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# Recrudescence of *Plasmodium falciparum* malaria 5 years after treatment in an HIV migrant: a case report with a peculiar presentation

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## SUMMARY

In the last two decades, several cases of delayed-onset malaria in migrants from endemic areas were reported. The decrease of acquired immunity over time, often enhanced by immune suppression, represents a possible underlying mechanism for recrudescence. Here we describe a case of *Plasmodium falciparum* malaria occurring five years after exposure in a patient infected with human immunodeficiency virus, originating from Ivory Coast. Peculiarly, bilateral subsegmental pulmonary embolism in the absence of deep venous thrombosis was also detected, requiring anticoagulant therapy. Treatment with dihydroartemisinin/piperaquine was followed by clearance of trophozoites and the patient was discharged home.

*Keywords*: malaria recrudescence, late-onset malaria, *Plasmodium falciparum*, pulmonary embolism; HIV.

## INTRODUCTION

*Plasmodium falciparum* is responsible for most malaria cases in endemic regions, especially in sub-Saharan Africa. Moreover, due to its propensity to cause severe disease, particularly in children and pregnant women, it accounts for the majority of malaria-related deaths worldwide [1, 2].
In the European Union (EU), 8638 confirmed malaria cases, mainly travel-related, were reported in 2019, with *P. falciparum* representing the most common etiological agent (88,2% of cases) when species identification was performed [3]. Although symptoms usually develop within a few weeks after travel, some cases of late-onset infection, occurring months or years after exposure, were described [4, 5-11].

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Here we present the case of a recrudescent *P. falciparum* malaria in a HIV-infected patient occurring five years after exposure.

## CASE PRESENTATION

A 28-year-old man, originating from Ivory Coast, was admitted to the emergency department of the tertiary-care University-hospital of Pisa, Italy, in August 2021. He complained of fever, headache and abdominal pain starting 72h earlier. The patient had suffered from malaria, treated with unspecified drugs, five years before, when he was still living in Ivory Coast. He moved to Italy in 2016 and had not travelled abroad since then. Moreover, in 2019, the patient was diagnosed with human immunodeficiency virus (HIV) infection, with initial $CD4^+$ T-cell count and HIV viral load of 40,3/$mm^3$ (2,7%) and 1010000 copies/mL, respectively. Despite being on antiretroviral therapy (ART) with tenofovir/emtricitabine/do-

lutegravir 25 mg/200 mg/50 mg per day with a suppressed viral load, he failed to restore $CD4^+$ T-cell count, which remained below 200/$mm^3$ (187/$mm^3$, 11,5% before admission). The patient was not vaccinated for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).

At physical examination he was pyretic (39,5°C) and tachycardic (110 beats/minute), with mild hepatomegaly and splenomegaly. Laboratory analyses revealed mild anemia (12,2 g/dL, laboratory range 13-18 g/dL), thrombocytopenia (73000/$mm^3$), C-reactive protein (CRP) 20,1 mg/dL and procalcitonin 17 ng/mL, D-dimer 6882 ng/mL with normal bilirubin and serum creatinine.

A nasopharyngeal swab for detection of SARS-CoV-2 genome tested positive and an arterial blood gas analysis showed mixed alkalosis with moderate hypoxemia (pH 7,52, pCO2 32 mmHg, pO2 74 mmHg, $HCO_3^-$ 27,6). Therefore, SARS-CoV-2-related pneumonia was suspected and a chest and abdomen computerized tomography (CT) scan was performed. While there were no signs of pneumonia, bilateral subsegmental pulmonary embolism of the lower lobes was detected, along with mild hepatomegaly and splenomegaly. In the hypothesis of a coronavirus disease (COVID-19) complicated by a bacterial coinfection, the patient was admitted to the COVID medical ward, where empirical antibiotic treatment with piperacillin/tazobactam 4,5 g every six hours was started, together with anticoagulant therapy with fondaparinux 7,5 mg per day for pulmonary embolism.

In the following days, despite antibiotic treatment, the patient remained febrile, with increasing CRP, procalcitonin and worsening anemia. Multiple blood cultures were negative. An active SARS-CoV-2 infection was not confirmed, as four subsequent nasopharyngeal swabs all proved negative. Finally, six days after the admission, a

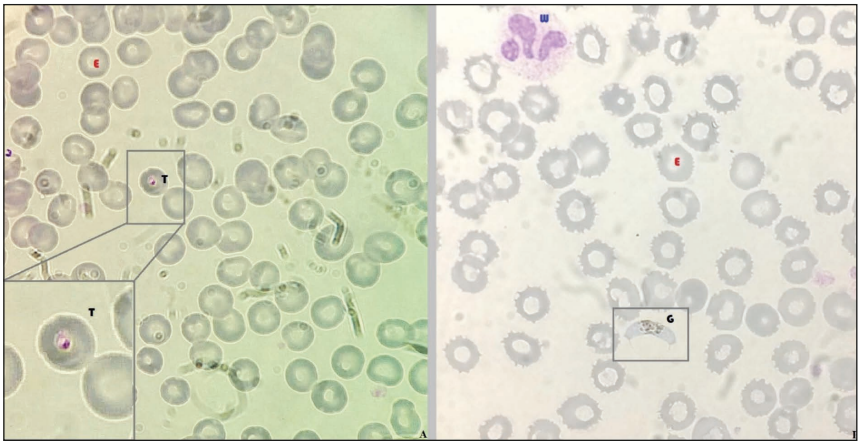


**Figure 1** - Thin blood smear with a trophozoite (T) (**panel A**) and a gametocyte (G) (**panel B**); W, white blood cell. E, erythrocyte.

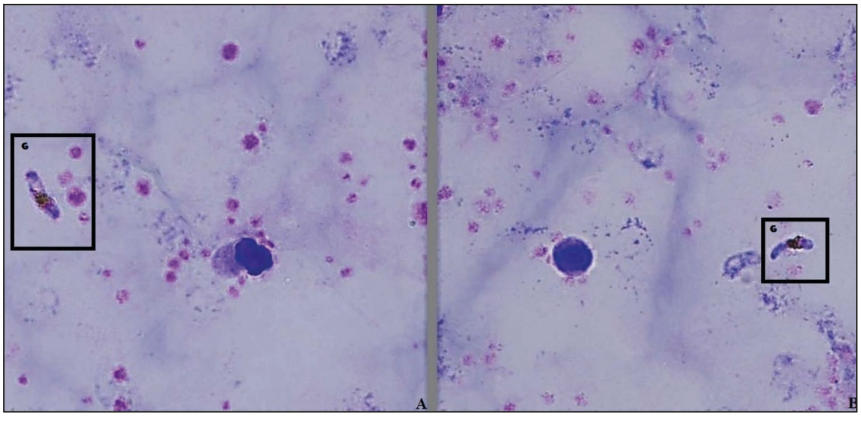


**Figure 2, panel A and panel B** - Thick blood smear with two Plasmodium falciparum gametocytes.

loop-mediated isothermal amplification (LAMP) test proved positive; the blood smear revealed the presence of *P. falciparum* gametocytes and trophozoites (Figure 1, Figure 2), with a thick film parasitaemia of 42/mm$^3$.
Antibiotic treatment was discontinued and oral dihydroartemisinin/piperaquine 320 mg/40 mg per day for three days was administered, with rapid defervescence and improvement of laboratory tests. Subsequent blood smears and thick films showed complete clearance of trophozoites with some persistent gametocytes (last parasitaemia 13/mm$^3$). Further, an echo-color Doppler of the lower limbs excluded deep venous thrombosis. The patient was then discharged with the indication to continue anticoagulant therapy with seleparin for three months. A LAMP test and a blood smear were repeated six weeks after discharge, both proving negative.

## DISCUSSION

We described a case of recrudescent *P. falciparum* malaria, occurring five years after the first episode, in a HIV-infected man originating from Ivory Coast. The patient denied any travel abroad since he moved to Italy, any use of intravenous drugs and did not receive any solid organ transplant or blood transfusion. Luggage malaria was excluded, because the patient denied any contact with people recently coming from endemic areas. Local transmission, with the patient's cohabitants representing a potential source of infection, appears unlikely. *Anopheles labranchiae*, regarded as the main malaria vector in Italy, is present in Tuscany. Nonetheless, recent entomological investigations, conducted for suspected locally-transmitted malaria cases, failed to demonstrate *Anopheles* species presence in several Italian areas, including Tuscany [13]. Besides, previous work suggested that *A. labranchiae* shows a low tropism for tropical *P. falciparum* strains, further reducing the probability of local transmission [14].
Our initial hypothesis of a SARS-CoV-2 disease complicated by a bacterial coinfection was not confirmed. Indeed, the first positive nasopharyngeal swab was followed by four negative swabs, ruling out an active SARS-CoV2 infection, and multiple blood cultures were negative. Then, considering the patient history, we hypothesized a late malaria recrudescence. In fact, although uncommon in non-immune travelers, several cases of late-onset malaria or late recrudescences, up to 13 years after exposure, have been reported in migrants coming from endemic areas [5-14].
Previous reports suggest that people living in high-transmission areas, due to repeated exposure, acquire some degree of immunity against *Plasmodium* asexual blood stages, resulting in the maintenance of low, often asymptomatic parasitaemia [15]. When exposure ceases, as for migrants moving to non-endemic areas, the slow decay of that protection is likely to allow parasites to replicate, leading to recrudescences over time. Several conditions impairing immunity, such as pregnancy, cancer and HIV infection, probably represent additional risk factors for recrudescence [5, 16]. Notably, two cases of *P. falciparum* malaria late reactivation have been described in patients treated with biological agents (namely, infliximab and tocilizumab) for inflammatory disorders [17, 18]; this is consistent with previous evidence showing the relevant role of tumor necrosis factor α (TNF α) and interleukin 6 (IL-6) in promoting parasite clearance [15]. Finally, *P. falciparum* recrudescences in patients undergoing splenectomy for suspected lymphoma were reported, further supporting the hypothesis that immune suppression, either iatrogenic or due to acquired diseases, may trigger malaria reactivation in people with low-level parasitaemia [19]. In our patient, HIV infection with a persistently low CD4$^+$ T-cell count notwithstanding ART could have reduced his ability to control *P. falciparum* replication as previously hypothesized, and the the recent SARS-CoV-2 infection may have further decreased T-cell number and activity [20, 21]. The mechanisms by which HIV infection may reduce malaria immunity is not fully understood. However, some authors observed lower levels of opsonizing antibodies directed against *P. falciparum* in HIV-infected patients, together with reduced phagocytic activity; this impaired parasite clearance, which is particularly relevant in patients with lower CD4$^+$ T-cell count, could partially explain the increased risk of parasitaemia seen in this population [22]. On the other hand, as shown by Moncunill et al., migrants from endemic areas are still able to develop humoral responses against several malarial antigens, particularly those associated to complicated malaria, such as Duffy binding-like alpha (DBL-α). This could account for protection

against severe malaria, as observed in our patient, who presented with uncomplicated disease and a very low parasitaemia [23].
Another peculiar feature of our case consists in pulmonary embolism (PE). While acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are well-known manifestations of severe malaria, PE is an uncommon finding in this context [22]. Conversely, PE, even in the absence of deep vein thrombosis, is a frequently detected as a complication of COVID-19, particularly when high-sensitivity tests, as CT pulmonary angiography (CTPA), are performed [23]. Although an active COVID-19 was excluded, a a recent SARS-CoV-2 infection, as suggested by the first positive nasopharyngeal swab, may represent a plausible explanation for bilateral, subsegmental PE.
In conclusion, late *P. falciparum* malaria recrudescences can occur, especially in migrants coming from high-endemicity areas. Thus, prompt laboratory testing should be performed in case of high clinical suspicion, particularly if concomitant conditions leading to immune suppression, such as HIV infection, exist.

**Authors' contributions**
A.F. and N.R. conceived and draft the manuscript; A.F., C.B. and R.I. took care of the patient;
A.F. and P.S. performed the literature search; L.R.S., G.T., M.F. and F.M. reviewed the manuscript; M.F. and F.M. supervised all the work

**Conflicts of interest**
The authors have no conflicts of interest to disclose.

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**Ethics approval**
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Pisa University (No. 17681). Samples were taken as part of the standard patient care and anonymized by the clinical personnel. Research personnel received and used the sample anonymously.

**Consent to publish**
Patients signed informed consent regarding publishing their data.

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