Case Report: Hyper-reactive Malarial Splenomegaly in a Patient with Human Immunodeficiency Virus

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Abstract. Both hyper-reactive malarial splenomegaly (HMS) and HIV infection are highly prevalent in sub-Saharan Africa, but the inter-relationships between the two conditions are not clearly defined. Diagnosis of HMS is particularly difficult in HIV-infected patients, and detection of circulating malaria parasites by polymerase chain reaction (PCR) may represent a useful diagnostic tool.

INTRODUCTION

Hyper-reactive malarial splenomegaly (HMS) syndrome is observed most often in African individuals, and its frequency is underestimated. HMS is also recognized as an imported disease in malaria-free areas, but with low frequency. Pathogenetic studies suggest a critical role of an aberrant immunologic response to malaria antigens after repeated exposures, resulting in splenic hypertrophy, sometimes associated with secondary hypersplenism. HIV infection is also widespread in sub-Saharan Africa, and several studies reveal complex interactions with malaria that may have dramatic population-based effects. However, the clinical significance of HMS in HIV-infected individuals is still scattered and incomplete. We report and discuss a case of HMS in an HIV-infected African immigrant in Italy.

CASE REPORT

In November 2004, a 57-year-old woman, born in Cameroon, who had entered Italy as an immigrant in August 2004, was admitted to the Infectious and Tropical Diseases Institute in Brescia, Northern Italy. She complained of abdominal pain, weight loss of 10 kg, and low-grade fever of 10-22.5°C. The hematocrit was 28.2%, hemoglobin was 9.3 g/dL, leukocytes were 2,820 × 10^3/mm^3, white blood cells (WBC) 2,520 × 10^3/mm^3 with abnormal differential count (lymphocytes = 50.5%, neutrophils = 22.5%, eosinophils = 14%), and platelets = 120 × 10^3/mm^3. Creatinine was 1.8 mg/dL, and urine analysis revealed nonselective glomerular proteinuria. Total serum gamma globulins were increased (44.2%), with IgG 3,105 mg/dL (normal range, 600–1,350 mg/dL) and IgM 990 mg/dL (normal range, 50–350 mg/dL). Iron pattern, liver enzymes, and chest x-ray were normal. The patient developed continuous fever up to 38°C, severe anemia (Hb 7.6 g/dL), and high creatinine serum levels (7.6 mg/dL). Anti-retroviral therapy was discontinued, and a new treatment regimen of lamivudine 150 mg/day, stavudine 30 mg twice/day, and nevirapine 200 mg/day was administered, the dose being adjusted for reduced renal function. After some days, vaginal fever was cleared and molecular assays for Plasmodium were negative, but hypersplenism and pancytopenia improved more slowly. Two months after mefloquine treatment, spleen size was reduced to 14.8 cm, and the abdominal pain improved accordingly. Total serum IgM normalized, and the IFAT malaria titer showed a 4-fold reduction (1:640).

Anti-retroviral therapy was started with dose adjustment for the renal function using lamivudine 150 mg/day, stavudine 15 mg twice/day, and nevirapine 200 mg/day. Three days afterward, fever was cleared and molecular assays for Plasmodium were negative, but hypersplenism and pancytopenia improved more slowly. Two months after mefloquine treatment, spleen size was reduced to 14.8 cm, and the abdominal pain improved accordingly. Total serum IgM normalized, and the IFAT malaria titer showed a 4-fold reduction (1:640).

Because of the increasing number of immigrants from areas where both malaria and HIV infection are highly prevalent, physicians in industrialized countries should consider HMS in the differential diagnosis of HIV-infected patients with marked splenomegaly.

Differential diagnosis of splenomegaly in HIV-infected individuals from the tropical belt is complex and should include several conditions, such as HBV, HCV, EBV, CMV, Leishmania, and Schistosoma infections as well as malignant lymphoproliferative disorders. In our case, all of these conditions were ruled out and the diagnosis of HMS was based on

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Fakunle’s criteria, which do not differ in HIV-seronegative or HIV-seropositive individuals: major criteria were marked splenomegaly, high antibody levels to *P. falciparum*, serum IgM at least 2 standard deviations above the mean laboratory value, and clinical and immunologic response to antimalarials. Among minor criteria, hypersplenism was present.

Initially, malaria parasites were not detected at microscopic examination because of the low sensitivity of the technique in cases of HMS. Evidence of malarial infection is indirect in many HMS patients, and is based on serological criteria; immunohistochemical demonstration of *P. falciparum* antigens in liver cells is a very specific but invasive method. Direct demonstration of specific malarial DNA in the blood with nested PCR and real-time PCR can provide further evidence for diagnosis of HMS. PCR investigations, even qualitative ones, are highly sensitive assays that have proved useful in diagnosis of persistent malaria infections and which might be useful confirmatory techniques in industrialized countries in diagnosis of HMS. In HIV-infected individuals, such evidence would prevent misleading diagnoses and use of inappropriate therapies.

To conclude, clinicians should be reminded that malaria can cause splenomegaly, regardless of HIV status, and that they still need to consider malaria in their differential diagnoses in patients with suitable travel histories. Further research is warranted, which ideally should be conducted in countries where both HIV infection and malaria are highly prevalent.

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