The Journal of Medical Laboratory Science & Technology South Africa. 2020;2(2):105-108
https://doi.org/10.36303/JMLSTSA.2020.2.2.57
Open Access article distributed under the terms of the
Creative Commons License [CC BY-NC-ND 4.0]
http://creativecommons.org/licenses/by-nc-nd/4.0

JMLSTSA
ISSN 2664 2549 EISSN 2708 3063
© 2020 The Author(s)
CASE REPORT

Fever in the returning traveller: Dual infection with SARS-CoV-2 and *Plasmodium falciparum* malaria

MA Parker,[1]* E Nell,[1,2]* A Mowlana,[1] MS Moolla,[1] S Karamchand,[1] L Murphy,[3] T Lovelock,[3] KS Kalombo,[3] A Parker,[1] ZC Chapanduka[1,2]

**Dual first authorship*
[1] Stellenbosch University, South Africa
[2] National Health Laboratory Services, Tygerberg Hospital, South Africa
[3] Eersterivier Hospital, South Africa
***Corresponding author, email:** erica.mari.nell@gmail.com*

Background: More than 90% of the global 400 000 annual malaria deaths occur in Africa. The current SARS-CoV-2 pandemic has resulted in more than 830 000 deaths in its first 10 months.

Case presentation: This case describes a patient who had travelled from Mozambique to Cape Town, presented with a mild febrile illness, and was diagnosed with both COVID-19 and uncomplicated *Plasmodium falciparum* malaria infection. She responded well to malaria treatment and had an uneventful COVID-19 admission. Her blood smear showed a low malaria parasitaemia and a relatively high gametocyte load.

Conclusion: We postulate that her clinical course and abnormal smear could well be due to reciprocal disease-modifying effects of the infections. The presenting symptoms of COVID-19 may mimic endemic infectious diseases including malaria, tuberculosis, *pneumocystis* pneumonia and influenza thus there is a need for clinical vigilance to identify and treat such co-infections.

Keywords: malaria, *Plasmodium falciparum*, COVID-19, SARS-CoV-2

Background

In 2018 there were 228 million reported cases of malaria in Africa, with an estimated 405 000 deaths, making malaria one of the top ten causes of deaths in Africa.[1] Africa accounted for an estimated 93% of malaria cases and 94% of worldwide deaths, while Mozambique accounted for an estimated 4% of all malaria cases worldwide in 2018.[1]

Coronavirus disease 2019 (COVID-19), is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and was declared a pandemic on 11 March 2020 by the World Health Organization (WHO). The Italian observational multicentre CORIST study showed that the use of hydroxychloroquine in hospitalised COVID-19 patients was associated with reduced mortality.[2] Randomised controlled trials (RCTs) have shown that hydroxychloroquine neither prevented development of COVID-19 symptoms after high or moderate risk exposure, nor improved clinical outcome when given as treatment to patients with mild to moderate COVID-19.[3,4] To our knowledge, there are no published RCTs assessing the effect of hydroxychloroquine in patients with severe COVID-19. Hydroxychloroquine was historically, the mainstay of malaria treatment, showing efficacy against all *Plasmodium* species until widespread *Plasmodium falciparum* (*P. falciparum*) resistance developed.[5]

SARS-CoV-2 gains entry to cells via its spike protein attaching to human angiotensin-converting enzyme 2 (ACE2) expressed on the cell surface. There is evidence, albeit limited, that the erythrocyte, haemoglobin and iron may have a role in the pathophysiology of COVID-19.[6] Since malaria infection is dependent on erythrocytes for replication, understanding the reciprocal effect of these two infections occurring simultaneously may reveal clinical, management and prognostic aspects of COVID-19.

We describe a case of a patient infected with both SARS-CoV-2 and *P. falciparum*, leading to both COVID-19 and malaria, respectively. To our knowledge, this is the first reported case of co-infection with COVID-19 and malaria.

Case presentation

A 16-year-old female was admitted to a designated COVID-19 hospital in Cape Town, South Africa. Her initial presentation was to a local district hospital where she complained of a nine-day history of fever and diarrhoea. She reported recently travelling more than 2 000 km by car from Mozambique to Cape Town over 17 days.

On systemic examination, she was haemodynamically stable, with a blood pressure of 121/82 mmHg, a pulse rate of 72 beats per minute, a respiratory rate of 18 breaths per minute and a peripheral oxygen saturation of 100% on room air. She had no jaundice or pallor and her systemic examination was unremarkable. There were no documented episodes of hypoglycaemia.

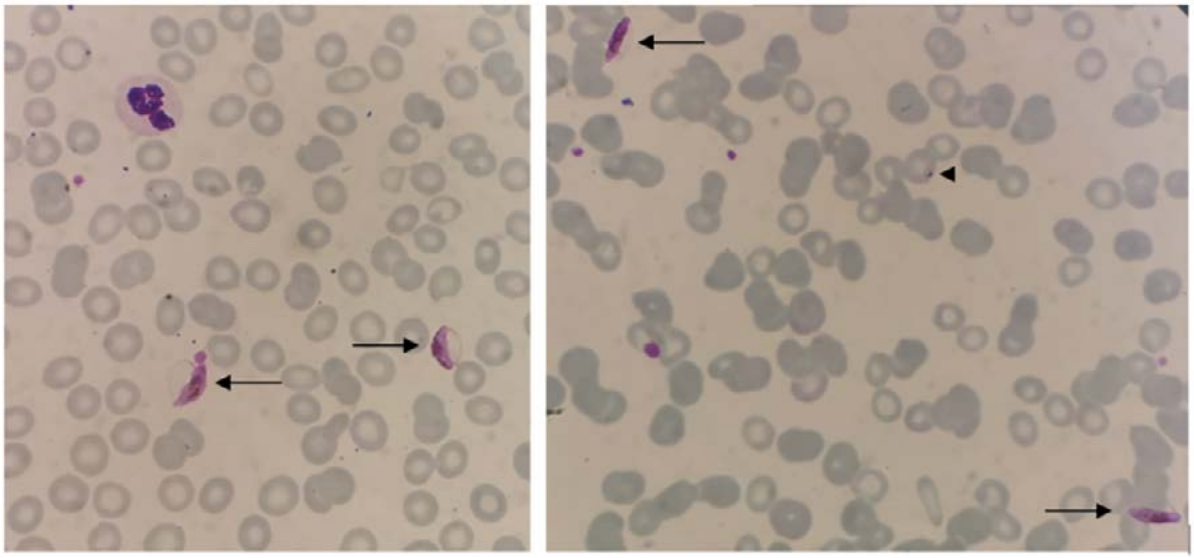

Figure 1: *Plasmodium falciparum* gametocytes (arrows) in a patient with concomitant COVID-19. Ring-form noted at the arrow head. Original magnification 100X.

Because she presented with an acute febrile illness and travel history of return from a malaria endemic area, she was tested for both SARS-CoV-2 and malaria. Malaria was confirmed on blood rapid antigen test screening and thick and thin smear microscopy (Table I). SARS-CoV-2 was detected by polymerase chain reaction (PCR) of a nasopharyngeal sample. The patient was commenced on oral artemether-lumefantrine and paracetamol.

Repeat thick and thin smears after initiation of artemether-lumefantrine showed persistence of a low parasitaemia of 0.5%. The typical banana-shaped (crescent) *P. falciparum* gametocytes (Figure 1) were present together with ring-forms whose species could not be identified with confidence morphologically. The possibility of a mixed *Plasmodium* infection could not be ruled out, thus the sample was sent for malaria PCR, which detected *P. falciparum* only (Table I). The total parasite load was

Table I: Blood results obtained over the course of admission for COVID-19 and *P. falciparum* malaria

Test	Unit	31/03/2020	02/04/2020
Sodium	mmoL/L	129	134
Potassium	mmoL/L	4.0	3.7
Urea	mmoL/L	7.2	3.5
Creatinine	µmoL/L	73	43
Total bilirubin	µmoL/L	54	15
Conjugated bilirubin	µmoL/L		10
Alanine transaminase (ALT)	U/L	17	14
Aspartate transaminase (AST)	U/L		20
Alkaline phosphatase (ALP)	U/L	68	64
Gamma-glutamyl transferase (GGT)	U/L	41	33
Lactate dehydrogenase (LD)	U/L		500
Lipase	U/L	103	
C-reactive protein	mg/L	298	206
Ferritin	µg/L	1 449	
White cell count	$x10^9$/L	4.29	5.41
Neutrophils	$x10^9$/L	2.88	2.96
Lymphocytes	$x10^9$/L	0.89	1.60
Haemoglobin	g/dL		8.4
Haematocrit	L/L		0.286
MCV	fL		80.9
Platelet count	$x10^9$/L	68	88
INR		1.10	
Malaria parasites	%	0.5	0.5
Malaria rapid test		Positive (*P. falciparum* only or mixed)	Positive for *P. falciparum* only
HIV ELISA		Negative	
Malaria PCR			*P. falciparum*

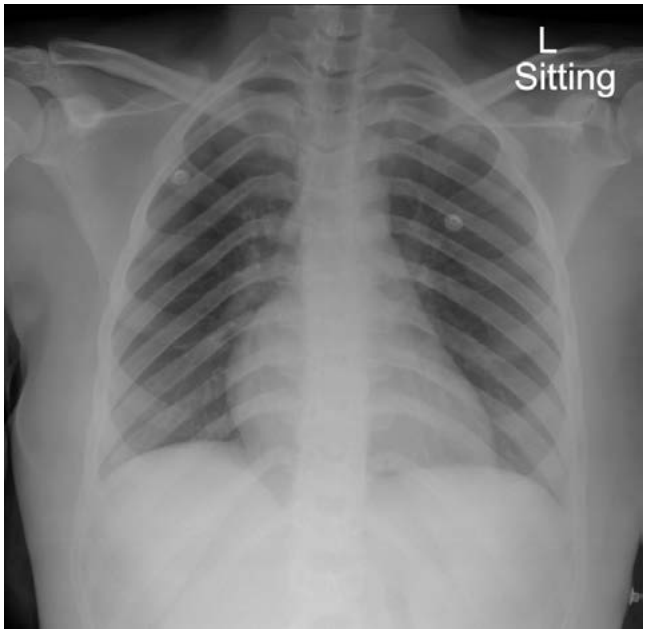

Figure 2: Chest radiograph performed on the day of admission in a patient positive for SARS-CoV-2 with no respiratory symptoms

9 176 parasites/ul and the gametocyte load was 899 parasites/ul, approximately 1 gametocyte for every 10 ring forms.

Chest radiograph was normal (Figure 2). Blood results are tabulated (Table I). Of note, the platelet count was 68 x 10^9/L at presentation which improved to 88 x 10^9/L after initiation of antimalarial treatment. The patient had a haemoglobin of 8.4 g/L which is likely due to malaria in her context.

A final diagnosis of uncomplicated *P. falciparum* malaria with uncomplicated COVID-19 was made and the patient was admitted to a COVID-19 isolation ward at Tygerberg Hospital. Treatment for malaria with artemether-lumefantrine was continued, with resolution of malaria symptoms and absence of malaria parasites on blood smear as determined by light microscopy. On day four of admission she was discharged for self-isolation and informed to contact the hospital if her COVID-19 symptoms worsened.

Discussion

Both malaria and COVID-19 may present with the same symptoms, especially in the absence of respiratory compromise which is usually only seen in moderate to severe COVID-19 disease. The patient's initial symptoms of fever and diarrhoea may be attributable to either disease. The challenges in the diagnosis of malaria within the COVID-19 pandemic where the index of suspicion has been skewed towards COVID-19, has been highlighted.[7]

The patient had laboratory proven *P. falciparum* uncomplicated malaria, i.e. the patient was not encephalopathic, had normal renal function, did not have recurrent hypoglycaemic spells and had a low parasite count. The patient had mild COVID-19 with no respiratory compromise. With the history of travel throughout South Africa, it is difficult to ascertain whether she acquired SARS-CoV-2 in South Africa or Mozambique. On 15 March 2020 a national state of disaster was declared in South Africa and a national lockdown was declared from 26 March 2020. We established that our patient arrived in South Africa on 18 March 2020 before the lockdown was in effect.

P. falciparum gametocytes were detected when the patient was admitted to Tygerberg Hospital. Clinical manifestations of malaria infection only occur during the asexual reproduction stages, while gametogenesis occurs without symptoms. The presence of gametocytes in our patient's blood signifies that she had been infected with malaria for at least a week, as it takes seven to ten days for *P. falciparum* to mature to gametocyte stage.[8] Her mild symptoms may be attributed to potential exposure-related immunity developed from previous malaria episodes, since she hails from a malaria endemic area.[9]

In our patient, the species of malaria was confirmed by PCR after the initiation of anti-malarial therapy. Nucleic acid testing is sensitive for the detection of parasites after initiation of treatment, as nucleic acids of dead malaria parasites are still detectable in the blood. It is for this reason that PCR is not a good method of determining response to anti-malarial treatment, but rather light microscopy is the preferred method.[10] The sensitivity of PCR is generally better than light microscopy at detection of malaria with a detection threshold of < 10 parasites/µl, with some platforms offering sensitivities as low as 0.002 parasites/µl.[10] Furthermore, PCR is useful if the species of malaria cannot confidently be ascertained by light microscopy or if there is concern about a mixed malaria species infection.[10]

The gametocyte load in our patient was very high. Gametocytes usually circulate in the blood at low levels, as only 0.2–1% of asexual parasites commit to gametogenesis with every erythrocyte cycle.[11] In our patient, the gametocytes made up 10% of parasites. Risk factors for gametocyte carriage include age < 15 years, blood groups O and B compared to blood groups A and AB, and treatment with chloroquine.[12] While children may be more likely to be gametocyte-positive, the density of gametocytes increases with age and this is due to factors attributed to increased acquired immunity with increasing age.[13] The age of our patient therefore does not completely explain the relatively high *P. falciparum* gametocyte load seen in our patient. Furthermore, while chloroquine therapy increases gametocyte carriage and alters parasite ringform morphology, artemether-based regimens, as received by our patient, are associated with reduced gametocyte carriage.[12] Gametogenesis is thought, at least partially, to be triggered by stress-related events.[13] Additionally, patients with severe anaemia and increased reticulocyte response have been shown to produce favourable conditions for gametogenesis. This is because reticulocytes have high RNA and haemoglobin synthesis and are less dense than mature erythrocytes making them preferable for gametocyte development within the bone marrow.[13] We hypothesise that in our patient, the degree of anaemia and concomitant COVID-19 which increased the systemic stress signals may have been the cause of the high *P. falciparum* gametocyte load.

Chloroquine was not prescribed in our patient, despite the concomitant malaria infection, because of the high rate of *P. falciparum* chloroquine resistance, and because at the time of

admission, there was no objective evidence from clinical trials evaluating hydroxychloroquine use for COVID-19. Subsequently, randomised controlled trials have shown no benefit in the use of hydroxychloroquine, with or without azithromycin in the treatment of mild to moderate COVID-19.[4]

The *in vitro* efficacy of hydroxychloroquine against SARS-CoV-2 suggests possible shared or similar pathways between SARS-CoV-2 and *Plasmodium* species.[14] Liu and Li postulate, based on *in silico* bioinformatics data, that SARS-CoV-2 may damage erythrocyte haemoglobin.[15] The methods used in this study have been criticised[16] and the study by Liu and Li[15] has not yet been published in a peer-reviewed article. However, the evidence for the role of the erythrocyte, haemoglobin and iron in the pathophysiology of COVID-19 is increasing.[6] Patients with severe COVID-19 have been shown to have an abnormal accumulation of porphyrins in the blood.[17] ABO blood groups have also been shown to be associated with outcome. Group O is associated with lower risk of severe COVID-19 compared with non-O blood groups, whereas blood group A is associated with higher risk compared with non-A blood groups.[18,19] Unfortunately, blood grouping on our patient was not performed. While the role of blood group antigen expression on endothelial cells and platelets is being hypothesised to be the mechanism of severity of the COVID-associated-coagulopathy, the impact of these blood group determinants on erythrocytes may further impact the virus-erythrocyte interaction. Additionally, iron metabolism and *P. falciparum* infection are closely linked.[20] Further *in silico* studies have identified that the cytoplasmic tail of the SARS-CoV-2 spike protein shares homology with hepcidin, suggesting the role that SARS-CoV-2 may play in local iron dysregulation.[21] These *in silico* studies need validation with larger properly designed *in vitro* and *in vivo* studies.

We hypothesise that by limiting haemoglobin availability to the *Plasmodium*, SARS-CoV-2 infection may have retarded the intracellular development of *Plasmodium* species. This may possibly explain the mild symptoms seen in our patient. This patient therefore presents with dual infection by malaria and COVID-19. The clinical course and atypical malaria smear findings could well be due to reciprocal disease-modifying effects of the infections.

Conclusion

This case study highlights the importance maintaining high levels of clinical suspicion of the normal spectrum of pathology seen in the population during the time of the COVID-19 pandemic. Dual pathology does occur, as demonstrated in this patient, thus healthcare professionals are urged to recognise and actively exclude common conditions with symptomatology mimicking COVID-19, and importantly, that pathologies may co-occur.

We postulate that there may be reciprocal disease modification in patients with combined *Plasmodium falciparum* and SARS-CoV-2 infections. The link between the reported efficacy of chloroquine in COVID-19 could provide insights into the effect of SARS-CoV-2 on haemoglobin metabolism. This may be elucidated by further study of COVID-19 patients with concomitant *Plasmodium* infection.

Conflict of interest

The authors declare no conflict of interest.

Funding source

None.

ORCID

MA Parker https://orcid.org/0000-0001-5742-8903
E Nell https://orcid.org/0000-0002-7932-3210
A Mowlana https://orcid.org/0000-0001-9678-533X
MS Moolla https://orcid.org/0000-0003-0274-6909
S Karamchand https://orcid.org/0000-0003-4435-6685
L Murphy https://orcid.org/0000-0002-8730-8715
T Lovelock https://orcid.org/0000-0002-3730-1646
KS Kalombo https://orcid.org/0000-0003-2517-0068
A Parker https://orcid.org/0000-0002-2005-698X
ZC Chapanduka https://orcid.org/0000-0002-5489-8392

References

1. World Health Organization. World Malaria Report 2019. Geneva; 2019. Available from: https://www.who.int/publications/i/item/world-malaria-report-2019. (Accessed 5 April 2020).
2. Di Castelnuovo A, Constanzo S, Antinori A, et al. Use of hydroxyquinine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study. European Journal of Internal Medicine. 2020; in press. https://doi.org/10.1016/j.ejim.2020.08.019.
3. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med. 2020;383:517-25. https://doi.org/10.1056/NEJMoa2016638.
4. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med. 2020;383:2014-52. https://doi.org/10.1056/NEJMoa2019014.
5. Chinappi M, Via A, Marcatili P, Tramontano A. On the mechanism of chloroquine resistance in Plasmodium falciparum. PLoS One. 2010;5(11). https://doi.org/10.1371/journal.pone.0014064.
6. Cavezzi A, Troiani E, Corrao S. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clin Pract. 2020 May 19;10(2):1271. https://doi.org/10.4081/cp.2020.1271.
7. Chanda-Kapata P, Kapata N, Zumla A. COVID-19 and malaria: A symptom screening challenge for malaria endemic countries. Int J Infect Dis. 2020;94:151-3. https://doi.org/10.1016/j.ijid.2020.04.007.
8. Sinden RE. Gametocytogenesis of Plasmodium falciparum in vitro: Ultrastructural observations on the lethal action of chloroquine. Parasitology. 1982;84(1):1-11. https://doi.org/10.1017/S003118200005160X.
9. Gupta S, Snow RW, Donnelly CA, Marsh K, Newbold C. Immunity to non-cerebral severe malaria is acquired after one or two infections. Nat Med. 1999;5(3):340-3. https://doi.org/10.1038/6560.
10. Mathison BA,Pritt BS. Update on malaria diagnostics and test utilization. J Clin Microbiol. 2017 Jul;55(7):2009-17. https://doi.org/10.1128/JCM.02562-16.
11. Sinden RE. The cell biology of sexual development in Plasmodium. Parasitology. 1983;86:7-28. https://doi.org/10.1017/S0031182000050824.
12. Grange L, Loucoubar C, Telle O, et al. Risk factors for Plasmodium falciparum gametocyte positivity in a longitudinal cohort. PLoS One. 2015;10(4):1-13. https://doi.org/10.1371/journal.pone.0123102.
13. Bousema T, Drakeley C. Epidemiology and infectivity of Plasmodium falciparum and Plasmodium vivax gametocytes in relation to malaria control and elimination. Clin Microbiol Rev. 2011;24(2):377-410. https://doi.org/10.1128/CMR.00051-10.
14. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discovery. 2020;6(1):1-4. https://doi.org/10.1038/s41421-020-0156-0.

15. Liu W, Li H. COVID-19: Attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv. 2020;Preprint (December 2019). https://doi.org/10.26434/chemrxiv.11938173.v5.
16. Read R. Flawed methods in "Attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism". ChemRxiv. 2020. https://doi.org/10.26434/chemrxiv.12120912.v2.
17. Juan IS, Bruzzone C, Bizkarguenaga M, et al. Abnormal concentration of porphyrins in serum from COVID-19 patients. Br J Haematol. 2020. https://doi.org/10.1111/bjh.17060.
18. Li J, Wang X, Chen J, et al. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. Br J Haematol. 2020. https://doi.org/10.1111/bjh.16797.
19. Ellinghaus D, Degenhardt F, Bujanda L, et al. The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis. medRxiv. 2020.05.31.20114991. https://doi.org/10.1101/2020.05.31.20114991.
20. Clark MA, Goheen MM, Cerami C. Influence of host iron status on Plasmodium falciparum infection. Front Pharmacol. 2014;5:84. https://doi.org/10.3389/fphar.2014.00084.
21. Ehsani S. Distant sequence similarity between hepcidin and the novel coronavirus spike glycoprotein: a potential hint at the possibility of local iron dysregulation in COVID-19. arXiv:2003.12191. https://doi.org/10.1186/s13062-020-00275-2.