VIA MEDICA

CASE REPORT

Int Marit Health
2022; 73, 1: 46–51
10.5603/IMH.2022.0006
www.intmarhealth.pl

ISSN 1641-9251
eISSN 2081-3252

Challenges in the diagnosis and treatment of malaria in Polish workers returning from Africa: a case series and review of literature

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ABSTRACT

Malaria is a parasitic disease caused in humans by five species of Plasmodium: P. falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi and transmitted through a female mosquito bite. In 2020, there were 241 million cases of malaria worldwide including 627,000 deaths. Traveling to malaria endemic areas is a significant risk factor, therefore, it is very important to use non-specific and pharmacological prophylaxis. Malaria symptoms usually appear 10–14 days after infection and the disease may be suspected, based on patient examination and medical history, in patients with fever who have stayed in malaria endemic areas. The initial symptoms of the disease are not pathognomonic and it is important to remember that not all malaria patients develop a fever. A prerequisite for successful treatment of this potentially life-threatening disease is well-targeted, timely diagnosis and immediate implementation of antiparasitic therapy. Despite significant progress in the fight against malaria across the world, the disease still poses a diagnostic and therapeutic challenge, especially when it develops as a result of an imported infection and when diagnosis is complicated by the presence of other diseases. A professional group that requires special attention are maritime workers.
In this study we present clinical cases of malaria which show how important it is in the clinical practice of various specialists to include malaria in the differential diagnosis of patients with fever returning from tropical regions.

(Int Marit Health 2022; 73, 1: 46–51)

Key words: *Plasmodium*, malaria, fever, tropical medicine

INTRODUCTION

Malaria is a parasitic disease caused in humans by five species of *Plasmodium*: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi* [1]. The disease is transmitted through a female *Anopheles* mosquito bite, when the insect pierces human skin with its stylet and introduces sporozoites (forms of *Plasmodium* that are invasive to humans) into the human bloodstream. Infection can also occur through blood transfusion and vertical route from mother to child (placenta) [2]. The life

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cycle of *Anopheles* mosquitoes (infection vector) is dependent on climatic conditions. The most favorable conditions include the temperatures from 16 °C to 33 °C [3], altitude up to a maximum of 2000–2500 m above sea level and air humidity above 60%. The presence of water bodies is also essential for mosquitoes to reproduce. Of the species of pathogenic parasites, the most dangerous to humans is *Plasmodium falciparum*, which can cause severe malaria [4].

There have also been reports of a *Plasmodium* infection in people who have never been to a malaria-endemic area. Airport and harbor malaria is a specific form of indigenous malaria, when an *Anopheles* mosquito infected with *Plasmodium* travels, for example in luggage, from an endemic area to a country where the disease is absent. Although airport and port malaria is rare (only 33 cases from 1969 to 2020 have been reported in the literature), an upward trend in the incidence has been observed in the last decade. More than a half of the confirmed cases took place in Europe [5], including France, Belgium, Switzerland and Spain [2, 6, 7]. This type of malaria commonly occurs in the summer months (July, August), during which time in southern Europe there is a climate similar to that of endemic regions. Although airport malaria is rare, the apparent absence of a history of risk factors may result in a delay in diagnosis and, consequently, in appropriate treatment of the patient [8].

It should also be remembered that even a short stay in an area where malaria vectors are present, such as an airport, when transferring to a connecting flight, may result in a *Plasmodium* infection [2, 5].

EPIDEMIOLOGY

In 2020, there were 241 million cases of malaria worldwide, compared with 227 million in 2019. The vast majority of cases (95%) were reported in Africa, followed by Southeast Asia (2.0%; 5 million), and the Eastern Mediterranean (2.3%; 5.7 million). More than 50% of the reported malaria cases occurred in six African countries: Nigeria (27%), the Democratic Republic of the Congo (12%), Uganda (5%), Mozambique (4%), Angola (3.4%), and Burkina Faso (3.4%).

In 2020, there were 627,000 deaths from malaria, compared with 405,000 deaths in 2018 and 558,000 deaths in 2019 [9, 10].

CLINICAL PICTURE

Symptoms of the disease usually appear 10–14 days after infection. In over 90% of patients, malaria occurs within a month after travel, although it may appear as late as even several months after returning from the endemic regions [11, 12].

Malaria may be suspected, based on patient examination and medical history, in patients with fever who have stayed in malaria endemic areas. The initial symptoms of the disease are not pathognomonic. Apart from fever, they may include: tachycardia, tachypnea, chills, general weakness, fatigue, excessive sweating, headache, cough, lack of appetite, nausea, vomiting, abdominal pain, jaundice, diarrhea, and muscle aches. It should be noted that not all malaria patients develop a fever [13]. Uncomplicated malaria is diagnosed in patients with mild symptoms, and it is confirmed by parasitological tests. Rapid immunochromatographic tests based on the detection of *Plasmodium* antigens may be useful, although because of their low sensitivity a negative result does not exclude malaria. On physical examination, signs of anemia and enlargement of the liver and spleen can be expected. A prerequisite for successful treatment of this potentially life-threatening disease is well-targeted, timely diagnosis and immediate implementation of antiparasitic therapy.

BUSINESS TRAVELERS

Traveling to malaria endemic areas is a significant risk factor. Protection against malaria in travelers to endemic countries (including business travelers) includes non-specific prophylaxis, i.e., protection against mosquito bites, and pharmacological prophylaxis.

Unfortunately, despite the rapid development of tropical medicine and increase in international arrivals, a significant proportion of travelers fail to adhere to the principles of prevention. A study conducted among workers posted to Zambia and Ghana showed that the principles of prophylaxis were only followed by 44% and 11% of the respondents, respectively [14]. Of all the United States residents hospitalized due to malaria only 23% reported that they respected the principles of prophylaxis while staying in endemic areas [15]. A similar result was obtained in a study conducted in Switzerland. The study demonstrated that only about 16% of people traveling to high-risk areas on business adhered to chemoprophylaxis in combination with personal protective measures. Unfortunately, this study also showed a lack of knowledge of the disease symptoms and its incubation period [14]. Interestingly, a survey conducted among missionaries working in Zaire revealed that approximately 62% of the respondents adhered to chemoprophylaxis of malaria, which was the highest rate of compliance in travelers to areas with high risk of malaria transmission reported to date [16].

The authors present cases showing difficulties in diagnosing and treating malaria in people returning from work trips to Africa.

CASE 1

A 27-year-old patient, a mechanic on a ship, who had previously stayed in Sierra Leone for 4 months, was admitted to the Department of Tropical and Parasitic Diseases in

Gdynia, Poland due to a fever of up to 40 °C accompanied by chills, weakness, muscle pain and headache. The symptoms occurred 6 days after returning to Poland. The patient denied abdominal pain, diarrhea, vomiting or cough. Before being admitted to our hospital, the patient was consulted by a doctor several times, but he was not tested for malaria.

The medical interview revealed that the patient had an open fracture of the right lower leg, which occurred in Sierra Leone 20 days before his return to Poland. The patient underwent surgical treatment at a local hospital in Sierra Leone and received antibiotic therapy (ceftriaxone, gentamicin, metronidazole).

While working on the ship the patient was taking malaria chemoprophylaxis (he did not remember the name of the drug), but it was discontinued during the hospitalization after the lower limb injury.

On admission, the general condition of the patient was fair. He had low blood pressure (95/55 mmHg), heart rate of 76/min, and fever (38.6 °C).

Physical examination revealed a fine blotchy rash and an oozing wound on the right lower leg, with a visible metal frame of the external fixation of the fractured bone. The patient was consulted by an orthopedist who did not find any evidence of wound infection.

Laboratory test results were as follows: elevated levels of procalcitonin (95.24 ng/mL), C-reactive protein (CRP; 63.8 mg/L), creatinine (1.64 mg/dL), D-dimer (5020 ng/mL), alanine aminotransferase (ALT; 53 U/L), and gamma-glutamyl transpeptidase (123 U/L), decreased platelet count (57 G/L) and hemoglobin concentration (11.5 g/dL). The rapid test for malaria was positive for *Plasmodium falciparum*; direct microscopic examination of the blood (thin and thick smears) revealed numerous rings of *Plasmodium falciparum*. Blood, urine, and wound swab cultures were negative. Serological tests for dengue showed presence of IgM- (36.2 NTU) and IgG-class (11.4 NTU) antibodies.

Abdominal ultrasound revealed splenomegaly (149 mm), a normoechogenic liver with the right lobe length of 140 mm and a lymph node measuring 13 × 6 mm in the hilum. Chest X-ray showed increased interstitial lung markings, and bronchitis was suspected.

During hospitalization, the treatment with artesunate at a dose of 2.4 mg/kg body weight/day and doxycycline at a dose of 200 mg/day was administered, followed by a combination of artemether with lumefantrine (20 mg/120 mg tablets) administered 4 tablets twice a day for 3 days. In addition, the patient received piperacillin with tazobactam, low molecular weight heparin, as well as antipyretic and hepatoprotective drugs.

The treatment resulted in a significant improvement in the patient's condition, a decrease in inflammatory parameters (CRP 8.7 mg/L, procalcitonin 2 ng/mL) and blood smear negativization. The patient was discharged home in good condition, without fever. There were no recurrences of the disease in the follow-up.

CASE 2

A 51-year-old patient was transferred to the Department of Tropical and Parasitic Diseases in Gdynia, Poland from the Emergency Department of the Specialist Hospital due to the diagnosis of malaria. Six days earlier, the patient had returned from Africa (Guinea), where he had stayed on business for 2 months. The patient was taking antimalarial prophylaxis (proguanil with chloroquine), but not regularly. During his stay in Africa, 3 days before his return to Poland, he had a motorcycle accident in which his left thigh was injured, resulting in the formation of a fluid collection. The patient had a fever of up to 40 °C for 5 days. During this time, he was twice referred for observation/consultation in the Hospital Emergency Department where the fluid collection in the thigh was evacuated twice (clear, colorless fluid). Amoxicillin/clavulanic acid was recommended and the patient was referred to outpatient care. Diagnostic tests for malaria were not performed, although the patient reported a stay in an endemic area. The tests performed during the second visit to the Hospital Emergency Department revealed the presence of *Plasmodium* schizonts in the blood smear.

On admission to our Department, the patient was in fair general condition, hemodynamically and respiratory stable, with good verbal response, and fever up to 39 °C. Physical examination revealed a fluid collection on the left thigh without signs of inflammation, and abrasions on the left upper limb. Laboratory test results were as follows: positive rapid malaria test (*Plasmodium falciparum*), anemia (12.5 g/dL), thrombocytopenia (48 g/L), elevated concentration of both CRP (218 mg/dL) and D-dimer (6512 ng/mL). Direct blood test (thick and thin smears) showed *P. falciparum* rings; parasitemia was 20%. A polymerase chain reaction test for malaria was positive for *P. falciparum*. No dengue-specific IgM- and IgG-class antibodies were detected by the serological test. Abdominal ultrasound showed an enlarged liver (160 mm) and spleen (157 mm) as well as an enlarged prostate with fibrosis. Chest X-ray showed no abnormality.

Treatment with artesunate at a dose of 2.4 mg/kg body weight in a five-dose regimen (0, 12, 24, 48, and 72 hours) and clindamycin at a dose of 1800 mg/day was administered. On the first day of treatment, the patient had a fever of up to 39 °C; he was agitated and restless, and had delayed verbal response. Saturation dropped to 88% and dark-colored urine was observed. Reassessment of laboratory parameters showed worsening of anemia (9.5 g/dL), hyperbilirubinemia (3.46 mg/dL),

high lactate dehydrogenase activity (811 U/L). Testing for glucose-6-phosphate dehydrogenase (G-6-PD) deficiency (7.7 U/g of Hb, normal range: 7–20.5) was ordered. A significant decrease in parasitemia was found in subsequent blood smears. The artesunate treatment was completed and the treatment was continued with a combination of artemether with lumefantrine (20 mg/120 mg tablets) administered 4 tablets twice a day for 3 days. Blood smears for malaria were negative. Improvement in the patient's clinical condition and laboratory parameters was observed. Due to the fact that the fluid collection on the left thigh was still present, a surgical consultation was provided — suction drainage in the surgical department was recommended.

CASE 3

A 23-year-old patient was transferred to the Department of Tropical and Parasitic Diseases in Gdynia from the Surgical Department (where he had stayed for 10 days) with suspicion of malaria. The patient had an accident at work on a ship in Sierra Leone about 3 weeks earlier (fracture of the humerus and soft tissue injury to the right arm, and injury to the right half of the chest). During hospitalization in Sierra Leone, thoracotomy and lower lobectomy of the right lung as well as external anastomosis of the fractures of the humerus were performed. The day before returning to Poland, the patient developed a fever above 39 °C with accompanying shivers and general weakness.

In Poland, he was admitted to the Department of Surgery, where he was diagnosed with: status post (S/P) multi-organ trauma, S/P lobectomy of the lower right lung, S/P external osteosynthesis of the right humerus, S/P skinning of the right arm area and autologous middle-thickness skin transplantation in this area, residual right-sided pneumothorax, residual hematoma of the right pleural cavity with a slight postoperative atelectasis of the right lung. Due to the persistent fever, malaria was suspected.

On admission to our department, the general condition of the patient was fair. The patient manifested the following symptoms: fever above 40 °C, chills, profuse sweating, lack of appetite. A physical examination revealed the scar after right-sided thoracotomy, the metal frame of the external osteosynthesis of the right humerus, the scar on the right thigh and the healing wound on the right shoulder after autologous skin transplantation. In addition, the patient was exhausted (he lost about 11 kg in a month) and was reluctant to leave the bed/perform any physical activity.

The following results were obtained from laboratory tests: a positive rapid malaria test (*P. falciparum*), anemia (10.5 g/dL), thrombocytopenia (84 G/L), increased CRP concentration (56 mg/L), increased D-dimer concentration (2299 ng/mL), increased ALT activity (111 U/L) and decreased albumin level (23.8 g/L). Direct blood test (thick and thin smears) revealed *P. falciparum* rings and gametocytes with parasitemia of about 1.5%.

Ultrasound examination of the abdominal cavity revealed an enlarged spleen (155 × 70 mm). Chest X-ray showed fluid in the pleural cavity and a raised diaphragm on the right side, visible shadowing of the lower field above the fluid corresponding to atelectasis, and areas of parenchymal consolidation probably corresponding to postoperative lesions.

Malaria treatment with artesunate with doxycycline was initiated, followed by a combination of artemether with lumefantrine; antibiotic therapy with amikacin, which was started in the Surgical Department, was continued. The fever subsided and the patient's clinical condition improved significantly. Pulmonary rehabilitation was started, which improved the dynamics of breathing. The patient was discharged home in good general condition, without fever. There were no recurrences of the disease in the follow-up.

DISCUSSION

Among the mosquito-borne diseases, malaria remains a major health concern in tropical regions around the world. The above cases show how important it is in the clinical practice of various specialists to include malaria in the differential diagnosis of patients with fever returning from tropical regions (including overseas workers). This is particularly important considering that these patients are not immediately referred to one of the few centers in Poland specializing in the treatment of tropical diseases. Every physician, regardless of their specialization, should be aware that diagnostic tests to exclude or confirm a *Plasmodium* infection are necessary in people who have recently returned from malaria-endemic areas. Unfortunately, the diagnosis of malaria in Poland is still a challenge for diagnosticians and doctors. In all the above described cases diagnosis of malaria was delayed from 6 to 10 days, which in case of an infection with *Plasmodium falciparum* may result in severe and life threatening complications.

According to the data from the GeoSentinel network published in 2017, more than a half (53%) of travelers diagnosed with malaria visited friends and relatives. The majority (83%) were exposed in sub-Saharan Africa. The median duration of the trip was 32 days; 53% did not have a pre-travel consultation. More than a half of the patients (62%) were hospitalized, and the majority of those hospitalized were children. The most commonly identified species was *P. falciparum*. However, more than 40% of travelers who stayed in a malaria-affected region for ≤ 7 days were found to be infected with *P. vivax* [17].

Laboratory findings that are characteristic of malaria include the presence of parasites in direct blood tests, anemia, thrombocytopenia, increased activities of transaminases, mild coagulopathies, and increased levels of urea and creatinine. Severe malaria is defined as malaria caused by *Plasmodium falciparum* [4] (parasitemia > 10%; > 500,000/microliter of blood) [11, 18] with one or more of the following symptoms: impaired consciousness (assessed according to the Glasgow scale), extreme fatigue (the patient cannot sit up, stand up or walk without assistance), seizures (more than 2 episodes in 24 hours), and laboratory abnormalities: metabolic acidosis, hypoglycemia, severe anemia or massive intravascular hemolysis, coagulation disorders, including disseminated intravascular coagulation, impaired kidney function, liver damage and/or jaundice (bilirubin > 3 mg/dL), pulmonary edema/acute respiratory distress syndrome, significant bleeding (e.g. nosebleed, bleeding gums, bloody vomiting, or stools), shock (systolic blood pressure < 70 mmHg).

The differential diagnosis of malaria should include dengue, chikungunya, meningitis, pneumonia, bacteremia, typhoid fever, leptospirosis, and viral hemorrhagic fever [19].

A delay in the diagnosis and treatment of malaria can lead to an increased number of complications and increased mortality from the disease. In uncomplicated cases, patients can be treated with oral antimalarials. In severe malaria, immediate initiation of intravenous treatment (optimally with monitoring for parasitemia) is essential. Artesunate or, when intravenous administration is not possible, intramuscular artemether is the preferred drug [9, 11]. If artemether is not available intravenous quinine or quinidine may be recommended. Artemisinin derivatives reduce parasitemia in a shorter time and are associated with a statistically significant reduction in mortality compared with quinine [18].

When collecting a medical history, it is extremely important to carefully review the travel history as well as details of the prophylaxis and vaccinations. The possibility of co-occurrence of other internal diseases with *Plasmodium* infection should also be taken into account.

In the 1970s, Europe was declared free from endemic malaria (Poland was certified malaria-free in 1967) [20]. However, the climate change favors the spread of mosquitoes and parasites. Increased economic migration, the influx of refugees and migrants from endemic areas may contribute to the formation of *Plasmodium* reservoirs in areas previously free from malaria. Since 2009, native malaria has been reported in Greece and isolated cases of malaria were reported in Spain, Italy and France [3].

Due to the development of tourism and increasing population migration, the disease is becoming a major health issue globally, including in Poland.

CONCLUSIONS

Despite significant progress in the fight against malaria across the world, the disease still poses a diagnostic and therapeutic challenge, especially when it develops as a result of an imported infection and when diagnosis is complicated by the presence of other diseases. A professional group that requires special attention are maritime workers.

Conflict of interest: None declared

REFERENCES

1. Tan KT, Arguin PM. Yellow Book 2020. Malaria. Oxford University Press:, New York 2020: 267–287.
2. Velasco E, Gomez-Barroso D, Varela C, et al. Non-imported malaria in non-endemic countries: a review of cases in Spain. Malar J. 2017; 16(1): 260, doi: 10.1186/s12936-017-1915-8, indexed in Pubmed: 28662650.
3. Piperaki ET, Daikos GL. Malaria in Europe: emerging threat or minor nuisance? Clin Microbiol Infect. 2016; 22(6): 487–493, doi: 10.1016/j.cmi.2016.04.023, indexed in Pubmed: 27172807.
4. Severe malaria. Trop Med Int Health. 2014; 19 Suppl 1: 7–131, doi: 10.1111/tmi.12313_2, indexed in Pubmed: 25214480.
5. Alenou LD, Etang J. Airport malaria in non-endemic areas: new insights into mosquito vectors, case management and major challenges. Microorganisms. 2021; 9(10), doi: 10.3390/microorganisms9102160, indexed in Pubmed: 34683481.
6. Guillet P, Germain MC, Giacomini T, et al. Origin and prevention of airport malaria in France. Trop Med Int Health. 1998; 3(9): 700–705, doi: 10.1046/j.1365-3156.1998.00296.x, indexed in Pubmed: 9754664.
7. Bouvier M, Pittet D, Loutan L, et al. [Airport malaria: mini-epidemic in Switzerland]. Schweiz Med Wochenschr. 1990; 120(34): 1217–1222, indexed in Pubmed: 2218443.
8. Isaäcson M. Airport malaria: a review. Bull World Health Organ. 1989; 67(6): 737–743.
9. WHO. World Malaria Report 2021. World Health Organization: Geneva, Switzerland. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021.n (6 Dec 2020).
10. Centers for Disease Control and Prevention. Malaria's Impact Worldwide. Global Health, Division of Parasitic Diseases and Malaria. https://www.cdc.gov/malaria/malaria_worldwide/impact.html (26 Jan 2021).
11. WHO Guidelines for malaria, 2021. World Health Organization: Geneva, Switzerland. 13 July 2021 (ppData/Local/Temp/WHO-UCN-GMP-2021.01-eng.pdf).
12. Morgan GS, Chiodini P, Evans M. Relapsing malaria: two cases of malaria presenting 8 months after return from Africa despite adherence to antimalarial chemoprophylaxis. Br J Gen Pract. 2012; 62(603): 555–556, doi: 10.3399/bjgp12X657017, indexed in Pubmed: 23265223.
13. Dorsey G, Gandhi M, Oyugi JH, et al. Difficulties in the prevention, diagnosis, and treatment of imported malaria. Arch Intern Med.

2000; 160(16): 2505–2510, doi: 10.1001/archinte.160.16.2505, indexed in Pubmed: 10979063.
14. Weber R, Schlagenhauf P, Amsler L, et al. Knowledge, attitudes and practices of business travelers regarding malaria risk and prevention. J Travel Med. 2003; 10(4): 219–224, doi: 10.2310/7060.2003.40574, indexed in Pubmed: 12946300.
15. Lim PL, Han P, Chen LH, et al. GeoSentinel Surveillance Network. Expatriates ill after travel: results from the Geosentinel Surveillance Network. BMC Infect Dis. 2012; 12: 386, doi: 10.1186/1471-2334-12-386, indexed in Pubmed: 23273048.
16. Burdon J. Use of malarial prophylaxis amongst a population of expatriate church workers in Northeast Zaire. J Travel Med. 1998; 5(1): 36–38, doi: 10.1111/j.1708-8305.1998.tb00455.x, indexed in Pubmed: 9772315.
17. Angelo KM, Libman M, Caumes E, et al. GeoSentinel Network. Malaria after international travel: a GeoSentinel analysis, 2003–2016. Malar J. 2017; 16(1): 293, doi: 10.1186/s12936-017-1936-3, indexed in Pubmed: 28728595.
18. South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. The Lancet. 2005; 366(9487): 717–725, doi: 10.1016/s0140-6736(05)67176-0.
19. Murdoch D. Diseases potentially acquired by travel to West Africa. https://www.uptodate.com/contents/diseases-potentially-acquired-by-travel-to-central-africa (Jan 21, 2021).
20. World Health Organization. Elimination of malaria. Chapter 5. World Malaria Report 2009. ttps://apps.who.int/iris/bitstream/handle/10665/44234/9789241563901_eng.pdf.