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Case report

Clinical recrudescence of chronic untreated *P. malariae* infection after BNT162b2 CoVID-19 vaccine

G. Ciusa[a,b,*], F. Guida Marascia[b], R. Virruso[c], A. Angheben[d], G. Guaraldi[a], A. Cascio[b]

[a] Department of Infectious Diseases, University of Modena and Reggio Emilia, Modena, Italy
[b] Infectious and Tropical Diseases Unit, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Palermo, Italy
[c] U.O.C. of Microbiology, Virology and Parassitology, A.O.U.P. "Paolo Giaccone", 90127 Palermo, Italy
[d] Department of Infectious—Tropical Diseases and Microbiology, IRCCS Sacro Cuore - Don Calabria Hospital, Negrar di Valpolicella, 37024, Verona, Italy

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ABSTRACT

We described a case of clinical reactivation of chronic *P. malariae* infection following CoVID-19 vaccination with BNT162b2 (Pifzer-Biontech CoVID-19 vaccine) in a 48-year old Italian man.The patient came to our attention for fever of unknown origin show a quartan pattern (every third day) associated to splenomegaly, the onset of the fever occurred one month after CoVID-19 vaccination with BNT162b2. *P. malariae* was diagnosed using Carestart™ malaria rapid test and Polymerase-Chain Reaction. Post-vaccine transient reduction of immune reactivity is described in literature, although the mechanism is unknown.

Introduction

Chronic subclinical malarial infection is a well-known clinical entity that can lead to a clinically relevant illness in case transient reduction of immune control. We described a case of clinical recrudescence of *P. malariae* infection following CoVID-19 vaccination with BNT162b2 (Pifzer-Biontech CoVID-19 vaccine) in a 48-year old Italian man.

Case report

A 48-year old Italian man with no significant medical history was evaluated for fever of unknown origin (FUO). The fever onset was one month before, with a quartan (every third day) pattern, it was associated with headache, chills, and body temperature reaching 40 °C, non responsive to ciprofloxacin and amoxicillin/clavulanate prescribed by a physician. Travel history revealed that he had traveled in malaria-endemic regions two times: to Zambia 13 years before, taking proper antimalarial chemoprophylaxis with atovaquone/proguanil, to Kenya 9 years before for two weeks, without taking any chemoprophylaxis. Since the second travel, he has been complaining of chronic weakness, with minimal impact on daily activities. No diagnostic procedures including malaria tests were performed.

At the onset of fever, the patient underwent a CAT scan, that did not reveal any pathologic findings at the chest, while splenomegaly was found at abdominal ultrasonography with a 17 cm cranial-caudal diameter. Remarkably, he had undergone vaccination for SARS-CoV-2 with BNT162b2 (Pfizer-BioNTech CoVID-19 vaccine) completing the cycle one month before fever onset, without any significant adverse event. One month later the patient appeared in good general conditions, at the clinical evaluation splenomegaly was confirmed.

Fever of unknown origin workout included blood exams which showed mild anemia (hemoglobin 10.5 g/dL, normal value 12–18 g/dL) and thrombocytopenia (PLT 135,000 cells/μL), no alteration of liver and renal function, C-reactive protein 35.6 mg/L (normal value < 5), D-dimer 924 ng/mL (normal value < 500 ng/dL), and no proteinuria. Blood cultures, serologies for HIV, Hepatitis B and C viruses, Epstein-Barr Virus and Cytomegalovirus, *Brucella* spp. and *Salmonella* spp. were negative, as was nasopharyngeal Real Time-Polymerase Chain Reaction (PCR) swab for SARS-CoV-2.

Quartan pattern of the fever plus splenomegaly suggested malarial infection: microscopic exam on blood smear was negative, but Carestart™ malaria rapid test detected malarial antigens, and PCR

* Corresponding author at:Department of Infectious Diseases, University of Modena and Reggio Emilia, Modena, Italy.
E-mail address: giac.ciusa@gmail.com (G. Ciusa).

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test documented *P. malariae* infection. The patient underwent to the conventional three-day treatment with chloroquine with progressive fever resolution. Ten days after the end of therapy new blood exams showed a reduction of anemia (hemoglobin 12.1 g/dL), PLT 276,000 cells/μL, and PCR 1.2 mg/L; the patient referred self-perceived improvement of general condition.

Discussion

Between the mid-sixties and the early seventies, the European region was declared malaria-free by the World Health Organization [1]. The epidemiological evidence shows that the risk of malaria spread in Italy associated with locally transmitted infection is very low, even in the areas considered most vulnerable because the former malaria vector *Anopheles labranchiae* survived after the malaria elimination campaign [2]. Between 2000 and 2018, 30 non-imported malaria infections were diagnosed in Italy, representing the 0.65% of malarial infections documented in that period [2].

Untreated malarial infection is a well-known condition that can progress to hyperreactive malarial splenomegaly in the case of *P. falciparum,* or subclinical infection with or without nephrotic syndrome, in the case of *P. malariae* [3]. Clinical reactivation of subclinical *P. malariae* infections has been described even decades after primary exposition to the parasite [4,5]. Very low risk of locally-acquired infection, presence of long-term weakness, and splenomegaly strongly suggest that our patient had a chronic infection. Chronic malaria can be clinically unmasked by partial loss of immune control due to malnutrition, travel, pregnancy, new onset of comorbidities [3], as well as the introduction of immunosuppressive therapy [5,6]. Although the mechanism is unknown, post-vaccine transient reduction of immune reactivity is described, like the reduction of tuberculin skin test sensitivity after measles, mumps, and rubeola immunization [7]. BNT162b2 vaccine showed excellent data of safety and efficacy against CoVID-19 in a large placebo-controlled phase III trial [8] and data from many following observational studies are consistent with these observations [9].

In the literature, reactivation of herpetic infections following BNT162b2 vaccination (mainly varicella-zoster, but also herpes simplex) has been described [10–13], which is consistent with a transient reduction of the immune control on latent infections. Although CoVID-19 associated *P. vivax* malaria relapse was described [14], no cases of post-vaccine clinical malaria reactivation have been reported up to now. Despite the time to onset of malaria reactivation after CoVID-19 vaccination in our case appears long (4 weeks), our patient does not present any other risk factor which could interfere with the immune system justifying clinical malaria. Moreover, Vogel et al. suggest up to 12 weeks of follow-up for case definitions of adverse events following immunization after CoVID-19 vaccination such as multi-inflammatory syndrome [15].

Further studies are needed to clarify the possible association between BNT162b2 and malarial clinical recrudescence, for the implication that it can represent bringing the global anti CoVID-19 vaccination campaign in endemic areas for malaria.

Ethical approval

None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Ciusa G., Guida Marascia F., Angheben A., Virruso R., Guaraldi G. and **Cascio A.** contributed writing this case report.

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Conflicts of interest

None.

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