Hyper-reactive Malarial Splenomegaly: A Case Report and Review of the Management and Pathogenesis.

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SUMMARY

Hyper-reactive malarial splenomegaly is thought to represent a dysfunctional immune response to recurrent malaria infection. A 14 year old male child with hms, hypersplenism, ascites and peripheral lymphadenopathy is reported. There was initial poor response to proguanil aggravated by non compliance. He was started on a combination of proguanil and chloroquine with counseling and showed good and fast response. A review of the management and recent concept of pathogenesis is presented.

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Key words: Hyper-reactive malarial splenomegaly, management, pathogenesis

INTRODUCTION

Hyper-reactive malarial splenomegaly (HMS) is an aberrant response to chronic malarial infection that is seen in areas of intense transmission of malaria. In Nigeria prevalence is 1 2% but is up to 80% among certain tribes of Papua New Guinea 1,2 In a report published from this center in 1992, prevalence was not documented and of the 39 patients reported their ages ranged from 13 to 69 yrs with a mean age of 44.4yrs.[3] The disease is incurable[4] but responds to malarial prophylaxis[1-3] Surgical management ie splenectomy has been found to result in complications including death.[1,5] The criteria[1,6,7] for diagnosis is based on the exclusion of other causes of spleen enlargement. Major criteria include a splenomegaly of at least 10cms, high antibody levels of plasmodia specie (=1:800), elevation of serum of IgM at least 2 SD above the normal mean concentration for the, regression of the spleen by at least 40% by 6 months of therapy and clinical and immunological response to antimalarial therapy. Other minor diagnostic criteria included hepatic sinusoidal lymphocytosis, normal immune response to phytohaemagglutinin stimulation, hypersplenism, familial occurrence and lymphocyte proliferation. The presence of malaria parasite in the blood film is not necessary for the diagnosis to be made.[1,6,7] The study by Bedo-Addo and Bates from Ghana in 2002 reported that 41% and 22% of 221 persons with a spleen of more than 10cm had a final diagnosis of HMS and B lymphoproliferative disorder respectively.[8] The were of the opinion that the criteria for making a diagnosis of HMS in resource poor countries should include an absolute lymphocyte count of less than 10 x 109/L in a person less than 40years of age and a decrease in spleen size of more than 40% after 6 months of treatment with antimalarials.8 They also noted that this will aid in differentiating this disease from malignant lymphoproliferative disorders but it has been reported that HMS may evolve into malignant lymphoma.[8]

This patient is presented to demonstrate the role of adherence in the management as well as the difficulties in making the diagnosis in our environment. The presence of some features that have not been reported in literature before is also highlighted.

CASE REPORT

NS a 14 year old adolescent presented at the University of Nigeria Teaching Hospital, Enugu, in 2006 with a 2 year history of abdominal discomfort, left sided abdominal mass and recurrent fevers. The abdominal mass increased in size with the febrile episodes. The abdominal discomfort was biting in nature and located at the left hypochondrium. He also had chest pain, headache and palpitations. He had never been transfused.

On examination he was found to be acutely ill looking, in mild respiratory distress, moderately pale, febrile (38.3^{o}C), anicteric with asymmetric abdominal distension. He had a splenomegaly of 23cm and a hepatomegaly of 4cm which was tender, firm and smooth surfaced. He also had crepitations in the right basal lung zone. A working diagnosis of and community acquired pneumonia and ?Hyperimmunereactive Malarial Splenomegally (HMS) was made. Investigations at that time (Table) showed low platelets, anaemia, leucopenia and increased globulin (we were unable to determine the electrophoretic pattern). His genotype was AA and malaria parasite was not detected in the peripheral blood. While on admission patient responded to proguanil, antibiotics and haematinics.

He defaulted to follow up and represented 7 months later with complaints of fever, abdominal mass and pain for 8 days and 3 days history of cough. He was found to be lethargic, anicteric, moderately pale with peripheral lymphadenopathy and febrile with an axillary temperature of 38.4^{o}C. The abdomen was distended with visible veins, tender hepatomegaly (9cm) splenomegaly (22cm), there were no clinical signs of peritonitis.

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Repeat ultrasound showed that he had ascites. Analysis of the ascitic fluid showed pus cells but there was no bacterial growth. The lymph node biopsy was non specific and thus we were able to eliminate a lymphoproliferatve disorder. He was transfused as his haemoglobin had decreased and treated with quinine and co-amoxiclav. Proguanil was restarted. At the time of his discharge he was afebrile and the spleen size had reduced to 17cm. Nine weeks later he developed fever and vomiting and the spleen was noted to have increased again to 24cm. We were unable to confirm his compliance with the paludrine. A full blood count done at that time showed anaemia and thrombocytopenia. Bone marrow aspiration done at this time showed dyserythropoiesis. Based on the response to antimalarials, the increase in immunoglobulin, age of less than 40yrs, his absolute lymphocyte count of less than 10 x 109/L as well as the genotype of AA and the negative bone marrow aspirate and lymph node biopsy for any malignancy we entertained a diagnosis of HMS.[6]

He was again treated with anti malarials (ACT) and antibiotics with good response. He was discharged after 15 days on parents request on weekly chloroquine and proguanil. His spleen size was 21cm at the time of discharge. He was also counseled on compliance with his drug intake. Eight weeks after his discharge his spleen measured 10cms which is in keeping with more than 40% reduction in less than 6 months.[6] He has been compliant with his drug intake and hospital visits. At the last contact with the patient one year after the last admission his spleen was no longer palpable but he was advised to continue his paludrine and chloroquine.

Table: Haematological and other parameters of the patient during the 1st 2nd and 3rd admissions.

Parameter/ date	1st Admission 20th Oct 2006	2nd Admission 4th May 2007	3rd Admission 24th July 2007
Haemoglobin g/dl	7.3	6.6	6.0
RBC (106/ml)	-	2.79	-
PCV (%)	-	21	20
MCHC	-	-	30.8
MCV(μm^3)	-	-	72.5
WBC (per mm^3)	2,100	5,800	4,700
Neutrophil (%)	42	24	30
Lymphocytes (%)	56	71	68
Eosinophils (%)	2	0	0
Basophils (%)	0	5	0
Monocytes (%)	0	0	2
Platelets (mm^3)	65,000	83,000	26,000
Malaria parasite	negative	++	+
Widal test	negative	-	-
HIV I and II	-	negative	-
Serum proteins	Inc globulin	-	Normal range
Abdominal US	Englarged spleen	+ ascites	-
Genotype	AA		

DISCUSSION

This patient presented with the classical symptoms of HMS of abdominal mass, left sided upper abdominal pain, hypersplenism (anaemia, thrombocytopenia and leukopenia) and clinical response to anti malarial drugs. Malaria parasites were not demonstrated in his peripheral blood smear at his first presentation which could be because malaria antigeneamia is not usually high in patients with HMS.[1, 6,7] In a case report in Australia malaria parasitaemia was not documented and the reason suggested was that the hyperactive spleen mopped up the malaria parasite as it became detectable after splenectomy.[10] It is possible that this explanation might apply to our patient. The re-appearance of malarial parasetemia in the two subsequent samples could be due to the effect of the proguanil on the hyperactivity of the spleen.

Our inability to fulfill other criteria for the disease eg increases in Igm faction of globulin, and demonstration of malarial antibodies was due to lack of laboratory facilities for the specific tests. We had also investigated for other common causes of enlarged spleen in this environment. His genotype was AA and the biopsy of the lymph node and bone marrow was negative for any specific pathology. Our patient responded well to paludrine as his relapse occurred any time he defaulted on his drugs. When he was started on a combination of paludrine and chloroquine his response was faster and this might have contributed to his adherence.

The finding of enlarged peripheral lymph nodes within the course of the ill health has not been documented in other studies but the biopsy result was negative for any pathology. Ascites seen in the child may occur but is said to be rare 1 but could have been infective in origin as cytology yielded pus cells but there was no bacterial growth. These resolved with the use of antibiotics and treatment of the primary disease. He also had features of hypersplenism and lymphocytosis which are features of HMS.[1,7]

Primary causes of massive splenomegaly include immune response, red blood cell destruction, congestive, myeloproliferative, infiltrative, and neoplasia.[1] HMS develops as a result of an atypical immune response to recurrent malarial infection. Certain racial and immunologic functions may be important in the pathogenesis of HMS. The populational and familial pattern of HMS in Papua New Guinea (PNG) has shown that it occurs among people with a high frequency of IGHG3 G haplotype.[11] In the same locality though, human lymphocyte antigen (HLA) phenotype studies found a higher frequency of HLA DR2 locus antigen that was not significant in the patients with gross splenomegaly.[12] Crane GG and Serjeanston13 later reported from the same PNG that there was a major sex linked gene that controlled the hyper response to malaria, though an autosomal locus could not account for the significant variation in spleen grade. In Ghana, Martin-Peprah *et al*[4] found that even though the relatives of HMS cases were more likely to have splenomegaly than controls there was no obvious pattern of mendelian segregation and concluded that in Ghana HMS aetiology is complex involving multiple genetic and environmental factors.

Although the exact mechanism of HMS is unknown most of the evidence implies that exposure to any specie of the malaria parasite elicits an exaggerated stimulation of polyclonal B lymphocytes leading to excessive and partially uncontrolled

production of immunoglobulin M (IgM) as the initiating event. Defective immunoregulatory control of B lymphocytes results in an increase in B lymphocytes and a decrease in T lymphocytes in the peripheral blood. There is also T lymphocyte infiltration of the hepatic and splenic sinusoids and increase in cryoglobulin, and autoantibody levels, and immune complexes. This leads to anaemia, deposition of large immune complexes in kupfer cells in the liver and spleen, and reticuloendothelial cell hyperplasia and hepatosplenomegaly.[1,7,15] The natural history of HMS has been documented to be a progressive disease with high mortality in the fully developed case.[4] The transmission from a simple malarial spleen to HMS usually occurs between 6 and 20 yrs of age.[16] This long period that occurs before manifestation of the disease makes the disorder rare in children below 8 yrs though it has been reported in a child of 3yrs[17] It is also postulated in West Africa there might be a promotion to Splenic Lymphoma with Villous Lymphocytes.[2,9]

Eradication of parasitaemia seems to be the common pathway for resolution as successful treatment of HMS has been with antimalarial drugs especially, paludrine or chloroquine and in some instances a combination of paludrine and sulphodoxine or chloroquine.[1,3] The drugs may have to be given for long periods (years) before a response is noted. The duration of treatment is unknown.[1] The place of splenectomy in the treatment of this disorder is still controversial. In some studies some benefit was reported in a highly selected group of patients[18] or when compared to those who did not have the benefit of medical treatment[5] and in others the mortality in those with splenectomy was higher than in those where medical management was used.[1] Generally, splenectomy in the management of HMS is not recommended as mortality is high from sepsis and thrombocytosis.[1,2,19] In our patient we combined paludrine and chloroquine as the response of the child to paludrine alone was thought to be inadequate before we realized that non compliance might have contributed to the non response. This latter regimen showed a quicker response with the spleen reducing by 12cms ie about 50% within 8 weeks of therapy. Physicians working in malaria endemic regions should always consider HMS in the differential diagnosis of an enlarged spleen. The use of combination therapy in its management might help in improving response and ensuring better adherence as seen in this patient.

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