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Seminar

Tropical Splenomegaly

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Palpable splenomegaly with or without hypersplenism (pancytopenia) is a common physical finding in the tropics, especially in areas where malaria is endemic. In many instances splenomegaly is accompanied by hypersplenism, when there is pancytopenia, the severity of which is usually related to the size of the spleen.

The splenic enlargement may be caused by four pathophysiological mechanisms: 1. extramedullary haemopoiesis (e.g. thalassaemia), 2. phagocytic activity (e.g. malaria), 3. congestion (e.g. portal hypertension due to cirrhosis), 4. infiltration (e.g. lymphoma), and 5. combinations of the above.

It is more practical to remember that splenomegaly is usually due to **haematological diseases**, **infections**, **portal hypertension** and rarely due to metabolic disease (e.g. Gaucher's disease) and local causes: cyst (parasitic or epithelial), abcess, tumour.

The presence of massive enlargement of the spleen usually indicates a chronic illness.

*The conditions associated with **mild** (<5 cm below coastal margin) **to moderate** (5-10 cm below coastal margin) **tropical splenomegaly** are many:*[1-4]

- Common tropical infections that are frequently accompanied by mild-moderate splenomegaly and fever include malaria, typhoid fever, brucellosis, HIV, tuberculosis (especially in HIV-infected patients), dengue, trypanosomiasis, relapsing fever, toxoplasmosis, and splenic abscess (splenic abscess is a well-recognised chronic tropical disease in West Africa and Zimbabwe where it occurs with no identifiable predisposing factor or cause, although some cases may be related to *S. typhi*). Always check HIV status and take a good history of contacts with tuberculosis e.g. contact with individuals who recently took antituberculous medications.
- Chronic haemolytic anaemias are common causes of mild to moderate splenomegaly in the tropics: Hb H disease, β-thalassaemia intermedia, spherocytosis, Hb CC, Hb SC, and Hb C β-thalassaemia. They are rarely associated with massive splenomegaly (except thalassaemia major, HbSC, and thalassaemia intermedia).

*In contrast, the causes of **massive tropical splenomegaly** are few:*

Massive splenomegaly is defined clinically as measuring >10 cm below coastal margin or splenomegaly below the umbilical level, and radiologically as measuring >20 cm in length on US or CT. Massive splenomegaly is common in many tropical African countries (e.g. 1-2% in Nigeria and 0.4-1.2% in Gambia).

In a study of 221 individuals with massive splenomegaly in West Africa (Bedu-Addo G, Bates I. Causes of massive tropical splenomegaly in Ghana. Lancet 2002;360:449-454), the commoner causes were the tropical splenomegaly syndrome (hyper-reactive malarial splenomegaly), B-lymphoproliferative disorders with accompanying lymphadenopathy (B-LPD), and splenic lymphoma with villous lymphocytes (SLVL), as shown in Table 1.

The relative frequency of massive splenomegaly causes differs in other tropical regions e.g. in eastern Africa (Sudan, Ethiopia, Kenya) where the climate is Dry-Tropical and in parts of India (West Bengal, Bihar) visceral leishmaniasis is a very common cause of massive splenomegaly; in the African Great Lakes (Great Rift Valley Lake region) e.g. Lake Victoria and Lake Malawi chronic schistosomiasis (*S. mansoni*) is as common cause of massive slenomegaly as hyper-reactive malarial splenomegaly. Chronic schistosomiasis is also endemic in Egypt ('Egyptian hepatosplenomegaly').

Note: an eosinophilic response to helminthic infection e.g. *S. mansoni* may not be apparent in the peripheral blood count because the eosinophils are held in the spleen, but it will be obvious in the bone marrow aspiration done for investigation of splenomegaly.

TABLE 1. Causes of massive tropical splenomegaly in Ghana.

	Number	Male: female ratio	Age (years, median [range])	Spleen size (cm, median [range])	Liver size (cm, median [range])
HMS	91 (41%)	1:3.6	26 (10-75)	13 (10-30)	5 (0-16)
B-LPD	27 (12%)	1.5:1	55 (16-71)	12 (10-26)	5 (0-13)
T-SLVL	21 (10%)	1:2	52 (20-75)	16 (10-41)	7 (0-18)
CML	18 (8%)	1.6:1	41.5 (8-62)	14.5 (10-27)	3.5 (0-10)
Other*	14 (6%)	1:1	28 (16-51)	14.5 (10-27)	5 (0-11)
Unknown cause	50 (23%)	1:3	24.5 (11-75)	15.5 (10-27)	5 (0-18)
Total	221 (100%)	1:1.8	31 (8-75)	14 (10-41)	5 (0-18)

HMS = hyper-reactive malarial splenomegaly, T-SLVL = tropical splenic lymphoma with villous lymphocytes, CML=chronic myeloid leukaemia , B-LPD = B-cell lymphoproliferative disorders

** Patients with Hb SC (n=4), portal hypertension (n=3), Schistosoma mansoni (n=2), thalassaemia intermedia (n=2), myelofibrosis (n=1), acute myeloblastic leukaemia (n=1), heavy-chain disease (n=1).*

Tropical splenomegaly syndrome or hyper-reactive malarial splenomegaly (HMS):[2-11]

It is an abnormal immunological response with characteristic overproduction of IgM due to recurrent infection by *P. falciparum*, *P. malariae,* or *P. vivax* in people who have lived for a long time (typically many years) in tropical regions in which malaria is hyperendemic i.e. regions with persistent, high levels of malaria occurrence (a **hyperendemic disease** is one that is constantly present at a high incidence and/or prevalence rate and affects all groups equally). HMS is the most important cause of massive splenomegaly in tropical Africa e.g. Ghana, Uganda, Nigeria, Malawi. HMS is also seen in India, South America (Amazon basin, Venezuela), Papua New Guinea, South-East Asia, and South China. Central to the pathophysiology of HMS is the prolonged exposure to malaria: a disordered immune response (genetic predisposition?) to malaria parasites leads to excess production of B-lymphocytes and immune complexes, with consequent reticuloendothelial hypertrophy. The production of B-cells may be enhanced by T-cell dysfunction.

The diagnosis of HMS is based upon the following criteria: (1) massive splenomegaly >10 cm, (2) hypersplenism, (3) high malarial antibody titres (especially IgM antibodies), (4) marked polyclonal hyperglobulinaemia (with serum IgM levels that are 2 times higher than the ULN), (5) hepatic or splenic sinusoidal lymphocytosis with polyclonal B-lymphocytes (cμ+), (6) normal response of lymphocytes to phytohaemagglutinin - lymphocyte transformation test (PHA-LTT) (old criterion) or absence of clonal B-cells by flow cytometry, immunoglobulin (*IGH*) gene rearrangement or immunohistochemistry in the bone marrow (new criterion), and (7) positive clinical and immunological response to long-term antimalarial prophylaxis (low dose antimalarials continuously): at least 40% reduction in spleen size after 6 months of antimalarials. The diagnosis of HMS depends upon fulfillment of all stated criteria.

HMS patients are afebrile and most commonly complain of abdominal distention or pain from the enlarged spleen.The spleen may be huge, reaching to the left iliac fossa and across the midline. There is usually hepatomegaly but there is no lymphadenopathy. The patients usually have symptoms of hypersplenism, mainly chronic anaemia which may require bood transfusion. The anaemia is typically normochromic normocytic, and — as in any case of massive splenomegaly — is due to: (1) increased red cell pooling in the spleen, (2) shortened red cell life-span due to increased destruction in the spleen, and (3) haemodilution from an increased plasma volume. There is a mild reticulocytosis and the bone marrow shows normal or hyperplastic erythropoiesis. The mechanisms of granulocytopenia and thrombocytopenia are similar. HMS patients often have mild neutropenia which may be mistaken for ethnic neutropenia, which is common in tropical Africa.

Blood films are negative for malaria parasites. The blood film shows red cell agglutination, tear drop red cells, poikilocytes, some atypical lymphocytes (reactive lymphocytes, plasmacytoid cells, even villous lymphocytes), absence of malaria parasites, and importantly absence of abnormal immature cells e.g. blasts. Although pancytopenia and leukopenia is the rule, some patients may present with a lymphocytosis with atypical lymphocytes

TABLE 2. Differential diagnosis of HMS from T-SLVL.

	HMS	T-SLVL
Age	usually <40 years (20-40 years)	usually >40 years
Sex	usually women	usually women
Blood lymphocyte count	$<10\times10^9$/l	may be $>10\times10^9$/l
Bone marrow biopsy	negative	positive
Serum paraprotein	typically no	may be present

Causes of massive tropical splenomegaly >10 cm:

- HMS
- B-LPD
- Kala-azar
- Chronic schistosomiasis
- CML
- Myelofibrosis

and circulating villous lymphocytes (ddx: SLVL). There may be an excess of bone marrow lymphocytes and plasma cells in HMS which are polyclonal.

Type III cryoglobulinaemia may develop with positive rheumatoid factor. Cold agglutinins (IgM antibodies) may also occur, sometimes in high titre. In 1% of patients (mainly pregnant women), an acute haemolytic anaemia may develop (haemolytic crisis of HMS). It is a severe, life-threatening form of Coombs (-) acute haemolytic anaemia but responds to steroids.

It is likely that HMS may progress to SLVL, possibly explaining why tropical SLVL (T-SLVL) is more common in women.

HMS should be distinguished from recurrent malaria, T-SLVL, and hepatosplenic lymphoma (HSTL):

- **recurrent malaria** is associated with chronic haemolysis, generally moderate splenomegaly (5-10 cm), which is commonly associated with hypersplenism, an increase in IgG level, often recurrent fever, and detection of parasites in blood film. Abundant pigment is present in bone marrow macrophages. The unstained bone marrow smears of patients who have had repeated bouts of malaria may appear slate grey or black because of the accumulation of haemozoin.
- to differentiate HMS from T-SLVL and HSTL, bone marrow aspiration, biopsy, and flow cytometry are required. Table 2 shows distinguishing features between HMS and T-SLVL.

Note:

- Massive tropical splenomegaly may be associated with splenic infarct(s) regardless of its cause. However, the presence of splanchnic vein thrombosis (i.e. splenic-vein, portal-vein, or mesenteric-vein thrombosis), cavernoma, and high-normal or high PLT are highly suggestive of a myeloproliferative neoplasm and investigation with bone-marrow biopsy and molecular testing for *BCR-ABL1, JAK2, CALR,* and *c-MPL* mutations is indicated. Splanchnic vein thrombosis is not a feature of HMS.
- HMS may be complicated by T-SLVL, and rarely, HMS may co-exist with another cause for massive splenomegaly such as myelofibrosis or essential thrombocythaemia.
- High-titre cold agglutinins are characteristic of two tropical diseases: HMS and African trypanosomiasis (but may also occur in B-lymphoproliferative disorders).

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