IDCases 31 (2023) e01653

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

A case report of late treatment failure in *Plasmodium falciparum* malaria in a traveler from the Democratic Republic of the Congo to India

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ARTICLE INFO

Keywords:
Malaria
P. falciparum
Late treatment failure
Travel malaria
Drug resistance
CQ sensitivity

ABSTRACT

A young male returned from the Democratic Republic of the Congo (DRC) to India after four months during his official work. Within a week of his arrival, he developed a high-grade fever with nausea and was hospitalized in a private hospital in New Delhi. He was diagnosed with malaria, treated with an artesunate injection as antimalarial, and discharged on day 5th from the hospital. A week later, he was diagnosed with malaria and dengue positive at ICMR-National Institute of Malaria Research, New Delhi. Artesunate with sulphadoxine and pyrimethamine (AS+SP) was administered following India's malaria treatment policy. However, high-grade fever, along with the asexual stage of the *P. falciparum* parasite, was observed within 28 days of treatment with AS+SP, signifying late treatment failure (LTF). Further, the molecular analysis from both the days of episodes was analyzed using genomic DNA from dried blood spots, revealing resistance to sulphadoxine-pyrimethamine with mutations at codons *pfdhfr* 51I, *pfdhfr* 59 R, *pfdhfr* 108 N, *pfdhps* 437 A, *pfdhps* 581 G. No functional mutation associated was found in *pfKelch*13, but interestingly the sensitive codons to chloroquine (CQ) (wild type *pfcrt*K76 and *pfmdr*N86) revealed the probably reversible CQ sensitivity in the sample from DRC.

Introduction

As per the National Drug Policy of India, Artemisinin Combination Therapy (ACT) is used to treat malaria caused by Plasmodium *falciparum* [15]. While rapid-acting artemisinin derivatives ensure early parasite clearance, the long-acting partner drugs responsible for residual parasite clearance may prevent the development of resistance. In patients recovering from severe *P. falciparum* malaria, the ACT is recommended as a standard treatment to reduce selection pressures in high-transmission zones after early parasite clearance [14]. A significant reduction in the global malaria burden was achieved as a result of the deployment of ACT, malaria rapid diagnostic tests, and protective techniques like insecticidal nets with a long lifespan and indoor residual spray; however, a challenge in malaria elimination is the rise of artemisinin resistance. In southeast Asia, ACT resistance is widespread and is characterized by delayed parasite clearance post-treatment [4].

The World Health Organization (WHO) reports a rise in malaria cases (14 million) in 2020 than in 2019. Most of this rise comes from countries in the -Africa continent, followed by the South East Asia countries. In Africa, the number of malaria cases per 1000 people increased from 222 to 232 in 2020 compared to the previous year. The WHO-SEARO accounts for about 2 % of malaria cases globally of the total malaria burden. India accounted for 83 % of cases in the SEA region.

Similarly, Congo had 12 % of the burden of malaria in the African region of WHO.; Congo accounted for 12 % of the total burden of malaria in the WHO-African region [9]. This report describes the case report of late treatment failure against ACT in an individual who traveled from a malaria-endemic country (DRC) to India.

Case history

A 40-year-old man returned to New Delhi, India, on November 5, 2019, from the DRC, Africa. On November 15, 2019, ten days after his arrival, he complained of fever, shivering, and headache and was hospitalized from 16th - 20th November 2019. He was diagnosed with *P. falciparum* malaria infection on the day of admission. After four days

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https://doi.org/10.1016/j.idcr.2022.e01653
Received 9 November 2022; Received in revised form 25 November 2022; Accepted 30 November 2022
Available online 16 December 2022

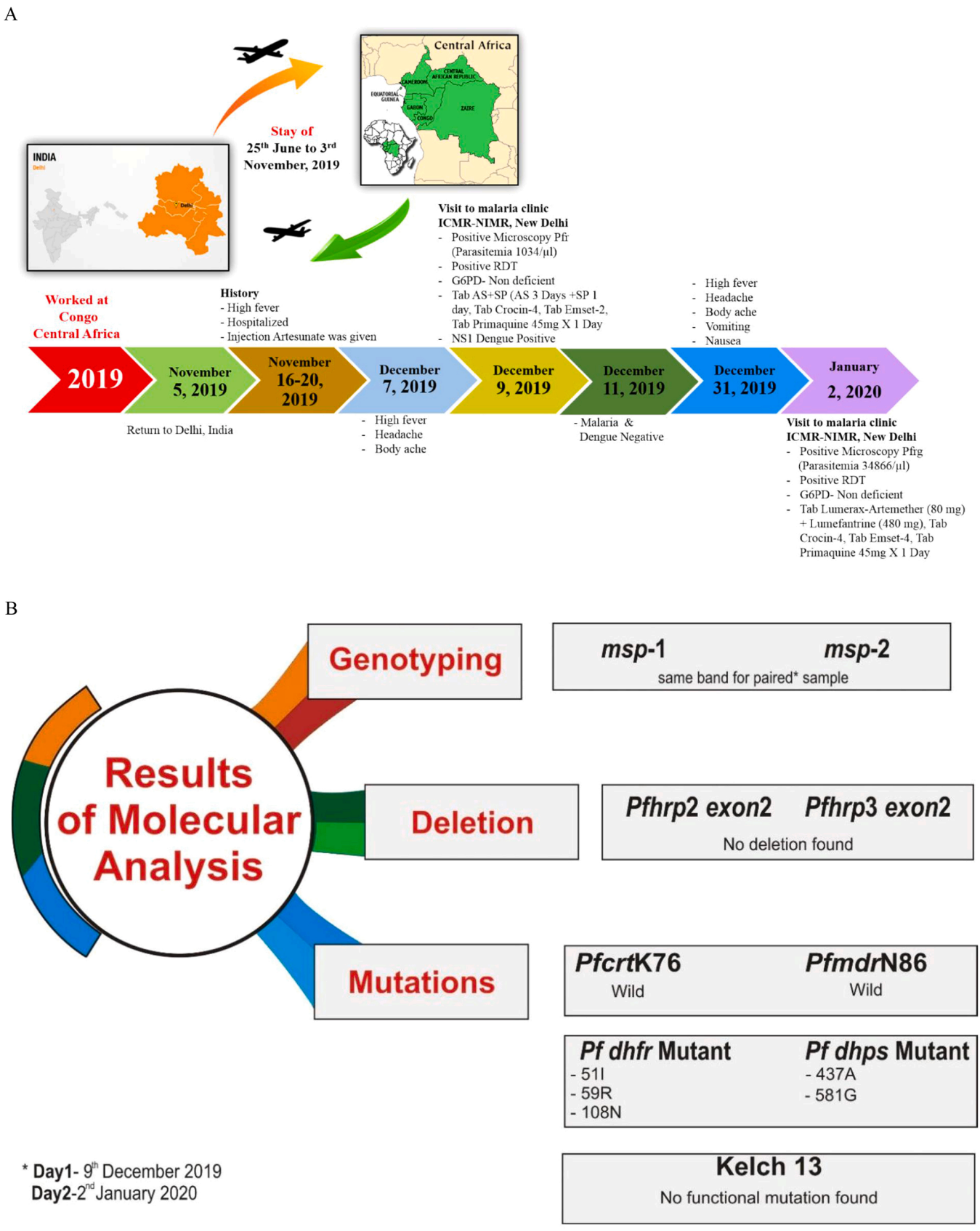

Fig. 1. [A]: Showing the time lines of events in a *P. falciparum* malaria patient who travel from DRC to India. [B] The molecular analysis of the paired samples revealed the same genotype of *pfmsp1* and *pfmsp2*, *pfhrp 2* gene deletion and mutations in different drug resistance markers.

in the hospital, he was discharged after receiving artesunate injections to treat his malaria infection. On December 7th, 17 days later, he again complained of fever, headache, and body aches, for which he took self-medication. On December 9, a doctor advised blood investigations for malaria and dengue. Malaria diagnosis was done through Rapid Diagnostic Kits (RDTs) and blood smear examinations at ICMR-NIMR (Fig S1). The RDT for malaria was positive for *P. falciparum* malaria and ELISA for dengue (NS1). The parasitemia level was 1034 parasites/μl of blood. ACT (AS+SP) was given as per National Drug Policy, along with antipyretics and antiemetics. Primaquine adult dose was given after confirming G6PD non-deficiency. He was also referred to the hospital for dengue management. The patient re-developed similar symptoms after 20 days on December 31, 2019. On January 2, 2020, he again visited the same facility for the malaria diagnosis, and the blood smear was positive for *P. falciparum* malaria with a parasitemia of 34,866/μl of blood. Later, the second line of treatment, AL (Artemether 80 mg, Lumefantrine 480) and Primaquine (45 mg) with antipyretics and antiemetics, were prescribed as per the National Drug Policy of India. The patient completed the treatment regimen of the AL course and recovered. The timelines of the events are shown in Fig. 1A.

The detection, species identification, and quantitation of parasitemia (parasites/μl) were performed by a WHO-L1-certified microscopist. Molecular analysis was performed after extracting DNA from paired samples using a commercially available DNA Extraction Kit. The genotyping markers were analyzed to differentiate from resurgence to secondary infection using the previously described protocol [11]. Single-nucleotide polymorphisms (SNPs) associated markers were also analyzed for drug resistance, including *pfcrt*K76, *pfmdr*N86, *pfdhps*, *pfdhfr*, and *Kelch-13* gene, which has been associated with artemisinin resistance [3,5]. Gene deletions were also analyzed using *pfhrp*2 and *pfhrp*3 gene deletion markers [6]. The results of the molecular analysis are delineated in Fig. 1B.

The genotyping result revealed that the paired samples had the same band size for *msp*-1 and *msp*-2 genes, signifying recrudescence. The sample was found resistant to *pfdhfr* 51I, *pfdhfr* 59R, *pfdhfr* 108N, *pfdhps* 437A, *and pfdhps* 581G indicating resistance to partner drugs sulphadoxine and pyrimethamine. However, no functional mutation was observed in *the Kelch-13* gene. Surprisingly, further analysis of CQ resistance genes was found to be sensitive for CQ with molecular marker results for *pfcrt*K76 and *pfmdr*N86. Because the infection came from DRC, which has a history of gene deletion in the *pfhrp2* gene, it was suspected of being a case of gene deletion. However, it was not.

Discussion

This report focuses on a patient who traveled between and from malaria-endemic areas with implications for prevention and diagnosis. Therapeutic studies to monitor antimalarial efficacy have been extensively carried out from 2011 to 2017 for treating *P. falciparum* malaria in India [2,7]. Suspecting more than 10% treatment failure in northeastern parts of India, a revision of drug policy for the treatment of asexual uncomplicated *P. falciparum* malaria to AL was implemented in the year 2014 [1]. According to data on therapeutic efficacy from 28 countries, between 2010 and 2018, the average efficacy rates for artemisinin combination therapy with lumefantrine, amodiaquine, and dihydro-artemisinin with piperaquine for *P. falciparum* were 98.0 %, 98.5 %, and 99.3%, respectively. [8]. Late treatment failures (n = 5) were reported in patients treated with AL, and one early treatment failure with delayed parasitological response during AS+SP treatment in Sweden. The failure rates in patients treated with AL were 5.2% (5/95) and 1 % of AS+SP (1/95), respectively [13].

A case of atovaquone and proguanil–resistant *P. falciparum* (confirmed genetically) malaria with 3% parasitemia after one week of complete treatment was reported in a non-immune traveler to East Africa [12]. In non-immune travelers from the Indian subcontinent, the first case of treatment failure in severe P. *falciparum* malaria treated with atovaquone/proguanil was reported. Further, this patient had a recrudescent infection and complications with neurological involvement after 14 days of direct observation treatment. Atovaquone resistance to treatment failure was confirmed by sequence analysis of the cytochrome b gene [10]. Therefore, detailed travel history and individual risk assessment should be considered and reported for every traveler to the destination country where the malaria elimination goal is in progress. The information generated will be helpful in the management of malaria treatment and guide the policy.

Key Messages

India has set the malaria elimination goal by 2027. Therefore, the government should screen travelers from different countries to India for malaria on arrival. The antimalarial drug resistance profiles should be studied using molecular tools in India.

Ethical approval

Study approved by ICMR-NIMR Institutional Ethical Committee.

Consent

The consent of patient in writing was obtained for publication of case report in a peer-reviewed journal.

Funding

None.

CRediT authorship contribution statement

Supriya Sharma: Investigation, Validation, Visualization, Formal analysis, Writing-original draft.**Naseem Ahmed:** Validation, Writing-original draft, review & editing, Visualization. **Nafis Faizi:** Review and editing. **Praveen K Bharti:** Review and editing. **Amit Sharma:** Review and editing. **Bina Srivastava:** Investigation- Microscope, Writing-original draft, review & editing.

Conflict of interest

None.

Acknowledgment

The authors are thankful to the participant for consenting to the case for publication and the staff of ICMR-NIMR fever clinic for overall support.

Author Agreement

All authors agree to the content of manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.idcr.2022.e01653.

References

[1] Anvikar AR, Arora U, Sonal G, Mishra N, Shahi B, Savargaonkar D, et al. Antimalarial drug policy in India: past, present & future. Indian J Med Res 2014; 139(2):205.

[2] Bharti PK, Shukla MM, Ringwald P, Krishna S, Singh PP, Yadav A, et al. Therapeutic efficacy of artemether–lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria from three highly malarious states in India. Malar J 2016;15(1):1–9.

[3] Djimdé A, Doumbo OK, Cortese JF, Kayentao K, Doumbo S, Diourté Y, et al. A molecular marker for chloroquine-resistant falciparum malaria. N Engl J Med 2001;344(4):257–63.
[4] Imwong M, Suwannasin K, Kunasol C, Sutawong K, Mayxay M, Rekol H, et al. The spread of artemisinin-resistant Plasmodium falciparum in the Greater Mekong subregion: a molecular epidemiology observational study. Lancet Infect Dis 2017; 17(5):491–7.
[5] Malmberg M, Ferreira PE, Tarning J, Ursing J, Ngasala B, Björkman A, et al. Plasmodium falciparum drug resistance phenotype as assessed by patient antimalarial drug levels and its association with pfmdr1 polymorphisms. J Infect Dis 2013;207(5):842–7.
[6] Mariette N, Barnadas C, Bouchier C, Tichit M, Ménard D. Country-wide assessment of the genetic polymorphism in Plasmodium falciparum and Plasmodium vivax antigens detected with rapid diagnostic tests for malaria. Malar J 2008;7(1):1–9.
[7] Mishra N, Srivastava B, Bharti RS, Rana R, Kaitholia K, Anvikar AR, et al. Monitoring the efficacy of antimalarial medicines in India via sentinel sites: outcomes and risk factors for treatment failure. J Vector Borne Dis 2016;53(2):168.
[8] Organization, W.H. , 2020. Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010–2019).
[9] Organization, W.H. , 2021. World malaria report 2021.
[10] Perry TL, Pandey P, Grant JM, Kain KC. Severe atovaquone-resistant Plasmodium falciparum malaria in a Canadian traveller returned from the Indian subcontinent. Open Med 2009;3(1):e10.
[11] Ranford-Cartwright L, Taylor J, Umasunthar T, Taylor L, Babiker H, Lell B, et al. Molecular analysis of recrudescent parasites in a Plasmodium falciparum drug efficacy trial in Gabon. Trans R Soc Trop Med Hyg 1997;91(6):719–24.
[12] Schwartz E, Bujanover S, Kain KC. Genetic confirmation of atovaquone-proguanil–resistant Plasmodium falciparum malaria acquired by a nonimmune traveler to East Africa. Clin Infect Dis 2003;37(3):450–1.
[13] Sondén K, Wyss K, Jovel I, Vieira da Silva A, Pohanka A, Asghar M, et al. High rate of treatment failures in nonimmune travelers treated with artemether-lumefantrine for uncomplicated Plasmodium falciparum malaria in Sweden: retrospective comparative analysis of effectiveness and case series. Clin Infect Dis 2017;64(2): 199–206.
[14] White N, Nosten F, Looareesuwan S, Watkins W, Marsh K, Snow R, et al. Averting a malaria disaster. Lancet 1999;353(9168):1965–7.
[15] WHO, 2010. World Health Organization guidelines for the treatment of malaria. In: WHO Geneva, Switzerland.