INTRODUCTION

The spleen has two major immunological functions: phagocytosis and antibody production. The large number of parasitic, bacterial and viral agents that afflict people in the developing tropical countries induce splenomegaly of varying magnitudes in many diseases (FAKUNLE, 1981). In 1967 for instance, Pryor (1967) recorded that 62% of the inhabitants of a village in New Guinea had splenomegaly to the level of the umbilicus. Marsden & Hamilton (1969), in a cross-sectional survey in Kampala, Uganda, found clinical splenomegaly in 50% of all medical in-patients.

The tropical splenomegaly syndrome (TSS) originally referred to cases of splenomegaly in the tropics for which no cause could be found, even after full investigation (Anonymous, 1967). Since then it has been associated specifically with a condition resulting from an aberrant immunological response to malaria (Marsden & Crane, 1976). Fakunle (1981) set major and minor diagnostic criteria (Table 1). The syndrome is distinct from the transient splenomegaly commonly observed in patients with acute malaria and from the chronic, massive splenomegaly of children in regions where malaria is highly endemic.

Other features found are abdominal swelling and pain, fatigue, weakness, cough, pallor, jaundice, hepatomegaly, anemia, thrombocytopenia and leukopenia (Fakunle, 1981; Pryor, 1967; Strickland, 1991; Anonymous, 1970). The syndrome is associated with increased numbers of lymphocytes in blood and bone marrow (Watson-Williams & Allan, 1968).

Studies investigating the pathogenesis indicate that serum samples from patients with hyperreactive malarial splenomegaly contain lymphocytotoxic antibodies (IgM) triggered by repeated exposure to malarial parasites with specificity for CD8 suppressor lymphocytes, thus leaving relatively unopposed the stimulating effect of CD4 helper lymphocytes on B cells, with consequent reticuloendothelial hypertrophy (Piesseens et al., 1985; Betticher et al., 1990).

In 1983 a distinguished group of malariologists proposed replacing the former denomination «tropical splenomegaly syndrome» by the term «hyperreactive malarial splenomegaly» (HMS) (Bryceson, Fakunle & Fleming, 1983). This new name serves: 1) to reflect more accurately the role of malaria in the syndrome’s pathogenesis; 2) to stress the excessive activity of the immune system; 3) to lessen the impression that the spleen is the only organ that is enlarged and hypercellular in such patients; 4) to differentiate the syndrome from the more common, simple forms of malarial splenomegaly (Barry & Brant, 1993).

MATERIAL AND METHODS

We studied the clinical history of all Guinean patients attended in the Department of Tropical Medicine of the National Health
RESULTS

Ten (66.6%) of the 15 Guinean patients were women and five (33.3%) were men. The average age among the patients was 38, ranging from 20 to 63 years. The average period of time between the first day of residence in Spain and the first contact with our Department was 75.7 days (range: 3 days - 16 months).

The first symptoms appeared after 12.5 months in the average (range: 3-36 months). The most frequent among them were: abdominal pain in 11 cases (73.3%), weight loss in 10 cases (66.6%), anorexia in 7 cases (46.6%), asthenia in 9 cases (60%), and anemia in 7 cases (46.6%).

Splenomegaly was present in all the cases with palpable spleen 10-18 cm (average 13.7 cm) under the thorax. A total of 13 (86.6%) patients presented palpable hepatomegaly (3-8 cm; average 5.5 cm).

The principal clinical and analytical data are displayed in Table 2.

The average IgM level of the 100 uninfected Guineans was 1.97 g/l, which is quite similar to the values measured in neighbouring countries (SAGOE, 1970; BATES et al., 1991). The local mean plus 2SD was 3.81 g/l.

All patients presented high malarial specific antibody titers: 1/1280 in 10 patients; 1/2560 in 1 patient; 1/5120 in 3 patients; 1/10249 in 1 patient.

Three patients were treated with quinine sulfate (650 mg every 8 hours during 5 days) and 12 were treated with halofantrine (500 mg every 6 hours, 3 doses). Three cases of HSM could not be followed up entirely as these patients returned to Equatorial Guinea. The 12 remaining patients underwent a chloroquine treatment (300 mg/week) during an average period of 8.2 months (range: 4-13 months).

All of the 10 persons in which the liver biopsy was performed presented hepatic sinusoidal lymphocytosis (HSL). However, malarial pigment was not observed in any of the cases. Three persons (20%) presented only a very low parasitaemia. One of these cases could be identified as Plasmodium falciparum infection (the other 2 as Plasmodium spp.).

The study of the bone marrow aspirates revealed that 13 of the 15 (86.6%) presented an increase in the number of lymphocytes. African trypanosomiasis was diagnosed in one of the HSM patients as trypanosomes were found in the bone marrow sample, as well as in the peripheral blood. No other parasite was found in any of the other cases.

DISCUSSION

HSM is a common disorder in natives of many places where malaria is endemic. Papua New Guinea has the highest recorded prevalence, with 60% of certain adult Angus affected (CRANE, GIBSON & VERRALL, 1985). It has also been reported from Brazil, India, Indonesia, many parts of the African continent and rarely in Caucasians (BUTTICHER et al., 1990; BHATTACHARYA et al., 1983; CHAGNON et al., 1989; KAGER, 1989; LOWENTHAL & HUTT, 1970; VAN DEN ENDIJK et al., 1994). Literature research (through Medline in 1994) did not reveal any reported cases of HSM in Equatorial Guinea.

The disorder can occur at any age after the acquisition of immunity to malaria (i.e. over 10 years) but appears most frequently in the third decade. Women are affected approximately twice as often as men (LOWENTHAL et al., 1980). This number is comparable to our constellation, in which 10 (66.6%) patients were women and 5 (33.3%) men, with an average age of 38 years (20-63 years).

Splenomegaly, high IgM and antimalarial antibody levels and response to antimalarials are obligatory. HSL, occurring in over 80% of cases (MARSH & GREENWOOD, 1986), is a minor criterion and it is also seen in Felty’s syndrome, non-tropical idiopathic splenomegaly or Duicie’s syndrome, and some rare cases of chronic lymphocytic leukaemia (CRAN, 1986).

Malarial pigment is not found in involved organs (MARDEN & HAMILTON, 1969; STRICKLAND, 1991), and malarial parasites are rarely detected in bloodsmears.

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>11</td>
<td>73.3</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>10</td>
<td>66.6</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>9</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>7</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly (cm)</td>
<td>15</td>
<td>100</td>
<td>10-18 (13.7)</td>
</tr>
<tr>
<td>Hepatomegaly (cm)</td>
<td>13</td>
<td>86.6</td>
<td>3-8 (5.5)</td>
</tr>
<tr>
<td>High IgMLM+2SD g/l</td>
<td>15</td>
<td>100</td>
<td>4.7-43.7 (13.4)</td>
</tr>
<tr>
<td>High IFA Malaria less 1/1280</td>
<td>15</td>
<td>100</td>
<td>1/1280-1/10240</td>
</tr>
<tr>
<td>Anemia Hb less 1/128</td>
<td>9</td>
<td>60</td>
<td>6.9-10.9 (9.2)</td>
</tr>
<tr>
<td>Thrombocytopenia less 150x109/l</td>
<td>8</td>
<td>53.3</td>
<td>63-137 (105)</td>
</tr>
<tr>
<td>High ESR</td>
<td>15</td>
<td>100</td>
<td>44-115 (89.6)</td>
</tr>
</tbody>
</table>

Table 2: Main clinical and analytical data observed in Guinean patients.
A splenic reduction of 40% constitutes a good response to the treatment and reductions of less than this (15-20%) are considered as moderate or no response (Bates et al., 1991). All of the 15 patients (100%) presented palpable splenomegaly of 10-18 cm (average 13.8 cm). In the case of 3 (20%) HSL patients it was impossible to record their clinical history till the end as they went back to Guinea before the end of the treatment. In the case of 5 (37.5%) of our patients the splenomegaly was still palpable 1-6 cm 6-13 months after start of treatment. This means a reduction of 60-90% (77.2%). Furthermore the IgM titers of these patients decreased to the normal level in every single patient. This evolution of the splenomegaly is similar to the evolution in other series (Bates et al., 1991; Onuegbu & Mba, 1992).

The IgM-titers of all the patients decreased and reached the normal level after 4-12 months (average 7.2 months) of treatment.

All of the patients in which we carried out the liver biopsy presented HSL. The observed absence of malarial pigment and the rare and low parasitisation correspond to the observations made in similar experiments (Marsden & Crane, 1976; Strickland, 1991; Anonymous, 1970; Barry & Brant, 1993; Hoffman, Piessens & Ratwayanto, 1984). However, the increase in the number of lymphocytes in bone marrow, present in 13 of the cases, was more frequent (Fakunle, 1981).

After treatment symptoms disappeared and anemia, thrombocytopenia and high ESR were cured in all patients.

If the patient resides in an endemic area the most effective preventive and curative treatment of HMS is lifelong antimalarial therapy (Fakunle, 1981; Marsden & Hamilton, 1969; Sagoe, 1970; Hoffman, Piessens & Ratwayanto, 1984; Bates, 1991; Lowenthal, O-Riordan & Hett, 1971; Hamilton et al., 1966), applying first a curative dose of antimalarial followed by prophylactic treatment. Diagnostic resolution of all parameters of HMS should be carried out regularly during prolonged therapy. The in case of reexposure to malaria, relapses appear very quickly if the treatment is not continued (Barry & Brant, 1993). Splenectomy should only be considered if the antimalarial treatment shows no effect (Girney, 1990).

The mode of action of the prolonged antimalarial treatment is still not fully understood. It may have (i) a direct influence on the lymphocytes, which may have a modulation effect on the immune system (Betticher et al., 1990; Papamitrou et al., 1986; Salmeron & Lipsky, 1983), or (ii) perhaps it inhibits the intraerythrocytic development of the parasites, lowering in this way the permanent antigenic stimulus to which the host’s immune system is exposed in endemic areas (Hoffman, Piessens & Ratwayanto, 1984; Crane, Hudson & Hudson, 1973; Marsh & Greenwood, 1986).

We think that HMS should be considered in the differential diagnosis of tropical splenomegaly.

With regard to the impossibility of carrying out diagnostic immunologic examinations in many tropical areas and the high mortality of untreated persons, we suggest applying antimalarial treatment and following up the patients. This could permit a diagnosis «ex juvantibus» in future.

ACKNOWLEDGEMENTS

Authors are very grateful to Dr. C. Amela and Dr. I. Pachón for statistical help and to M. R. Ortiz for excellent technical assistance.

REFERENCES


Betticher (D.C.), Nicole (A.), Pugin (P.) & Regamey (C.), 1990.—The hyperreactive malarious splenomegaly syndrome in a European: has the treatment a modulatory effect on the immune system? Journal of Infectious Diseases, 161: 157-159.

Bhattacharya (D.N.), Harries (J.R.) & Emerson (P.A.), 1983.—Tropical splenomegaly syndrome (TSS) in a European. Transactions of the Royal Society of Tropical Medicine and Hygiene, 77: 221-222.


Chagnon (A.), Talard (P.), De Jaurégui-Hubery (J.P.), Mavart (B.), Pierré (C.), Carli (P.) & Dussarot (G.), 1989.—Splenomegalie malarique hyperreactive chez un europeen revenant d’Afrique Centrale. La Presse Medicale, 18: 938.


Hamilton (P.J.S.), Gubb (D.A.M.), Hett (M.S.R.), Luthi (E.) & Wilks (N.E.), 1966.—Anemia in pregnancy associated with


