

## Hyperreactive Malarial Splenomegaly Syndrome—Can the Diagnostic Criteria Be Improved?

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**Abstract.** Hyperreactive Malarial Splenomegaly Syndrome (HMSS) was described and defined before sensitive tests for malaria were available. We present a series of seven individuals who were referred to our clinics with possible HMSS. Chronic malaria was demonstrated in those successfully treated but not in those who failed to respond to therapy. This observation suggests that the newer molecular malaria assays have a role to play in the identification of individuals who are likely to respond to treatment for HMSS in non-endemic regions.

### INTRODUCTION

Hyperreactive malarial splenomegaly syndrome (HMSS), previously tropical splenomegaly syndrome, is a poorly understood condition thought to represent an exaggerated immune response to recurrent or persistent malarial infection.<sup>1</sup> HMSS is characterized by a polyclonal hypergammaglobulinemia and raised immunoglobulin M (IgM). Malarial infection stimulates the transient production of lymphocytotoxic IgM antibodies specific for activated CD8<sup>+</sup> lymphocytes.<sup>2</sup> In HMSS, these antibodies persist, leading to an imbalance between CD4<sup>+</sup> and CD8<sup>+</sup> T cells, and associated with nonspecific B-cell activation.<sup>3</sup> IgM aggregates are phagocytosed by the cells of the reticuloendothelial system, stimulating macrophage and T-cell hyperplasia and eventually resulting in massive hypertrophy of these tissues.<sup>4</sup>

Published criteria for the diagnosis of HMSS are based on 1) the exclusion of other causes of splenomegaly; 2) immunity to malaria, defined as a strongly positive antibody test; 3) splenomegaly of at least 10 cm; 4) a serum concentration of IgM at least two standard deviations above normal; and 5) a clinical and immunological response to malaria prophylaxis.<sup>1</sup> An additional criterion 6) was suggested in 1997: evidence of polyclonal nature of circulating lymphocytes (to distinguish from hematological malignancy).<sup>5</sup> The optimal management of HMSS in non-endemic settings and the role of malaria polymerase chain reaction (PCR) remain unclear. In the below section Cases and in Table 1, we summarize seven cases of “tropical splenomegaly” which were managed in our clinics since 2003.

### CASES

**Case 1.** A 22-year-old pregnant woman from Sierra Leone was admitted to hospital with shortness of breath and fatigue. She had migrated to the United Kingdom 4 years before. Physical examination revealed gross splenomegaly. On two occasions, blood film microscopy showed only anemia. However, a solitary trophozoite of *Plasmodium falciparum* was noted on a third film, performed 1 month after her initial presentation. Subsequent testing revealed a raised serum total IgM and strongly positive malaria serology.

She was treated with a 3-day course of oral quinine (600 mg three times daily) and subsequently started on chloroquine 300 mg once weekly, which she took for a month. She developed hemolytic anemia 2 months after stopping chloroquine (after further travel to Sierra Leone), but blood films and PCR were negative for malaria. Chloroquine was restarted but changed to proguanil 100 mg once daily (OD) after 3 weeks. Her splenomegaly and anemia completely resolved within 2 months.

**Summary assessment.** Chronic malaria with HMSS and hemolysis; possible reinfection.

**Case 2.** A 61-year-old woman from Sierra Leone, who had arrived in the United Kingdom 6 months before, was referred with abdominal pain. Ultrasound scanning of her abdomen showed 15 cm splenomegaly and increased periportal liver echogenicity, suggesting periportal fibrosis. Schistosomal serology was positive and ova of *Schistosoma mansoni* were seen on stool microscopy. Histologic examination of liver biopsy showed pipestem fibrosis. A diagnosis of hepatosplenic schistosomiasis was made, and she was treated with praziquantel 20 mg/kg twice.

Five years later, she returned to clinic complaining that her abdominal pain had never improved and had recently become more severe. Schistosomal serology was now negative. Blood film microscopy was negative for malaria but serology was strongly positive. Review of the initial histology revealed hemozoin pigment in Kupffer cells. This finding raised the possibility of chronic malaria, (hemozoin is only occasionally seen in chronic schistosomiasis). She was commenced on chloroquine 300 mg weekly and proguanil 100 mg OD. A repeat ultra sound scan 2 months later confirmed complete resolution of the splenomegaly.

**Summary assessment.** Chronic malaria with HMSS undiagnosed on initial presentation.

**Case 3.** A 16-year-old Somalian woman, resident in the United Kingdom for 6 months, presented with abdominal pain and fever. Gross splenomegaly was noted on examination. Malaria serology was strongly positive and IgM raised. Multiple blood films were negative for malaria, but PCR for *P. falciparum* DNA was positive. She was treated with quinine for 1 week and was subsequently given 6 months of chloroquine (300 mg weekly) and proguanil (200 mg daily), with complete resolution of her splenomegaly.

**Summary assessment.** Chronic malaria with HMSS.

**Case 4.** A 33-year-old Nigerian man presented with lethargy and abdominal pain. He had not traveled to a malarial area in the preceding 7 years. Gross splenomegaly was noted on examination. Malarial serology was positive and serum IgM

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TABLE 1  
Summary of patient characteristics and clinical features

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Year of diagnosis	2005	2003	2007	2009	2008	2010	2010
Age (years)	22	61	16	33	19	24	30
Sex	F	F	F	M	F	M	M
Years since last travel	4	1	1	6	2	8	2
Total IgM (NR 0.4–2.3 g/L)	7.06	7.17	8.46	7.1	0.8	2.38	7.8
IgG ELISA/OD at diagnosis*	> 4,000 (c/o 0.153)	4.038 (c/o 0.116)	> 4.0 (c/o 0.153)	N/A	3.515 (c/o 0.128)	3.778 (c/o 0.144)	3.44 (c/o 0.132)
IFAT titer at diagnosis (dilutions)†	1:2560	1:2560	1:2560	1:160	1:640	1:320	1:1280
Spleen size (maximum dimension on radiology) (cm)	17	15	18	16	16	28	25
LDH (IU/L)	715	600	396	719	239	420	Not performed
Hemoglobin (g/dL)	9.8	12.2	7.3	11.7	11.6	12.9	12.9
Blood film appearances	Macrocytosis, polychromasia	Polychromasia, reactive white cells, normal platelet morphology	Moderate polychromasia	Thrombocytopenia	Thrombocytopenia, occasional reactive lymphocytes	Anisocytosis, reactive white cells, thrombocytopenia with no clumping	Hypochromasia, microcytosis, target cells
White cells ( $\times 10^9/L$ )	4.8	4.4	4.6	8.0	1.7	1.6	1.0
Monocytes ( $\times 10^7/L$ )	0.2	0.3	0.4	0.4	0.2	0.1	0.1
Lymphocytes ( $\times 10^9/L$ )	0.9	1.5	1.2	2.5	0.6	0.4	0.2
Neuts ( $\times 10^7/L$ )	3.7	2.6	3.0	4.6	0.9	1.0	0.6
Platelets ( $\times 10^9/L$ )	75	148	140	4	8	21	14
Other diagnosis	None	Schistosomiasis, pulmonary hypertension	None	None	Hepatitis B	Schistosomiasis	Schistosomiasis, hepatic cirrhosis
Malarial PCR	Not done	Not done	Positive PCR	Not done	Negative	Negative	Negative
Evidence of chronic malaria‡	Single trophozoite on blood film	Hemozoin pigment in liver	None	Antigen positive	None	None	None
Clinical response to therapy	Yes	Yes	Yes	Yes	No	No	No
Meets present criteria for diagnosis of HMSS	Yes	Yes	Yes	Yes	No	No	No

ELISA = enzyme-linked immunosorbent assay; HMSS = hyperreactive malarial splenomegaly syndrome; IgM = immunoglobulin M; OD = optical density; PCR = polymerase chain reaction; NR = normal range; IFAT = indirect fluorescent antibody test; LDH = lactate dehydrogenase; N/A = not applicable.

\*Neat serum tested. Cutoff was mean of the negative controls plus 0.100. For ELISA: recombinant malarial antigens (proprietary) were used.

†IFAT used synchronized falciparum schizonts.

‡Blood film sensitivity: routine 50 parasites/ $\mu L$ , expert microscopists: 5 parasites/ $\mu L$ . We examined 200 fields in a thick film. Rapid diagnostic tests were evaluated in the World Health Organization Proficiency Testing Program at 200 parasites/ $\mu L$ .

was 7.1 g/L. No malarial parasites were seen on examination of a blood film but a malarial antigen test (BinaxNow; Alere) was positive. He was treated with a short course of mefloquine followed by 6 months of chloroquine and proguanil, after which his clinical and hematological abnormalities were resolved. Five years later, his symptoms returned. On this occasion, his splenomegaly did not respond to antimalarial therapy. He subsequently died of a widespread anaplastic malignancy of uncertain origin.

*Summary assessment.* Chronic malaria with HMSS. Subsequent malignancy.

**Case 5.** A 19-year-old woman from Cote d'Ivoire was referred for investigation of splenomegaly and pancytopenia. Malarial serology was positive but serum IgM was not raised. She was also seropositive for Hepatitis B virus (HBsAg+, HBe-, anti-HBe+). Microscopy and PCR of whole blood for malaria species was negative on several occasions. She received 4 months of weekly chloroquine 300 mg, but her splenomegaly and cell counts did not improve.

*Summary assessment.* No evidence of chronic malaria. Cause of splenomegaly uncertain.

**Case 6.** A 24-year-old man was referred to a hospital for investigation of splenomegaly and pancytopenia. He was born in Sierra Leone and had migrated to the United Kingdom 8 years before. Blood tests on presentation showed anemia, thrombocytopenia, and leucopenia. Further testing showed a high antimalarial antibody titer and raised total IgM. Malaria PCR was negative. After 8 months of treatment with chloroquine, his splenomegaly was unchanged. He was then prescribed a prolonged course of atovaquone-proguanil (one tablet OD), with no improvement. He remains under review.

*Summary assessment.* No evidence of chronic malaria. Cause of splenomegaly uncertain.

**Case 7.** A 30-year-old man, who had recently migrated to the United Kingdom from Sierra Leone, was referred to a hospital with abdominal pain. He had experienced febrile episodes (with occasional jaundice) every 2–3 months for many years and these had been treated in Sierra Leone with empirical antibiotics and antimalarial therapy. Examination showed gross (25 cm) splenomegaly. He was diagnosed with hepatitis B and D, liver cirrhosis, and schistosomiasis on the basis of positive serological tests and biopsy.

The degree of splenomegaly was felt to be incompatible with liver cirrhosis and a diagnosis of HMSS was considered. Antimalaria antibody titers were found to be strongly positive and serum IgM was raised. Malaria PCR was negative. He was treated with proguanil 100 mg daily and chloroquine 250 mg twice weekly for a year, followed by atovaquone-proguanil for over 3 years, again with no improvement. He recently re-presented with new onset ascites, likely to be due to decompensation of his hepatitis B/D-related cirrhosis.

*Summary assessment.* No evidence of chronic malaria. Splenomegaly likely related to cirrhosis.

## DISCUSSION

This series is the largest described in a non-endemic setting, and the cases illustrate some of the challenges in the diagnosis and management of such a poorly understood condition. All were treated with prolonged courses of antimalarial

drugs, as they would have been in their countries of origin. The choice of drug may have been guided by the suggestion (from the early 1990s) that chloroquine has an immunological effect on HMSS in addition to its antimalarial properties.<sup>6</sup> Although historical reports have implicated chronic (as opposed to recurrent) malaria in many cases of HMSS,<sup>7,8</sup> the possibility of subclinical malarial infection was not appreciated in these cases and the diagnosis would have been impossible because of the lack, until recently, of a sensitive diagnostic tool.

Four of the seven cases that we reported responded to antimalarial therapy. It is notable that each of these individuals had evidence of active low-grade malarial infection. Those who failed to respond to the treatment had no detectable malarial DNA on a validated PCR (PCR sensitivity: 0.01 parasite/ $\mu$ L<sup>9</sup> compared with blood film sensitivity at London School of Hygiene and Tropical Medicine: 5 parasites/ $\mu$ L) (Debbie Nolder and Peter Chiodini, personal communication). A variety of drugs were used, and we assume that, where it was used alone, proguanil was effective due to the low rate (about 25%) of antifolate resistance in Sierra Leone at this time.<sup>10</sup> These observations confirm what is unprovable in an endemic malarial area—that, in the absence of reinfection, elimination of chronic malaria leads to resolution of HMSS.

The diagnostic criteria for HMSS were last amended in 1997, before the advent of molecular tests for malaria. Since then, studies have confirmed that chronic malaria is strongly associated with splenomegaly in endemic areas (80% versus 3.5% with no splenomegaly).<sup>11</sup> Scattered reports of cases of HMSS in non-endemic areas have documented successful treatments with short courses of antimalarial therapy, rather than the prolonged prophylactic courses used in the tropics.<sup>12–14</sup> These data, together with our finding of chronic malaria in those who responded to antimalarials, suggest a role for PCR in identifying individuals with splenomegaly who will respond to treatment for HMSS, and we therefore recommend that this may be added to the diagnostic criteria for HMSS.

The management of cases of splenomegaly that do not respond to antimalarial therapy represents a particular challenge. The surgical risks of splenectomy are often considered to be unacceptable, which leaves these patients at risk of bleeding and traumatic splenic rupture. The development of lymphoma also appears to be a significant risk in HMSS.<sup>14,15</sup> Unfortunately, it can be impossible to distinguish HMSS from splenic lymphoma with standard clinical and hematological techniques.<sup>5</sup> In cases where chronic malaria has been excluded using PCR or after a trial of therapy, and if other relevant infections such as visceral leishmaniasis and viral hepatitis have also been excluded, early splenectomy to minimize these risks may be appropriate.

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