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Hyperimmune malarial splenomegaly in a malaria-endemic area of southwest Burkina Faso: case of Bobo-Dioulasso

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Abstract

Introduction Hyperreactive malarial splenomegaly (HMS) is one of the main causes of massive splenomegaly in malaria-endemic zones. Diagnosis is often challenging in Bobo-Dioulasso. This study aimed to describe the clinical and socio-demographic profile, and the reasons for delay in the diagnosis of HMS cases recorded in the Medicine and Medical Specialties wards of Souro Sanou Teaching hospital.

Methods A retrospective descriptive study was conducted from August 2022 by focusing on HMS cases diagnosed in the Infectious Diseases and Clinical Hematology wards of Souro Sanou Teaching Hospital.

Results Overall, 65 patients met our inclusion criteria over the 12-year period. Burkinabe nationals and have been residing in Burkina Faso since their birth. 79% (79%) of the patients were seen for medical consultation with the reason for consultation being a voluminous mass in the left hypochondrium. Indigence, self-medication, and lack of information were essential elements in late diagnosis of HMS in Bobo-Dioulasso. All patients were treated with a single tablet of Artemether (80 mg) and Lumefantrine (480 mg) in the morning and evening for 3 days, followed by sulfadoxine–pyrimethamine per week. Nine months later, patients were clinically asymptomatic.

Conclusion This study provides a database on hyperreactive malarial splenomegaly (HMS) in the south-west region of Burkina Faso. Rapid and accurate diagnosis of the disease and appropriate use of effective antimalarial drugs would significantly reduce the burden of HMS in Sub-Saharan African countries.

Keywords Splenomegaly, Malaria, Hyperreactive, Endemicity, Bobo-Dioulasso

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Introduction

Splenomegaly is an abnormal increase in the size of the spleen, which has multiple causes. Hyperreactive malarial splenomegaly (HMS) is one of the main causes of massive splenomegaly in malaria-endemic areas [1–3]. HMS is characterized by an intense immune response during repeated or prolonged episodes of plasmodial infections and its prevalence in women is two to three times higher than in men in sub-Saharan Africa [4]. Diagnosis can be difficult, due to an unspecific clinical presentation and the high cost and inaccessibility of laboratory diagnostic tests in resource-limited countries leading to delay in diagnosis since conventional malaria diagnostic tests such as the thick and thin blood smears often yield are negative results [4].

In Burkina Faso, malaria is a major public health problem due to its extent, severity and socio-economic consequences. The latter include low life expectancy of patient, rate of children's education, productivity at work, and family and national savings. In 2018, malaria was the leading cause of consultations (39.25%), hospitalization (41.36%) and death (17.22%) in healthcare facilities [5]. However, this high mortality rate is preventable and treatable. In Burkina Faso, strategies and interventions such as early and proper management of malaria cases have been implemented in public, private and community facilities to reduce this reduce death related to malaria.

Unlike the tropical regions, HMS is not well known known in Burkina Faso and its prevalence ranged from 31 to 76% [6] in African countries. The main complications of HMS are acute infectious diseases, anemia and rupture of spleen [7]. Better description of HMS is still needed in Burkina Faso to increase medical awareness, reduce the rate of misdiagnosis, prevent the progression of the syndrome to splenic lymphoma and avoid splenectomy. This study aimed to describe the clinical and sociodemographic profiles, as well as the reasons for delays in the diagnosis of HMS cases recorded in the Medicine and Medical Specialties wards of Souro Sanou Teaching hospital.

Table 1 HACKETT's clinical grading was used for classification of splenomegaly as described in the table below

STAGE	CLINICAL MANISFESTATION
stage 1	just palpable spleen only with deep inspiration
stage 2	palpable spleen but not below a horizontal line passing half way between the costal margin and umbilicus
stage 3	palpable spleen but not below a horizontal line passing through the umbilicus
stage 4	spleen palpable, reaching the horizontal line passing through the anterior superior iliac spines
stage 5	spleen sinking into the left iliac fossa

Methods

Study setting

The study was carried out in the town of Bobo -Dioulasso, in south-west Burkina Faso. Malaria is endemic in this region with permanent transmission and a seasonal peak in September-November after the rainy season [5].

Study design and patient selection

A retrospective descriptive study was conducted from August 20, 2010, to December 31, 2022, focusing on HMS cases in the Infectious Diseases and Clinical Hematology wards.

The inclusion criteria of the patient included mainly physical examination revealing massive splenomegaly confirmed by abdominal ultrasound, a high level of Immunoglobulin M ("IgM"> 3.5 g/l), plasmodial serology greater than or equal to " 1/800" and regression of splenomegaly by at least 40 cm after 6-month antimalarial treatment [4] in the absence of other causes of splenomegaly such as schistosomiasis, bilharziasis, viral hepatitis B and C, HIV, hemoglobinopathies or any other causes of chronic hemolysis, and hematological malignancies.

Late consultation was defined as a delay of more than one month, while loss of follow-up refers to a patient who has stopped coming for a consultation.

Data collection and analysis

Sociodemographic, clinical, biological and therapeutic data were collected from consultation logbooks on a survey form. Variables consisted of the socio-demographic data (age, sex, occupation), clinical data, duration of stay in endemic zone, first onset of symptoms, time of diagnosis, reasons for delay in diagnosis, biological data, therapeutic data and evolution of the syndrome. A survey form was used for data collection. Data was typed using Microsoft Excel (version 10, Windows 2013) and analyzed using Stata 2013 software. Qualitative variables were reported as proportions and quantitative variables as means with standard deviations.

Ethical considerations

The authorization of the Director General of the Souro Sanou Teaching Hospital was obtained before conducting this study. Approved by the institutional ethics committee of the Sourô Sanou Teaching Hospital. The Data of all patients were kept confidential.

Results

Sixty-five (65) patients were included in this study over a period of 12 years (Fig. 1). All our patients were born in Burkina Faso and have been residing in the country since birth.

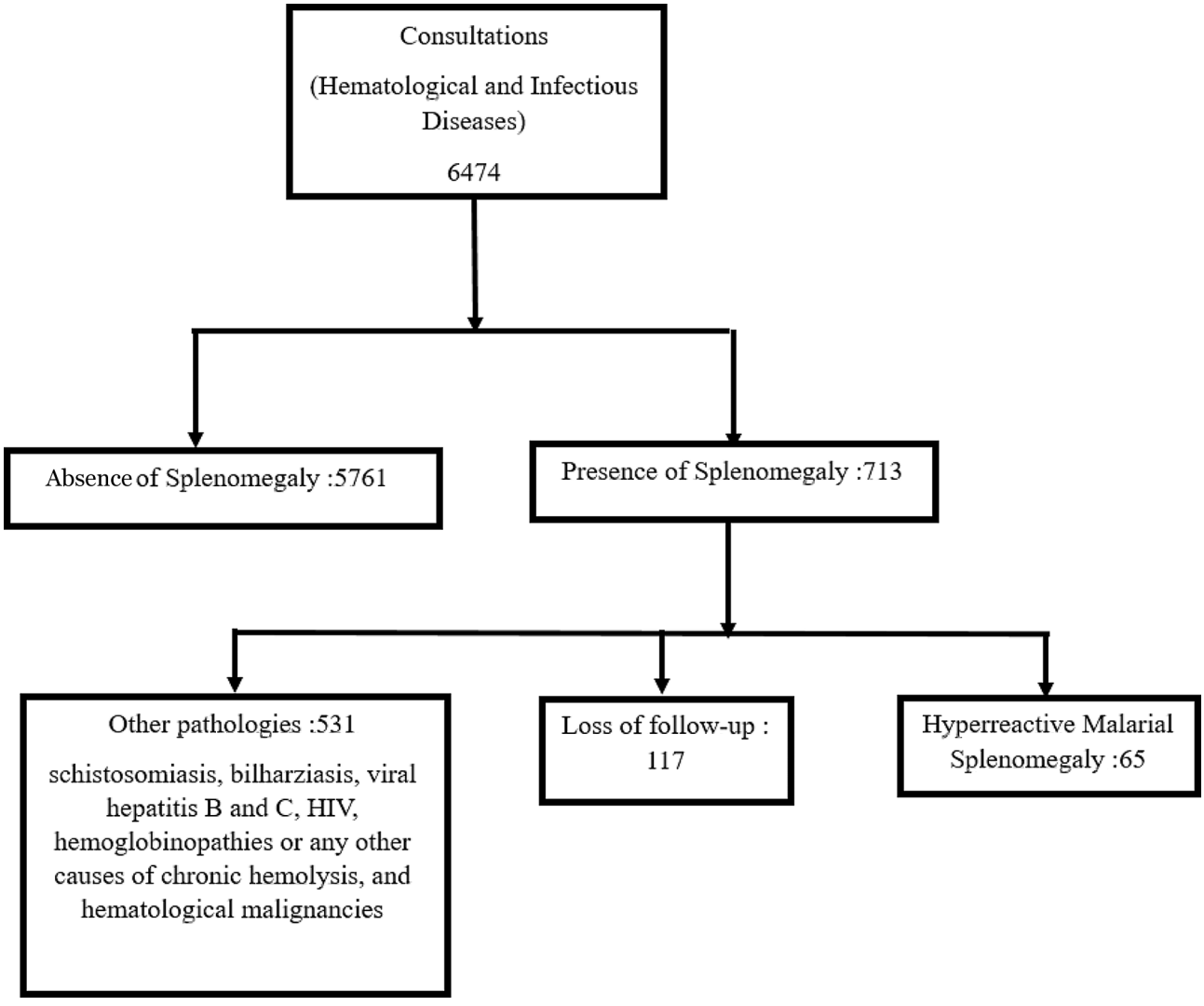

Fig. 1 Data flow chart

Socio-demographic profile of patients

The average age of the patients was 25±5 years with predominance of female participants 48/65 (73.8%), single participants 39/65 (60%), participants from informal sector 18/65 (26.7%), participants with secondary education 26/65 (40%), and participants living in urban areas 52/65(80%) (Table 2).

Clinical profile of patients

In this study, 51/65 (79%) patients came for consultations beyond two months with enlarged splenomegaly and/or heaviness in the left hypochondrium (Table 3).

The average duration of consultation before the diagnosis of hyperreactive malarial splenomegaly was 1.4±1.2 months [1–5 months].

There was no fever in all the patients and the majority 56/65 (86.1%) had general signs (asthenia, anorexia, weight loss) (Table 2). However, asthenia was frequently reported in 33/65 (50.7%) patients of patients with voluminous, and sometimes sensile splenomegaly (Table 4).

Biological Profile of patients

Biologically, the mean hemoglobin value was 11.8 g per 100 ml±2.1 g/l. The mean leukocyte count was 5.4 g/l±3 g/l, and platelet count was 158 g/L±16 g/l. Protein electrophoresis showed mean hypergammaglobulinemia at 32 g/l [27–35[. Immunoglobulin M (IgM) assay gave a mean value of 5.1 g/l [2.8–6 g/l]. Hematozoa were not detected in 60/65 (93.3%) of cases through thick and thin blood smears. Hematozoa were present in only one patient with a parasitaemia of 124 GRP/µL. Anti-P. falciparum antibodies were also present, with a mean of 6340±1280. Thus, had an absence of viral and parasitic antigens and/or antibodies (HBV, HIV, HCV, bilharzia and leishmaniasis) was observed in 67.7% (44/65) patients.

Table 2 Clinical and socio-demographic Profile of the patients with Hyperreactive Malarial Splenomegaly

Variables	Modalities	Patients *n* (%)
Gender	Male	17 (26.2)
	Female	48 (73.8)
School level	Primary	23
	Secondary	26 (40)
	University	16
Profession	Unemployed	17
	Student	16
	Informal sector	18 (26.7)
	Public sector	14
Matrimonial status n(%)	In couple	26 (40)
	Single	39 (60)
Residential area	Bobo-Dioulasso	52 (80)
	Other	13 (20)
CLINICAL INFORMATION		
Screening circumstances	Amaigrissement + Abdominal heaviness	15
	Asthenia + Abdominal mass	23
	Splenomegaly	11
	Asthenia + pain at echography	16
General signs	asthenia	39
	anorexia	30
	weight loss	15
Classification of Hackett	III	45
	IV	20

Table 3 Distribution of 65 patients according to reasons for long delay in diagnosis

Reasons	Number of patients (*n*)
High cost of examinations	65
Self-medication	38
Negligence of patients	15
Lack of information	20
Other[‡]	10

[‡]distance from the healthcare center, the fear

Table 4 Distribution of the 65 patients by diagnostic delay and circumstances of discovery

	Diagnosis time (months)			Total number (*n*)
	< 2	2–4	> 5	
Circumstances of discovery				
Asthenia + HCG pain	2	6	8	16
Weight loss + abdominal heaviness	4	9	2	15
Asthenia + Abdominal mass	5	17	1	23
Splenomegaly	3	7	1	11
Toatal number (n)	14	39	12	65

HCG: Pain in the left hypochondrium

Therapeutic profile of patients

All patients were treated with 80 mg Artemeter and 480 mg Lumefantrine every morning and evening for 3 days with single tablet followed by sulfadoxine-pyrimethamine treatment per week. After 6 months of treatment, the general physical conditions of 10 patients werre improved and the spleen was not palpable, but ultrasound showed splenomegaly measuring around 15 cm in 47 patients, and the average IgM level had fallen from 5.1 to 2.5 g/l. Serologically, the mean of anti-P-falciparum antibody titer was 1650. Patients were clinically asymptomatic after nine months.

Discussion

This study aimed to describe the clinical and socio-demographic profile, and the reasons for delay in the diagnosis of HMS cases recorded in the Medicine and Medical Specialties wards of Souro Sanou Teaching hospital. It represents a database on hyperreactive malarial splenomegaly (HMS) in the south-west region of Burkina Faso. According to the National Malaria Control Program, the epidemiological profile of diseases in Burkina Faso remains dominated by infectious diseases, including malaria, which represents a major public health problem due to its extent, severity and socio-economic consequences [5, 6]. In Bobo-Dioulasso, patients with splenomegaly are often referred to hematology, infectious diseases and/or internal medicine wards of the Souro Sanou Teaching Hospital. In this study, 65 patients met our inclusion criteria during the period of the study (12 years). Previous studies also reported the existence of HMS across some African regions where malaria is endemic [1, 8, 9].

In this study, the average age of the patients was 25 years. This correlates with previous studies carried out in malaria-endemic countries [7, 10]. The predominance of women in this current study was also shown in a study conducted by Bedu-AddoG and Bates in 2002 in Ghana [3]. Regarding the diversity in clinical profile and high fatality rate [6], HMS should be revealed and managed in patients without fever and living in malaria-endemic areas.

In this current study, splenomegaly was the major sign, which persisted for several weeks. It was responsible for abdominal pain in 16 of our patients as compared to a previous study [3].

There was IgM hyperproduction (5.1 g/L) in this study. This was well described in a study of 49 expatriate patients with HMS [11]. Indeed, these patients had resided in sub-Saharan Africa for a median period of 32 years and the average IgM levels were 7.63, 8.17 and 16.4 g/L in patients whose spleens were measured by ultrasound at less than 14, 14 to 18 and more than 18 cm, respectively [11].

The hyperproduction of IgM in these endemic areas is due to repeated episodes of plasmodial infections, which often result in strong stimulation of B cells. T-cell-dependent activation of plasmodial antigen-specific B cells can lead to hyperproduction of anti-plasmodial antibodies. In addition, plasmodial proteins can stimulate B cells non-specifically, leading to the production of polyspecific IgM, including autoantibodies (rheumatoid factor, cold hemagglutinins, antithyroid antibodies) and nonsense IgM [11]. Indeed, a deficiency in suppressor T-CD8 lymphocytes may be the mechanism responsible for the hyperproduction of specific and non-specific IgM during the occurrence HMS [12]. It has been hypothesized that Plasmodium-induced anti-CD8 autoantibodies may be responsible for this T-cell suppressor deficiency [13]. Hyperproduction of IgM leads to the formation of immunocomplexes containing complement factors and cryoglobulins. The presence of these immunocomplexes in the membranes of macrophages and liver Küpffer cells triggers the proliferation of reticuloendothelial cells, resulting in hypertrophy of the spleen (and, to a lesser extent, the liver) and may be responsible for anaemia as shown in the majority of the patients of our study. This lymphocyte hyperreactivity is only induced by Plasmodium antigens.

Increased serum IgM levels is prior to the appearance of clinically perceptible splenomegaly by several years, and thus represent the first stage in the evolution of this disease [13, 14]. Other immune system features were described in Fulani ethnic that is predisposed to HMS characterized by CD1 gene polymorphism, specific cytokine expression profile of IL4 and TNF by Natural Killer T (NKT) cells [13].

Delay in diagnosis was common in this study like in most studies conducted in African with a long delay in consultation, approximately 1.2 months, and an altered general state of patients at admission [6, 15]. The reasons for late diagnosis were multiple and dominated by the high cost of diagnostic equipment, negligence of symptoms in patients, lack of information and self-medication. In addition, healthcare system in Burkina Faso is organized into primary, secondary, and tertiary healthcare levels. Progress has been made in improving access to primary and secondary healthcare by building health infrastructures and training medical and paramedical staff. However, these efforts remain largely insufficient. Splenomegaly is a symptom found in many pathological conditions in tropical zones. This could explain the confusion in diagnosis of this pathology and wandering of patients in several peripheral structures, resulting in limited access to specialized care and delays in the diagnosis of certain pathologies such as HMS. These delays should enable innovations in the accessibility of diagnosis by the population through implementation of universal insurance and the training of healthcare personnel, particularly nurses and medical assistants mostly needed in rural areas. This could limit the risk of diagnostic errors as HMS often poses a problem of differential diagnosis in our working context. These new approaches could reduce the risk of complications, while shortening treatment times.

Therapeutically, we administered Artemeter/Lumefantrine, the first-line treatment for malaria treatment in our context, followed by several weeks of sulfadoxine/pyrimethamine treatment [16, 17]. This long treatment regimen was reported in various case studies [18, 19]. Unfortunately, there was no normalization of spleen size after six months. In malaria-endemic zones such as ours, splenectomy may represent a key sign when there is a massive splenomegaly [20], and often characterized by painful tumour syndrome and/or hypersplenism with profound anaemia, altered general condition and/or presenting a risk of rupture. This was not observed in the current study. Efforts should be made to avoid splenectomy in patients because of the increased risk of infection in asplenic patients. Splenectomy often results in reactive hepatomegaly, which also has a poor prognosis [21]. In addition, several studies have shown that patients with splenectomy are twice susceptible to malarial infections as compared to subjects without splenectomy [22, 23].

Conclusion

Hyperreactive malarial splenomegaly (HMS) often occur during repeated episodes of malaria infection. In Bobo-Dioulasso, the Southwest region of Burkina Faso, the diagnosis of HMS should be revealed in patients who have lived for several years with splenomegaly associated with an increase in IgM level and positive plasmodial serology. The triad of indigence, self-medication and lack of information was the key factors in the late diagnosis of hyperreactive malarial splenomegaly (HMS) in Bobo-Dioulasso. It underscores the major gaps that need to be filled, not only in terms of raising public awareness, but also in terms of training and equipping facilities in order to improve rapid and accurate diagnosis of the disease. Ensuring appropriate use of effective antimalarial drugs could also reduce the burden of HMS in Sub-Saharan African countries such as Burkina Faso.

Abbreviations

CD1	Cluster de différenciation 1
CD1	Cluster de différenciation 1
HBV	Hepatitis B virus
HCG	Left hypochondrium pain
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMS	Hyperreactive malarial splenomegaly
IgM	Immunoglobulin M
IL4	Interleukin 4
NKT	Cellules Natural Killer T
T-CD8	Cytotoxic T lymphocytes

TNF Tumor necrosis factors

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Author contributions
Z J, TC and S L B designed the study plan. Z J, T C and S Y participated in the literature search and preparation of the first version of the protocol, drafting of the manuscript, analysis and interpretation of the results.A K S and I S read and approved the article. All authors read and approved the final manuscript.

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Data availability
Data sets generated and analyzed during the course of the present study are available from the corresponding author upon reasonable request.

Declarations

Ethical declaration and consent to participation
Not applicable.

Competing interests
The authors declare no competing interests.

Consent for publication
Not applicable.

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