otherwise remain undiagnosed, potentially averting severe outcomes [12,13].

Furthermore, this case illustrates the broader implications for public health and clinical practice, particularly in non-endemic regions like India, where imported cases of malaria pose diagnostic and therapeutic challenges. Clinicians must be aware of the diverse presentations of malaria and the importance of thorough diagnostic evaluation, including both conventional and unconventional methods, to guide effective treatment strategies. This case also reinforces the critical role of timely intervention and appropriate use of ACTs in improving patient outcomes and preventing the spread of malaria.

CONCLUSION

This case report emphasizes the need for heightened clinical awareness and comprehensive diagnostic approaches when evaluating patients with a history of travel to malaria-endemic regions. While the classical presentation of malaria involves acute febrile illness, atypical manifestations such as severe anemia and splenomegaly should prompt consideration of malaria, especially in travelers. Bone marrow examination can be a valuable diagnostic tool in such cases, ensuring timely and appropriate treatment.

Details on patient follow-up and long-term recovery after treatment will be the subject of further studies.

This case highlights the critical role of ACTs in the management of falciparum malaria and reinforces the importance of early diagnosis and treatment to prevent complications.

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REFERENCES

1. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. *Lancet.* 2014;383(9918):723-735. http://doi.org/10.1016/S0140-6736(13)60024-0
2. Meibalan E, Marti M. Biology of Malaria Transmission. *Cold Spring Harb Perspect Med.* 2017;7(3):a025452. http://doi.org/10.1101/cshperspect.a025452
3. Marasinghe DH, Cheaveau J, Meatherall B, et al. Risk of malaria associated with travel to malaria-endemic areas to visit friends and relatives: a population-based case-control study. *CMAJ Open.* 2020;8(1):E60-E68. http://doi.org/10.9778/cmajo.20190070
4. Schmid S, Chiodini P, Legros F, D'Amato S, Schöneberg I, Liu C et al. The risk of malaria in travelers to India. *Journal of Travel Medicine.* 2009;16(3):194-9. http://doi.org/10.1111/j.1708-8305.2009.00332.x
5. Miller CE, Bain BJ. The Utility of Blood and Bone Marrow Films and Trephine Biopsy Sections in the Diagnosis of Parasitic Infections. *Mediterr J Hematol Infect Dis.* 2015;7(1):e2015039. http://doi.org/10.4084/MJHID.2015.039
6. Parikh MP, Krishnan S, Ganipisetti VM, Flores S. Classic image: peripheral blood smear in a case of Plasmodium falciparum cerebral malaria. *BMJ Case Reports.* 2014; 2014: bcr2014205820. http://doi.org/10.1136/bcr-2014-205820
7. Shaikh MS, Ali B, Janjua M et al. Plasmodium in the bone marrow: case series from a hospital in Pakistan, 2007-2015. *Malar J.* 2021;20(1):254. http://doi.org/10.1186/s12936-021-03792-1
8. Obaldia III N, Meibalan E, Sa JM, Ma S, Clark MA, Mejia P, et al. Bone marrow is a major parasite reservoir in Plasmodium vivax infection. *MBio.* 2018 Jul 5;9(3):10-128. http://doi.org/10.1128/mbio.00625-18
9. Ngasala BE, Chiduo MG, Mmbando BP et al. Efficacy and safety of artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in mainland Tanzania, 2019. *Malar J.* 2024;23:101. http://doi.org/10.1186/s12936-024-04931-0

10. Aninagyei E, Tetteh CD, Oppong M, Boye A, Acheampong DO. Efficacy of Artemether-Lumefantrine on various Plasmodium falciparum Kelch 13 and Pfmdr1 genes isolated in Ghana. *Parasite Epidemiol Control.* 2020;11:e00190. Published 2020 Oct 26. http://doi.org/10.1016/j.parepi.2020.e00190
11. Yeka A, Harris JC. Treating uncomplicated malaria in children: comparing artemisinin-based combination therapies. *Curr Opin Pediatr.* 2010;22(6):798-803. http://doi.org/10.1097/MOP.0b013e32833fac44
12. Silamut K, Phu NH, Whitty C et al. A quantitative analysis of the microvascular sequestration of malaria parasites in the human brain. *Am J Pathol.* 1999;155(2):395-410. http://doi.org/10.1016/S0002-9440(10)65136-X
13. Aguilar R, Magallon-Tejada A, Achtman AH, Moraleda C, Joice R, Cisteró P et al. Molecular evidence for the localization of Plasmodium falciparum immature gametocytes in bone marrow. *Blood.* 2014;123(7):959-66. http://doi.org/10.1182/blood-2013-08-520767