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HIV Infection Diagnosis in a Late Presenter Patient during a Severe Imported Falciparum Malaria: A Challenging

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Abstract

BACKGROUND: Malaria and HIV share the same epidemiological spreading and coinfection may be clinically challenging. In 2019, nearly all malaria cases reported by EU/EEA countries were imported. Severe falciparum malaria is a medical emergency often associated with poor outcome, even when treated with appropriate therapy.

CASE PRESENTATION: Here, we described an unusual case of a late presenter HIV diagnosis made during the management of a severe falciparum malaria in an Italian traveler returning from Nigeria, who did not take antimalaria prophylaxis. Clinical course was complicated by the occurrence of several superinfections caused by deep immunosuppression, and bilateral subsegmental pulmonary embolism.

CONCLUSION: Although critical conditions, malaria prompt diagnosis and treatment, along with HIV diagnosis and the successful treatment of occurred superinfection, resulted in a positive outcome.

Introduction

Although the differences regarding transmission and pathogenesis, malaria and HIV infection have a comparable spreading, being constant in sub-Saharan Africa, Southeast Asia, and the Indian subcontinent [1].

Worldwide, HIV infection statistics reported approximately 37.7 million people living with HIV and 680,000 deaths observed in 2020 [2], [3].

On the other hand, 1.2 billion people are at risk for malaria infection, resulting in 500 million infections and more than 1 million deaths each year [1].

Because of the similar geographic distribution with high incidence and prevalence in the same settings, HIV/malaria coinfection is likely to occur, especially in patients with advanced immunosuppression, and interactions between the two diseases lead to major public health issues and adverse outcomes [4].

As a matter of fact, scientific literature revealed that patients with HIV infection, aside from immunosuppression issues [5], were at increased risk of malaria serious events, such as higher parasitemia and central nervous system involvement [6], [7], [8], [9].

Besides, in non-endemic countries, malaria is one of the most common imported diseases and it should be suspected in all febrile returned travelers, as well as HIV infection should be presumed in every patient with unexplained fever and consistent symptoms and signs of immunosuppression [10].

HIV late presenters still symbolize a challenge for clinicians, often too difficult to deal with due to the threat of suboptimal and poor results.

We reported a case of a late-presenter HIV infection diagnosed during a recent identification of severe malaria, complicated with multiple bacterial and fungal bloodstream infection.

Case Presentation

A 47-year-old Italian male was admitted to ED because of 2 days of fever (T max 39°C), severe headache, jaundice, and impaired consciousness. The patient had returned 5 days earlier from Nigeria, where he regularly went for work. He did not take anti-malarial chemoprophylaxis during the last visit.

He had no comorbidities, and he did not take any drugs. He had an unremarkable clinical history, except for two previous episodes of malaria (the last in 2016) caused by *Plasmodium falciparum* requiring few days of hospitalization and resolved with oral artesunate treatment.

On admission he was febrile (T 38.5°C), tachycardic (HR 110 bpm), blood pressure was 90/60 mmHg and peripheral oxygen saturation was 95% in room air. Glasgow Coma Scale was 11.

Clinical examination showed superficial lymphadenopathy along with hepatosplenomegaly.

Laboratory examination showed anemia (Hb 8.0 g/dl), low platelet levels (66.000/mmc), normal white blood cells count with lymphopenia (6000/mmc WBC, 85% neutrophils, 10% lymphocytes); high inflammatory markers levels (ESR 86 mm/h; CRP 34 mg/dl), and procalcitonin was 3 ng/ml. Creatinine level was 4.8 mg/dl (eGFR with CKD-EPI was 14 ml/min). Transaminases were slightly elevated (ALT 70 UI/l, AST 68 UI/L) as well as bilirubin levels (4.5 mg/dl). Glucose levels were normal, levels of pancreatic enzymes were also elevated (amylases 600 UI/L, lipases 500 UI/L).

Due to his clinical and epidemiological history, an immunochromatographic rapid test was performed resulting positive for *P. falciparum* infection, and a thin blood smear confirmed the diagnosis and revealed 5% parasitemia. The diagnosis of severe malaria was made, and the patient was transferred to the Intensive Care Unit.

Due to the shortage of artesunate iv, the patient started treatment with quinine dihydrochloride iv plus doxycycline iv. After 72 h the parasitemia was <1% and within 96 h the patient cleared the parasitemia. The treatment was administered for 7 days monitoring electrocardiogram to assess QTc, without abnormalities. The patient performed three hemodialysis sessions due to the high creatinine levels.

Because of clinical conditions amelioration and sensory improvement, the patient was transferred to the Nephrology Unit in order to monitor kidney injuries and assess the need to perform again hemodialysis.

Meanwhile, he developed high fever (T max 39°C) along with high procalcitonin (74 ng/ml) and inflammatory markers levels. Two sets of blood cultures and urine cultures resulted positive for carbapenem-resistant Klebsiella pneumoniae (kpc gene resulted positive) and therapy with ceftazidime/avibactam plus fosfomycin, both dosed on the basis of eGFR, was administered. In addition, two further blood cultures resulted positive for Candida albicans and caspofungin was added to the therapy. Transthoracic echocardiogram showed no abnormalities.

Due to the persistence of diffuse lymphadenopathy, confirmed with a head/thorax/abdomen CT scan, associated with worsening lymphopenia and high beta2-microglobulin levels (12 mg/dl), an HIV test was performed resulting positive. HIV-RNA was 150.000 copies/ml, CD4 T-cells count was 1 cells/mmc, CD8 T-cells count was 8 cells/mmc, CD4/CD8 ratio was 0.17. HBV, HCV, and syphilis serological tests resulted negative.

Combination antiretroviral therapy was started with bictegravir, emtricitabine, and tenofovir alafenamide. Furthermore, CT scan highlighted bilateral subsegmental pulmonary embolism and anticoagulant therapy was started.

RT-PCR on patient's blood showed 82.360 copies/mmc of CMV-DNA, and it was performed ophthalmic examination and esophagus-gastroscopy to rule out both CMV retinitis and esophagitis/colitis. Therapy with ganciclovir iv was then administered for 2 weeks.

Antibiotic therapy was administered for 10 days, and blood cultures after 7 days were negative for bacteria; caspofungin was administered for 14 days after a negative blood culture for Candida (overall, 18 days of caspofungin therapy). After 2 months of hospitalization, the patient was discharged and referred to an HIV clinic as outpatient.

Discussion

Accounting for 229 million infections in 87 endemic countries and approximately for 409 000 deaths in 2019, malaria represents one of the world's major public health problems [11].

As regards European countries, a total of 8641 malaria cases were reported in 2019: France declared the highest number of cases (2840), whereas Italy reported 792 cases [11].

According to the 2019 ECDC report, nearly all malaria cases reported by EU/EEA countries were imported.

We reported a case of imported severe *P. falciparum* malaria occurred in an apparently healthy Italian man returning from Nigeria, who did not take anti-malarial prophylaxis.

As reported by guidelines [12], malaria is considered a medical emergency and it should be

guaranteed its prompt diagnosis and early treatment within 24–48 h of symptoms onset.

Our patient had at least three criteria for severe malaria definition according to the WHO guidelines [13]: jaundice due to hyperbilirubinemia, high creatinine levels, and hyperparasitemia (>5%).

Furthermore, traveling to eastern Africa, having European origin, absence of appropriate chemoprophylaxis, diagnostic delay, and diagnosis during the fall-winter season has been associated with severe imported *P. falciparum* malaria in non-immune subjects [14].

Ordinary clinical practice establishes that RDT results would be confirmed by microscopic examination of Giemsa-stained (thin and thick blood) films which remains the gold standard procedure for the diagnosis of malaria [15] decreasing false-negative result rate.

Although artesunate iv represents the first-line therapy, in this case, prompt quinine iv administration along with doxycycline led to parasitemia clearance in 3 days of therapy, without adverse drug reactions [16].

From clinical perspective, HIV late presenters patients still represent a challenging task in terms of diagnosis and therapeutic management [6], [17] and it may be more laborious when HIV is covered up by other evident diseases such as malaria.

Our patient had no previous history of drug abuse, he denied having any type of unprotected sexual intercourse and he had never used blood products. He had no piercings or tattoos.

Diffuse lymphadenopathy, lymphopenia, and high beta2microglobulin levels should make clinicians suspicious about HIV infection, especially for travelers from countries with high infection rate.

Effects of malaria in PLWHIV are synergic and are represented by an increasing HIV viremia along with a more rapid decline in CD4 T-cell count, whereas HIV infection causes high parasitemia levels in malaria-infected patients [18].

Specifically, *P. falciparum* infection, which parasitemia is higher in HIV infected patients with a low CD4 cell count, together with HIV extensively interact with host immune system in specific site, such as brain barrier, increasing susceptibility of severe (cerebral) malaria [19].

For the patient we described, HIV infection diagnosis was concomitant to severe opportunistic infections, such as bacteremia and candidemia, although successfully treated with appropriate therapies. Malaria and HIV coinfection led to a deeper immunosuppressive condition which often poorly affect the outcome of both the diseases [20], [21], also compromising treatment success of other occurring infections [22], [23]. Moreover, it is also fundamental to screen these patients for other infections, such as HBV [24] and HCV [20], sharing both the ways of transmission and epidemiological characteristics.

In this case, the prompt diagnosis and treatment of severe imported malaria, along with the diagnosis of HIV infection and the successful treatment of occurred superinfection, led to a fortunate outcome. This type of case highlights the concept that clinicians should never let down the guard regarding HIV diagnosis, even if they are facing other severe conditions, especially when there are several correlations between them.

Availability of Data and Materials

Data sharing were not applicable to this article, as no datasets were generated or analyzed during the current study.

Patient Consent for Publication

Written informed consent was obtained from the patient for publication of this case report.

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