

Hyper-Reactive Malarial Splenomegaly Syndrome (HMSS)

Erwa Eltayib. Elmakki¹

1. Department of Internal Medicine, Division of Gastroenterology, Jazan University

✉ **Corresponding author:** Erwa Eltayib. Elmakki, erwamakki@gmail.com

Disclosures can be found in Additional Information at the end of the article

Abstract

Hyper-reactive malarial splenomegaly syndrome (HMSS) is a massive enlargement of the spleen due to an exaggerated immune response to repeated attacks of malaria. Tropical splenomegaly syndrome (TSS) is the most frequent cause of massive tropical splenomegaly in malarious areas [1-2]. It is seen more commonly among residents of endemic areas of malaria. It occurs mainly in tropical Africa, but also in parts of Vietnam, New Guinea, India, Srilanka, Thailand, Indonesia, South America, and the Middle East. TSS is characterized by massive splenomegaly, hepatomegaly, marked elevations in levels of serum IgM, and malaria antibody.

Categories: Internal Medicine

Keywords: lymphocytosis, malaria, high igm, gastroenterology, tropical splenomegaly syndrome (tss), hyper-reactive malarial splenomegaly syndrome (hmss)

Introduction And Background

Hyper-reactive malarial splenomegaly syndrome (HMSS) is a massive enlargement of the spleen due to an exaggerated immune response to repeated attacks of malaria. TSS is the most frequent cause of massive tropical splenomegaly in malarious areas [1-2]. It is seen more commonly among residents of endemic areas of malaria. It occurs mainly in tropical Africa, but also in parts of Vietnam, New Guinea, India, Srilanka, Thailand, Indonesia, South America, and the Middle East (Figure 1).

TSS is characterized by massive splenomegaly, hepatomegaly, and marked elevations in levels of serum IgM and malaria antibody. Hepatic sinusoidal lymphocytosis is also seen. In about 10% of African patients, it may be associated with peripheral lymphocytosis (B cells) [3]. TSS is more common in females than in males, with a female-to-male rate of 2:1. However, one study from Sudan revealed men to have a higher incidence [4]. TSS is most common in young and middle-aged adults, although the condition probably commences during childhood. TSS is rare in children less than eight years old but has been documented in three-year-old children [5].

Received 12/01/2012

Review began 11/11/2012

Review ended 12/01/2012

Published 12/01/2012

© Copyright 2012

Elmakki. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 3.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

How to cite this article

Elmakki E Eltayib (2012-12-01 03:11:30 UTC) Hyper-Reactive Malarial Splenomegaly Syndrome (HMSS). Cureus 4(11): e72. DOI 10.7759/cureus.72

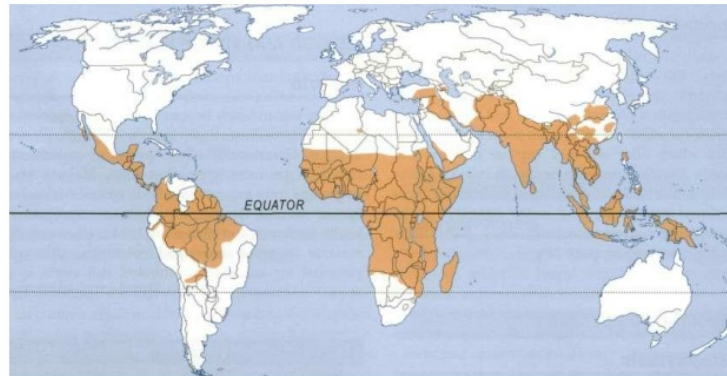


FIGURE 1: Geographical distribution of Malaria

Review

A case report

A 32-year-old African male presented with a six-month history of left-sided abdominal mass which gradually increased in size, associated with dragging pain in the same area. He also had loss of weight and anorexia, but no fever, cough, night sweats, vomiting, or diarrhea. Past medical history included recurrent attacks of fever that usually responded to (over-the-counter) anti-malarial medications but was otherwise unremarkable. His physical examination revealed normal vital signs, pallor and hepato-splenomegaly, spleen extended to the umbilicus, no ascites, lymphadenopathy, or signs of chronic liver disease. Laboratory tests showed: Hb: 9.5g/dl, WBC: 2800/cmm, platelets: 95,000/cmm, normochromic normocytic anemia, normal liver and renal function tests, negative blood film for malaria (repeated twice), positive anti-plasmodium falciparum antibodies, high serum IgM level (200 mg/dl), normal serum IgG, negative HIV serology, negative mantoux test, and normocellular bone marrow. Abdominal ultrasonography reported huge splenomegaly, plus hepatomegaly, no cirrhotic features, intra-abdominal lymphadenopathy, ascites, or evidence of portal hypertension. Chest x-ray was normal. The patient was put on proguanil, 200 mg daily; three month later, his condition started to improve in terms of subsidence of symptoms, correction of hematological disturbances and regression of splenic size; he was advised to have life-long anti-malarial treatment.

Pathogenesis

Studies on the pathogenesis of HMSS suggest a critical role of aberrant immunologic response to malaria antigens after repeated infection, resulting in splenic hypertrophy, sometimes associated with secondary hypersplenism [6].

The interaction between repeated malarial infection and genetic factors class II HLA DR2, IGHG3G (Igg-3 chain C region) and enviromental factors lead to the production of cytotoxic IgM antisuppressor lymphocyte (CD8+) antibodies. This results in inhibition of suppressor T-cells. T-cells are the regulator IgM production. This ends up with uninhibited B-cell formation of IgM and

cryoglobulins (IgM aggregates and immune complexes). The need to clear these macromolecular aggregates stimulates the reticuloendothelial system, leading to hyperplasia. This causes the progressive and massive enlargement of the spleen and liver. The spleen is greatly enlarged and shows dilated sinusoids lined with reticulum cells with marked erythrophagocytosis and lymphocytic infiltration of the pulp. The liver shows sinusoidal dilatation, infiltration with lymphocytes, and hyperplasia of the Kupffer's cells with phagocytosis of cellular debris and red cells [7].

Clinical presentation

The most common presenting symptoms of TSS are chronic abdominal swelling (64%) and dragging abdominal pain (52%), mainly during adult life [8]. Almost all patients (97%) have weight loss. Bleeding complications, such as epistaxis, is uncommon because thrombocytopenia secondary to hypersplenism is usually mild [9]. Some patients may experience recurrent sharp pains in the upper abdomen, possibly due to perisplenitis or splenic infarcts. Other patients may have weight loss and cachexia. On examination, there is massive splenomegaly and hepatomegaly (Figure 2). The patients typically lack malarial parasitaemia and fever on presentation [10].



FIGURE 2: Massive Splenomegaly

Diagnosis

For diagnosing TSS, other causes of massive splenomegaly need to be excluded, such as visceral leishmaniasis (kal-azar), schistosomiasis (portal hypertension), myelofibrosis, and chronic myeloid leukemia (CML) (Table 1).

Visceral leishmaniasis

HMSS

Portal Hypertension

Schistosomiasis

Myeloproliferative diseases

eg: Chronic myeloid leukemia (CML), polycythemia vera, essential thrombocythemia

Lymphoproliferative disorders eg: lymphoma and chronic lymphatic leukaemia (CLL).

Idiopathic non-tropical splenomegaly

Spleen cysts or tumours

Gaucher disease

Thalassemia major

TABLE 1: Differential Diagnosis of Massive Splenomegaly"

However, exclusion of other disease processes causing splenomegaly is not enough to establish a diagnosis of hyper-reactive malarial syndrome (HMS). Fakunle was the first one who described diagnostic criteria for the definitive diagnosis of HMS. Bates and Bedu-Addo modified these major criteria in 1997 [11-12] (*Table 2*).

Major criteria include the following:

- Gross splenomegaly 10 cm or more below the costal margin in adults for which no other cause can be found
- Elevated serum IgM level 2 standard deviations or more above the local mean
- Clinical and immunologic responses to antimalarial therapy
- Regression of splenomegaly by 40% by 6 months after start of therapy
- High antibody levels of Plasmodium species ($\geq 1:800$)

Minor criteria include the following

- (1) Hepatic sinusoidal lymphocytosis
- (2) Normal cellular and humoral responses to antigenic challenge, including a normal phytohemagglutination response
- (3) Hypersplenism
- (4) Lymphocytic proliferation
- (5) Familial occurrence

TABLE 2: Diagnostic criteria for HMSS"

Laboratory features

In TSS, the peripheral smear shows normocytic normochromic anaemia with elevated reticulocyte count. Pancytopenia may also be seen as a result of hypersplenism. Malarial parasites are not found in the peripheral blood. There is elevation in the serum levels of polyclonal IgM with cryoglobulinaemia, reduced C₃ and the rheumatoid factor may be positive.

Increased levels of IgM and antimalarial antibody, hepatic sinusoidal lymphocytosis on liver biopsy, and response to antimalarial therapy (improvement in clinical condition as well as reduction in IgM and malarial antibody titre within three months of continuous antimalarial treatment) favour a diagnosis of tropical splenomegaly syndrome [13].



FIGURE 3: Ultrasound image of massive splenomegaly

Treatment

Antimalarials are the cornerstones of treatment of HMSS. The selection of drug is based on the pattern and prevalence of drug resistance in the patient's geographic area. In malaria endemic areas, treatment should be prolonged (months to years) and continued regularly. However, the exact duration of treatment has not been ensured. Response may be seen within months after commencing treatment, and relapses may occur when therapy is discontinued [14].

Antimalarials clear the antigenic stimulus caused by repeated malarial infections and helps the immune system to return to normal. The selection of antimalarial depends upon the local sensitivity pattern. Chloroquine weekly or Proguanil daily have been found to be effective. Pyrimethamine may be an alternative to the above medications [15]. Data regarding the usefulness of other antimalarial drugs in HMSS is limited. The response to therapy is guided by reduction in splenic size, a decrease in serum IgM levels, correction of anemia and other blood dyscrasias, and general improvement in the patient's well-being.

Severe anaemia may require blood transfusion. Bearing in mind the risks of splenectomy, it may be useful in only those with splenic lymphoma. Splenic irradiation or antimetabolic therapy are not of benefits and may be even dangerous [16].

Conclusions

Take home message

- 1) HMSS results from abnormal immunological response due to repeated attacks of malaria and is usually seen in those who live in malaria endemic areas.
- 2) The main features of this syndrome are hepato-splenomegaly, high IGM levels, and hepatic lymphocytosis on liver biopsy, in addition to features of hypersplensim.
- 3) HMSS should usually be included in the differential diagnosis of massive splenomegaly, especially in tropical and subtropical countries.

4) Lifelong anti-malarials are the mainstay of treatment of HMSS.

Additional Information

Disclosures

This study did not involve human or animal subjects/tissue. No conflict of interest disclosures were provided.

References

1. **Fakunle YM.** Tropical splenomegaly. Part 1: Tropical Africa . Clin Haematol 1981, 0:963-75.
2. **McGilvray ID, Serghides L, Kapus A, Rotstein OD, Kain KC.** Nonopsonic monocyte/macrophage phagocytosis of Plasmodium falciparum-parasitized erythrocytes: a role for CD36 in malarial clearance. Blood 2000, 96:3231-3240.
3. **Weather DJ, Ledingham JGG, Warrell DA.** Tropical splenomegaly syndrome . In Oxford Text Book of Medicine. 3rd. Edited by DA Warrell, TM Cox, JD Firth. New York, NY: Oxford University Press; 1996:
4. **Allam MM, Alkadarou TA, Ahmed BG, et al..** Hyper-reactive Malarial Splenomegaly (HMS) in malaria endemic area in Eastern Sudan. Acta Trop 2008, 105:196-9.
5. **Verma S, Aggarwal A.** Hyper-reactive malarial splenomegaly: rare cause of pyrexia of unknown origin. Indian J Pediatr 2007, 74:409-11.
6. **Greenwood BM, Fakunle YM.** The tropical splenomegaly syndrome: a review of its pathogenesis . In The role of the spleen in the immunology of parasitic diseases. Edited by proceedings of the meeting held in Geneva, June 12-14, 1978. Basel, Switzerland: Schwabe; 1979:229-44.
7. **Fakunle YM.** Tropical splenomegaly. Part 1: Tropical Africa . Clin Haematol 1981, 10:963-75.
8. **Mitjà O, Hays R, Malken J, Ipai A, Kangapu S, Robson J.** HMS-related hemolysis after acute attacks of Plasmodium vivax malaria. Am J Trop Med Hyg 2011, 85:616-8.
9. **Grane GG.** Hyperreactive malarious splenomegaly "Tropical splenomegaly syndrome" . Parasitol Today 1986, 2:4-9.
10. **Fakunle YM.** Tropical splenomegaly. Part 1: Tropical Africa . Clin Haematol 1981, 10:963-75.
11. **Bates I, Bedu-Addo G.** Review of diagnostic criteria of hyper-reactive malarial splenomegaly . Lancet 1997, 349:1178.
12. **Hoffman SL, Piessens WF, Ratiwayonto S, et al..** Reduction of suppressor T lymphocytes in the tropical splenomegaly syndrome. N Engl J Med 1984, 310:337-341.
13. **Van den Ende J, van Gompel A, van den Enden E, et al..** Hyperreactive malaria in expatriates returning from sub-Saharan Africa. Trop Med Int Health 2000, 5:607-11.
14. **Manenti F, Porta E, Esposito R, Antinori S.** Treatment of hyperreactive malarial splenomegaly syndrome. Lancet 1994, 343:1441-2.
15. **Sagoe AS.** Tropical splenomegaly syndrome: Long-term proguanil therapy correlated with spleen size, serum IgM, and lymphocyte transformation. BMJ 1970, 3:378-382.
16. **Crane GG.** Hyperreactive malarious splenomegaly (tropical splenomegaly syndrome) . Parasitol Today 1986, 2:4-9.