IDCases 34 (2023) e01892

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Tropical splenomegaly in a migrant-in-transit crossing the Darien gap, Panamá: A probable case of hyper-reactive malarial splenomegaly

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ARTICLE INFO

Keywords:
Malaric hyperactive splenomegaly
Malaria
International health
Migration
Sub-Saharan Africa
Darien

ABSTRACT

Hyper-reactive malarial splenomegaly (HMS), or tropical splenomegaly syndrome, is a severe complication of chronic and recurrent infections caused by *Plasmodium spp*. This condition typically results in splenomegaly greater than or equal to 10 cm and a constellation of laboratory findings, including the absence of identifiable parasites in peripheral blood smears. However, patients with HMS demonstrate serological or molecular evidence of infection. Despite being a familiar entity in malaria holoendemic countries in Africa, and regions of Papua New Guinea, the pathophysiology, natural history, and treatment of the syndrome remains to be fully elucidated. Herein, we describe a highly suggestive case of HMS in a Senegalese patient migrating northbound to reach the U.S.-Mexico border and for whom we provided medical care during his crossing of the Darien Gap in Panama. We also reviewed the literature on diagnosing and treating HMS in-depth.

Introduction

Hyper-reactive malarial splenomegaly (HMS) is a chronic form of recurrent malaria infection that is often life-threatening. HMS results from chronic or recurrent infection by *Plasmodium spp* [1]. The diagnosis is challenging since it requires meeting epidemiological, clinical, and laboratory criteria. Early recognition and treatment of this clinical entity are essential, given its elevated associated mortality [2]. Identifying HMS in non-endemic settings for malaria is particularly important given the increasing global migration and international travel to and from malaria-endemic regions [2]. Herein, we report the case of a patient who was recruited as part of a research project called *Rapid Health Assessment in migrants in transit at the Migratory Reception Stations (ERM) of Panama in the province of Darién, Panama* [3], who sought medical attention once he arrived at a Migrant Reception Center (ERM) in San Vicente, Panama after a treacherous 10-day journey traversing the Darien gap.

Case description

A 26-year-old male from Touba, Senegal, arrived in the Americas via Brazil to reach the U.S.-Mexico border. He flew from Dakar into Mato Grosso, Brazil, 21 days before reaching the ERM in Panama. He traveled from Mato Grosso by land, subsequently crossing regions of Peru, across Quito, Ecuador, reaching the Colombian border through Tulcán, and then arriving in Pasto, Ecuador. From there, he traveled to Turbo, Colombia, and took a boat to cross the Colombia-Panama border. It took him approximately ten days by foot to cross the Darien rainforest.

During his journey through the region of Darien, he often drank water from rivers and creeks and reported extensive exposure to arthropods. Three days before entering the ERM, he started developing myalgias, headaches, chills, and edema of the lower extremities. Using a medical interpreter, the patient reported no significant medical or surgical history. His vaccination status was unknown, and he was not

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https://doi.org/10.1016/j.idcr.2023.e01892
Received 16 August 2023; Accepted 5 September 2023
Available online 6 September 2023

receiving any medications. He reported requiring empiric malaria treatments in Senegal but not within the last year.

His physical exam was remarkable for BP of 117/77 mmHg, HR 90, RR of 20, Sp02 of 97 %, and a temperature of 33 °C. The spleen was firm, not tender, and palpated approximately 13 cm below the left costal margin (Fig. 1). No peripheral lymphadenopathy or hepatomegaly was noted. Laboratory testing was obtained according to the study protocol [3] (Table 1), demonstrating a hemoglobin of 10 g/dl, a rapid diagnostic test (RDT) positive for *P. falciparum*, and a negative thick smear for malaria (Fig. 2). Expert parasitologists from the Instituto Conmemorativo Gorgas de Salud, Panamá (ICGES) performed all laboratory testing, including blood smear microscopy and interpretation of RDT for malaria. After completing a 3-day treatment course of artemether-lumefantrine (Coartem©), the patient continued his journey bound to the Mexico-U.S. border. The patient was lost to follow-up given his transient migratory status in Panama; however, in communications via social media within three weeks with the patient, he reported substantial clinical improvement.

Discussion

Hyper-reactive malaria splenomegaly, or tropical splenomegaly syndrome, as previously known, is the result of an aberrant immune response to chronic antigenic stimulation in people with prolonged or recurrent infections caused by *Plasmodium* spp. [4]. HMS is characterized by hypergammaglobulinemia due to the production of cytotoxic IgM antibodies against CD8+ and CD5+ T-cell lymphocytes, resulting in an increased CD4+ to CD8+ ratio and polyclonal B-cell activation. The uninhibited production of IgM leads to the formation of cryoglobulins and lymphoid hyperplasia with consequent normocytic and normochromic anemia and splenomegaly. The syndrome requires repetitive exposure to *Plasmodium* spp for several years with an average latency period of approximately five to ten years [5]. Genetic factors are important in susceptibility and subsequent disease manifestations. In Papua New Guinea, for example, the HLA-DR2 haplotype or HLA heterozygosity is associated with a higher incidence of HMS. In Ghana, close relatives of patients with a history of HMS were identified as having subclinical splenomegaly than in controls [6]. HMS is a major public health concern in countries with endemicity of *Plasmodium falciparum*. It is common in Papua New Guinea, Gambia, Nigeria, Zambia, Kenya, Ghana, and Sudan. It can also occur in non-endemic countries due to migration. There are reports of HSM from South America. In 1988, a survey took place to search for evidence of HSM among the Yanomami population of the Venezuelan Amazon. The survey found that 44 % of the 110 evaluated had an enlarged spleen index. Only three people had a positive blood smear for *P. falciparum* and *P. vivax*. Of the total population, 23 patients were diagnosed with HSM [15].

Confirming a diagnosis of HMS requires the presence of clinical, epidemiological, and laboratory criteria. A report in 1981 suggested

Grade	Size description of the spleen
I	The spleen is not palpable, even in deep inspiration.
II	Palpable spleen under the costal rim, usually when making deep inspiration
III	Palpable spleen, but not beyond the horizontal line between the costal margin and umbilicus, measured in a vertical line from the left nipple.
IV	Palpable spleen below the umbilicus but not below the horizontal line between the navel and the pubic symphysis
V	Beyond Class IV

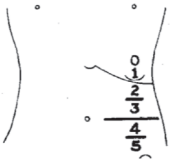

Fig. 1. Classification of spleen size according to Hackett [9].

Table 1
Screening laboratories performed as part of the Darien migrant study protocol [3].

Complete blood cell count	Anemia of chronic inflammation
HIV ELISA, 4th generation	Negative
RDT malaria for *P. falciparum/. Vivax*	Positive
Dengue IgM	Negative
Zika IgM	Negative
Chikungunya IgM	Negative
Hepatitis B panel	Negative
Hepatitis C IgG	Negative
Hepatitis A panel	Negative
Thick smear of peripheral blood	Negative
Trypanosoma cruzi serology	Negative

Fig. 2. *P. falciparum* malaria RDT compared to other study participants.

major and minor diagnostic criteria for considering the possibility of HMS [5,7]. Major criteria included persistent splenomegaly greater than 10 cm below the costal ridge without other apparent causes, the elevation of antimalarial IgM antibodies higher than two standard deviations, and a favorable clinical and immunological response to long-term antimalarial prophylaxis. The *minor criteria* include sinusoidal hepatic lymphocytosis, normal cellular and humoral immune response to an antigenic test (including stimulation with phytohemagglutinin), hypersplenism, lymphocyte proliferation and occurrence of similar clinical phenomena in other members of the family or tribe [8]. Later reports suggested considering the presence of spleen enlargement greater than 11 cm as a diagnostic criteria for HSM after excluding other etiologies [9]. This classification to quantify the degree of spleen enlargement has

Table 2
Selected causes of tropical splenomegaly in Latin America.

Infectious	Non-Infectious
Visceral Leishmaniasis	Liver Cirrhosis
Schistosomiasis	Lymphoma
Malaria	Chronic Leukemia
Histoplasmosis	Infiltrative disorders
Paracoccidioidomycosis	Myeloproliferative
Tuberculosis	disorders
Infectious Mononucleosis caused by Epstein-Barr virus	

been used since the 1940s (See Table 2).

Frequent laboratory findings occurring in patients with HMS are related to hypersplenism: pancytopenia, increased reticulocytes, and elevated indirect bilirubin elevation. An important feature of HMS is the absence of detection of parasites in peripheral blood smear microscopy. For example, field studies of HMS conducted among the Yanomami population and patients from different regions demonstrated that all cases had negative thick blood smears [10–12]. Indeed, thick blood smears typically fail to detect the protozoan in contrast to positive results with other diagnostic methods such as RDTs and PCR-based assays in patients with HMS. However, as with any other clinical scenarios in identifying malaria infection, it is essential to interpret the RDTs with caution. RDT threshold falls in the range of 5–15 parasites per μL. Patients with positive rheumatoid factor may have false positive RDT, non-specific binding of heterophilic antibodies, and persistence of malaria antigens after recent parasite clearance post-treatment [13]. In malaria-endemic areas, several factors influence this clearance: parasite density, type of treatment, acquired immunity, and age. A recent systematic review found substantial variability in the RDT's positivity from 1 to 63 days after treatment [14]. Therefore, a proper history of previous malaria infection is imperative and not the only element for the diagnosis of HMS.

Less stringent and more sensitive diagnostic criteria than the original HMS criteria include molecular tests to detect subclinical parasitemia. In response to these diagnostic shortcomings, researchers in Italy suggested the establishment of a new entity termed early hyper-reactive malarial splenomegaly (e-HMS) [3]. The criteria must include an elevated antimalarial antibody titer and either splenomegaly (craniocaudal measurement of 12 cm or more per ultrasound or a palpable spleen by physical exam), elevated IgM (> 2.5 g/L) and ruling out other causes of splenomegaly (i.e., schistosomiasis, viral hepatitis B, viral hepatitis C, HIV, brucellosis, leishmaniasis, autoimmune diseases, cirrhosis, hemoglobinopathies, and other hematological conditions) [3]. Although this diagnostic criterion is sensitive, it lacks specificity and could misidentify other treatable entities as e-HMS. Despite this limitation, it is prudent to recommend the institution of presumptive treatment for e-HMS with antimalarials when considering this diagnosis particularly in resource-limited settings, given the prognostic implications for HMS [11].

Early diagnosis of HMS is crucial because severe complications can happen during the disease: acute episode of malaria, hemolytic anemia, and splenic rupture. HMS is also considered a premalignant state that may evolve into chronic lymphocytic leukemia, hairy cell leukemia, or splenic lymphoma with hairy lymphocytes. Some authors argue that HMS and lymphoproliferative diseases are clinically indistinguishable.

The identification of splenomegaly in clinical facilities in Latin America calls for a broad differential diagnosis **(**Table 2**)**. A medical history, physical examination, laboratory tests, histopathology, and travel history may assist in identifying the etiology of splenomegaly [15]. Although some authors consider lymphocytic infiltration of splenic sinusoids as diagnostic criteria of HMS, it is not pathognomonic of this condition since it is also identified in other conditions including Felty Syndrome, Dacie Syndrome (non-tropical idiopathic splenomegaly), hairy cell leukemia, malignant histiocytosis, mononucleosis, and chronic lymphocytic leukemia with elevated IgM production [5].

There is no consensus on the treatment of HMS, and there are no published randomized clinical trials. Therapy depends on where the diagnosis of HMS is made in an endemic or non-endemic setting **(**Table 3**)**. Long-term use of chloroquine, alone or with primaquine, has provided clinical benefit when used in endemic settings. It reduces spleen enlargement, increases hemoglobin levels, and lower mortality rates [16]**.** It is recommended to continue lifelong antimalarial therapy in cases of HSM if the patient resides in areas of endemicity [17] **(**Table 3**).** In non-endemic settings, where the risk of exposure is low, shorter courses or intermittent courses of antimalarial therapy may be prudent [17]. The natural history of this disease has yet to be fully understood. HMS patients in Papua New Guinea and Uganda have a 50 % mortality rate within five years, which jumps to 85 % for hospitalized patients with significant splenomegaly [18]. Some patients may require splenectomy when not responding to repeated courses of antimalarials [4]. Our patient received therapy with artemether/lumefantrine for three days as recommended by Panamanian treatment guidelines, followed by a terminal dose of primaquine.

Table 3
Recommended therapy for hyperreactive malarial splenomegaly*.

Therapy	Country
Endemic Countries	
Chloroquine weekly	New Guinea, Papua New Guinea, India
Daily Proguanil	Nigeria, Kenya
Chloroquine + primaquine	India, Uganda
Mefloquine	Sudan
Quinine	-
Pyrimethamine	Tanzania
Artemether	Sudan
Sulfadoxine/Pyrimethamine	Sudan
A short course of antimalarial therapy + corticosteroids	Sudan
Standard antimalarial therapy without corticosteroids	Sudan
Non-endemic countries	
Chloroquine ± doxycycline or Proguanil or Pyrimethamine	Italy, Belgium, and Spain
Quinine + clindamycin	Other countries
Pyrimethamine – sulfadoxine	
Mefloquine	
Atovaquone – proguanil	
Halofantrine	
Artemisinin	

* Adapted from [4].

There are many limitations to this case report since there are many remaining unanswered considerations: we could not exclude many other causes of splenomegaly other than those included in the study protocol [3]. We were also unable to quantify antimalarial antibodies since this is not a widely available diagnostic laboratory tool in Panama and the costs associated with this test. We made a presumptive diagnosis of HMS based on clinical grounds and supported by epidemiological history, and laboratory data: a negative peripheral blood smear read by expert parasitologists and positive RDT in a patient from a hyperendemic malaria area in West Africa. The lack of clinical follow-up is also important to consider when assessing clinical improvements after the institution of antimalarial therapy. In this regard, we were only able to confirm reports of his clinical improvement via social media messaging.

In summary, HMS is a complication resulting from chronic and/or recurrent exposure to *Plasmodium* spp., which is a potentially fatal complication and considered in many cases a premalignant condition. Clinical suspicion of HMS requires clinical, epidemiological, and laboratory criteria. In resource-limited settings, clinicians should consider HMS in the differential diagnosis of a patient presenting with a febrile illness, splenomegaly, negative blood smear microscopy but positive RDT for malaria and/or positive molecular detection of *Plasmodium* spp in serum. Ideally, ruling out other potential causes of fever and splenomegaly should be a priority. However, as it occurred in our case, the provision of medical care in resource-limited settings calls for clinicians consider instituting presumptive therapy with antimalarial drugs when there is clinical suspicion of HMS given the negative clinical outcomes of this condition when left untreated. Finally, there is an urgent need for more accessible field diagnostic methods for neglected tropical diseases and malaria for use particularly during humanitarian crises in resource-constrained settings as it currently occurring with the ongoing human migratory crisis across South and Central America, and Mexico.

Ethical approval

Publication of this case report was approved the Panamanian National Ethics Board Review.

Consent

We have consent from the patient (written and verbal) to publish the case.

Funding

Funding was provided by Instituto Conmemorativo Gorgas de Estudios de la Salud, Community Development Network of the Americas, Acino Swiss Farma, GSK, Neglected Tropical Diseases Fund, and Fulbright Global Award (CFP). Additional contributions have come from Sagrav SA and Omega Diagnostics, and some of the diagnostic tests have been donated through individual research funds from Panamá s National Research System of SENACYT. Funding sources did not have a role in data design, implementation, or analysis.

CRediT authorship contribution statement

MP, NAH, CFP: data collection, analysis, and writing of the initial draft and subsequent reviews. **JAS, RC, YD, LN, JAG:** participated in the editing of the initial and final version of the manuscript, and review of the literature.

Conflict of interest

Laura Naranjo is a GSK employee. All the information in this paper is her opinion and does not reflect the position of GSK.

Acknowledgments

We are thankful to the Center for Research and Diagnosis of Emerging and Infectious Disease, Meteti, Darién of the Instituto Conmemorativo Gorgas de Estudios de la Salud (ICGES), Community Development Network of the Americas, UNICEF, Médecins Sans Frontières, Panamás Ministerio de Salud, Servicio Nacional de Fronteras (SENAFRONT), and Servicio Nacional de Migración for their ongoing support. We are additionally thankful to those who have contributed thus far to this project: Acino Swiss Farma, Ann Knudson, Oklahoma University's Physicians Pharmacy, Sagrav SA, and Omega Diagnostics.

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