Caso Clínico / Clinical Case

LIVER DISEASE DUE TO *SCHISTOSOMA GUINEENSIS* - A REVIEW*

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Resumo

Baseados no caso de uma doente natural da ilha de São Tomé, com doença intestinal e hipertensão portal por doença hepática em resultado de infecção por *Schistosoma guineensis*, os autores fazem uma revisão concisa deste tipo de schistosomíase, incluindo o ciclo de vida do parasita, diagnóstico da infecção, anatomia patológica, imunopatogénese, quadro clínico, complicações da doença e terapêutica. A distribuição geográfica do *Schistosoma guineensis* está restringida de uma forma geral à África Central Ocidental, na região do Golfo da Guiné, e é a única espécie de *Schistosoma* presente na ilha de São Tomé. Habitualmente considerada uma doença relativamente ligeira da parte terminal do cólon, muitas vezes assintomática, outras vezes manifestada por disenteria schistosómica, os autores referem além do propósito, quatro casos de infecções em naturais da mesma ilha, que apresentaram problemas graves, dois com envolvimento do sistema nervoso central, um com doença hepática e envolvimento cardiopulmonar, e o caso de um adolescente com doença hepática e atraso de crescimento devido a níveis baixos de factores de crescimento insulínico 1 e 2 (IGF1 e IGF2) (antigamente chamadas somatomedinas). É importante ter conhecimento destas possibilidades evolutivas, de forma a que a terapêutica possa ser feita em tempo útil e assim se obter um bom resultado terapêutico.

Summary

Based on the case of a patient from the island of São Tomé who presented with intestinal and liver disease with portal hypertension due to infection with *Schistosoma guineensis*, the authors provide a concise review of this type of schistosomiasis, including the parasite life cycle, diagnosis, pathology, immunopathogenesis and the clinical picture of the infection, as well as posible complications and treatment. *Schistosoma guineensis* is geographically restricted to Central Western Africa and is the only *Schistosoma* species on the island of São Tomé. Usually considered to be a relatively minor disease of the lower bowel, the authors refer to four other cases on the same island that presented with serious problems, two with central system nervous disorders, one with a liver disorder and cardiopulmonary involvement, and one with liver disease and failure to thrive due to low levels of insulin growth factors IGF1 and IGF2 (formerly called somatomedins). It is important to be aware of the symptoms that may be found, so therapy can be given in time to obtain a good outcome.

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INTRODUCTION

Schistosomiasis is an important poverty-related health problem and the various types of *Schistosoma* infections are believed to affect more than 200 million people around the world, of whom more than half are symptomatic, 20 million exhibit severe disease manifestations with around 200000 related deaths (1). There are six major species of human *Schistosoma*, the adult worms which live in: (1) *S. japonicum* - in the capillaries of the superior and inferior mesenteric veins around the walls of the bowel (2) *S. mekongi* - with behaviour very similar to that of *S. japonicum* (3) *S. mansoni* - in the tributaries of the inferior mesenteric veins around the lower bowel wall (4) *S. haematobium* - in the veins of the vesical plexus around the bladder and along the ureters, and sometimes through ectopic migration in the minor capillaries of the inferior mesenteric vein around the rectum (5) *S. intercalatum* and (6) *S. guineensis* - in the inferior mesenteric veins, generally lower than *S. mansoni (*3).
The **diagnosis** of an unidentified form of schistosomiasis includes the clinical presentation, a complete physi-

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cal examination, a demonstration of the eggs of *Schistosoma* species in faeces/urine and/or in tissue biopsies, complemented by one or various serological tests. Some radiological signs are of importance in defining the clinical stage of the disease and also in evaluating the response to therapy (4,5).

Immunological methods can detect antibodies or antigens in serum. Antibody measurement has the drawback of not being able to discriminate between active, previous disease or re-infection in endemic areas, but it has an important role in individual diagnosis outside endemic areas (6). The circulating antigens are specific for the different life stages of *Schistosomas* (*cercariae*, adult worms, miracidia), but the most useful for diagnosis are the excretory-secretory antigens of adult worms, also known as gut-associated antigens. These are a group of molecules derived from the gut of the parasite and that are released in the circulation of the host by the regular regurgitation of digested blood by adult worms (7). Their presence in a patient indicates an active infection with viable worms. Two gut-associated antigens are regularly studied: 1) a circulating anodic antigen (CAA); 2) a circulating cathodic antigen (CCA). The specifity of antigen detection assays relies on the use of monoclonal antibodies with a high affinity to one or more epitopes of CAA or CCA and is almost 100%. CAA and CCA can be measured by a variety of immunological methods: indirect haemagglutination, ELISA or time-resolved immunofluorescent assay. At the present time, from a clinical perspective, the most advantageous application of antigen detection assays seems to be assessment of the eficacy of chemotherapy(8). Since CAA has an estimated serum half-life of two days, parasitological cure - or drug failure - can be detected within 10 days after therapy with praziquantel (9).

Two stable, endemic, geographically isolated strains of *S. intercalatum* were previously believed to exist, the Lower Guinea strain and the Congo strain, having a number of differences in morphological, biological and biochemical characteristics. However, the differences found in egg morphology, pre-patent periods in the intermediate and definitive hosts, intermediate host-parasite relationships, different type of intermediate host, breeding systems of intermediate host (10) , mating system of intermediate host (11), characteristics of certain isoenzyme patterns, the existence of hybrid breakdown between *S. intercalatum* (Cameroon) and *S. intercalatum* (Zaire) characterised by an impaired viability of larval offspring from the F2 generation onwards (12), and molecular and genetic differences, have enabled several authors to recently establish that the two strains are really two completely different species of *Schistosoma*, that is, *S. guineensis* corresponding to the old Guinea strain and *S. intercalatum* to the Congo strain (13,14,15). In this paper however and due to the great volume of bibliography referring to the old terminology of *S. intercalatum*, whenever we considered it relevant we will refer to *S. guineensis / S. intercalatum.*

Interspecific sexual interactions between human *Schistosomas* probably have a role in limiting the distribution of *S. guineensis / S. intercalatum*. The competitive sexual processes show that both *S. haematobium* and *S. mansoni* are always competitively dominant over *S.guineensis / S. intercalatum*. This led Jourdanne J (16) to consider that there were three kinds of transmission foci of these *Schistosomas*. The first located in forest areas of Central Africa (Democratic Republic of Congo, Cameroon and Gabon). In foci within rain forest, neither *Schistosomas mansoni* nor *haematobium* can complete their life cycles due to the absence of the appropriate intermediate hosts. The second include foci in São Tomé and Equatorial Guinea. The third is mixed foci where the occurrence of *S. mansoni* and *S. haematobium* do not allow the definitive establishment of *S. guineensis* / *S. intercalatum*. The presence of these species of *Schistosomas* in these foci is occasional if there was only one introduction of the parasite (Angola, Chad, Central African Republic, Nigeria, Uganda, Sudan), or may be characterised by successive invasions and extinctions in relation to a series of introductions by infected migrant populations (Dogon country, Mali).

The **Bulinus forskalii** group of fresh water snails are the intermediate hosts of the *S. guineensis* species on the island of São Tomé. The cercariae emerge from the snails mostly between 6 and the 19 hours with a peak between 12 and 14 hours. The cercariae penetrate the skin of people swimming in river/lake waters, somethimes causing pruritus. The metamorphosed larvae - *schistosomula* - migrate to the pulmonary and then to the hepatic circulation, where they mature to adult worms in 6 weeks and then migrate to their final venous multiplication sites. This invasive stage is often asymptomatic or the symptoms are less intense than those experienced with the three most common types of *Schistosomas*. The females lay their eggs in tissue and into the lumen of the intestine (17). Human pathology due to *Schistosomas* is mainly caused by processes of immunological reaction to eggs deposited in tissues, especially exemplified at first line in *S. guineensis* infection by schistosomal dysentery. When eggs are swept back to the liver with the portal blood flow they lodge in the narrower branches of the portal system, around which granulomas can develop and later become fibrous tissue. Ectopic migration of eggs could explain very rare cases of pathology in other organs.

At least in *S. mansoni* the **immunopathogenesis** of

schistosomiasis has been attributed to increased serum interleukin-13 concentration (18). CD4 (+)T cell responses and macrophage activation are essential components of *schistosoma* egg-induced granuloma formation. Previous studies implicated host derived cytokine tumour necrosis factor (TNF) as a potential mediator of macrophage recruitment and activation during *Schistosoma* infection. On the other hand Davies S(19) provided evidence that TNF plays an unexpected role in maintaining adult *Schistosoma* viability in portal system and in limiting hepatocellular damage in response to *Schistosoma* egg.

***S. guineensis* eggs** are lozenge-shaped, more slender and elongated than the eggs of *S. haematobium*, have a terminal spine with a slight bend (20) and measure 170-190 µm by 56-95 µm. The eggs of *S. guineensis* / *S. intercalatum* are generally found in faeces or in rectal biopsies / scrapings. In tissues, the shells of these eggs give a positive (red) reaction to Ziehl-Neelsen stain that helps to differentiate them from the terminal-spined eggs of *S. haematobium* (21).

S. guineensis infection is often asymptomatic, but it causes microscopic lesions in the intestine (mainly the rectum), the liver and genital organs of both men and women. Genital lesions generally have a more insidious evolution (22). On sigmoidoscopy the mucosa has a granular appearance and petechial patches with mucus and blood, oedema, hyperaemia and ulcerations, sometimes adenopapilomatous inflammatory pseudopolyps, can be detected. Fisher A (23) did a complete review of pathology, data obtained in biopsies of their patients with *S. intercalatum infection*. Biopsy of lower bowel mucosa showed ulcerations and cellular infiltrates with typical granulomas. In the submucosa there was evidence of fibrous tissue, hyalinisation and calcification of eggs with few cellular infiltrates. In liver biopsies he found small granulomas in portal triangle, but he did not record any marked vascular changes nor any obstructive lesions in the presinusoidal portal venules. Pigment in Kupffer cells and histiocytes was more extensive than in *S. mansoni* infections. These features are also found in *S. guineensis* infections.

The key pathogenic event in this disease is the occurrence of **granulomas** around the *Schistosoma* eggs trapped in host tissues. The main lesion of hepatosplenic schistosomiasis *mansoni* and *japonicum*, described in 1904 by Symmers W(24), is "pipestem" fibrosis in the portal tracts of the liver with pylephlebitis and peripylephlebitis caused by *Schistosoma* eggs. It is a portal fibrosis without bridging, nodule formation or significant hepatocellular destruction (25). Although even recently several eminent authors denied the existence of cases of portal hypertension due to liver *S. guineensis* disease (26,27,28), the authors of this review present some data from literature referring to some occasional reported cases of liver disease and portal hypertension due to *S. guineensis* infection.

The authors present a case of *S. guineensis* infection with involvement of lower bowel and schistosomic fibrous liver disease with portal hypertension, successfully treated with praziquantel.

CLINICAL REPORT

A 27 year-old creole woman from the Mezochi district (Figure 1) of the Island of São Tomé who has been living in Portugal for 7 years without returning to Africa, was admitted to our Unit in FEB 05 after a 6 months course of erroneously prescribed lamivudine therapy on an "Hepatitis Virus Unit" for suspected HBV hepatitis. She had, however received two doses of HBV vaccine in 1998 which were prescribed by her General Practice Clinician with unknown previous baseline serology. In SET 03 she experienced transitory and intermittent amenorrhoea and nausea, and from then on variable leucopenia, a high percentage of eosinophilis (relative eosinophilia), thrombocytopenia, low prothrombin time %, borderline transaminases, HBV serology favouring carrier HBV state and undetectable HBV DNA. In 2003

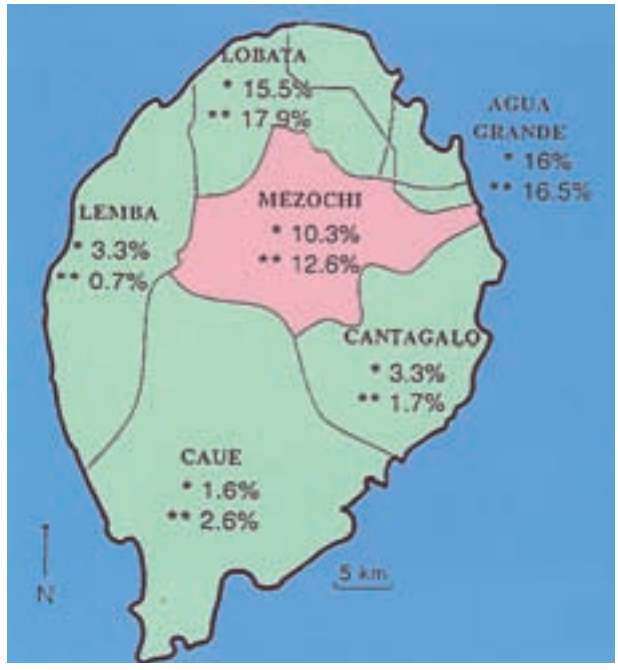

Figure 1 - Sketch map of the island of São Tomé showing the prevalence of Schistosomas in schoolchildren by districts * 1991 and ** 1992. In red, the Mezochi district where our patient was born (adapted from Ref. 46).

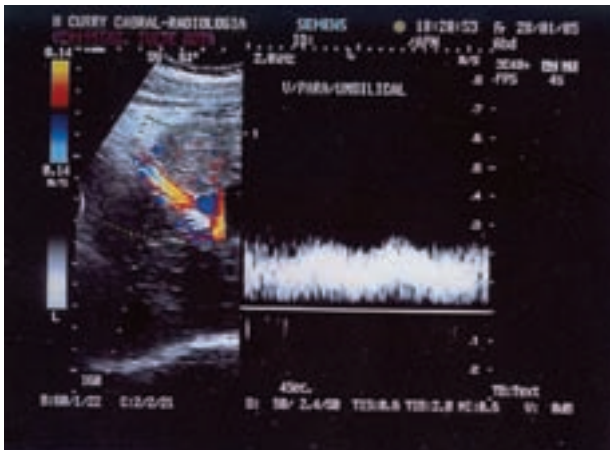

Figure 2 - Doppler ultrasonography of the liver showing permeation of the paraumbilical vein.

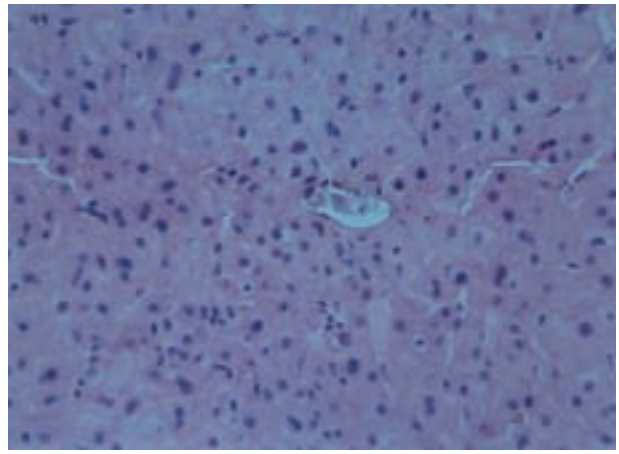

Figure 3 - HEX100: Liver biopsy - *S. guineensis* egg (with terminal spine).

endoscopy of the esophagus, stomach and duodenum revealed "gastritis".

On admission she was asymptomatic but had moderate hepatomegaly / splenomegaly. She reported that she had frequently swum in a small, quiet, clean river during childhood / adolescence and had developed frequent, undiagnosed abdominal colics and sometimes mucus in the stool. LAB tests revealed: no anaemia, leucocytes ranging from 2600 to 1600/mm^3, % eosinophils 7.3 to 11.5% (N 0.0-6.7%), thrombocytes 80000 to 63000/mm^3, % prothrombin time 58.2% (N 70.00-120.00), INR 1.50 (0.9-1.20), APTT 30.4' (N 26.0-36.0), bilirubin 0.5 mg/dl (N 0.20-1.3), alkaline phosphatase 66 UI/L (N 38-126), AST 44 to 74 UI/L (N 17-59), ALT 58 to 176 UI/L (N 21-72), negative HAV IgM antibody, HBV serology favouring a carrier state (positive HBsAg, negative HBsAb, negative IgM HBcAb, positive IgG HBcAb, negative HBeAg, positive HBeAb), undetectable serum HBV DNA for one year, negative serology for HCV, EBV, CMV, HIV and Herpes virus. Blood tests for autoimmune hepatitis (ANA, DNA, SMA, AMA, pANCA, LKM-1 and LKM-3, LE cell test) were negative, as well as those for hepatitis due to hereditary diseases (a1-anti-trypsin deficiency and Wilson's disease). Serial parasitological examinations of stools were negative, but she serology was positive for schistosomiasis: indirect hemagglutination = 1:320 (reaction indicative of evolutive infection: ≥ 1:160), confirmed by positive *Cercariae* Hullen Reaction and positive IgG = 0.638 on ELISA reaction (positive reaction ≥ 0.500). Abdominal ultrasound and hepatoportalsplenic Doppler ultrasound revealed splenomegaly and hepatomegaly primary due to hypertrophy of the left lobe and of the caudate lobe, diffuse heterogeneity of the liver with repermeability of the paraumbilical vein (Figure 2) and higher than normal calibre of a sinuous splenic vein with spontaneous anastomosis with the left renal vein. These data were suggested portal hypertension. Liver biopsy showed "pipestem type" portal septal fibrosis with scarce inflammatory infiltrate (Figure 3) and one partially degenerated of *Schistosoma guineensis* egg (Figure 4). No granulomas were detected in the biopsy sample of the liver. There was no evidence of the characteristic pathologic features indicative of HBV or HCV liver infection, namely no nodular or diffuse lymphocytary inflammatory infiltrates, no liver cell ballooning degenerative hepatocytolysis, no marginal necrosis, no portal liver fibrosis with irregular borders and no steatosis. Neither were there any histological features of any other type of liver disease. Rectal biopsy demonstrated numerous subepithelial / submucosal *S. guineensis* eggs, most of which were calcified (Figures 5,6). We treated the patient with a one-day dose of 40 mg/kg of praziquantel, with good therapeutic response. Improvement was seen in all laboratory values. Three months after therapy, the IgG on ELISA reaction was 0.328. Leucopenia and thrombocytopenia before lamivudine therapy were inter-

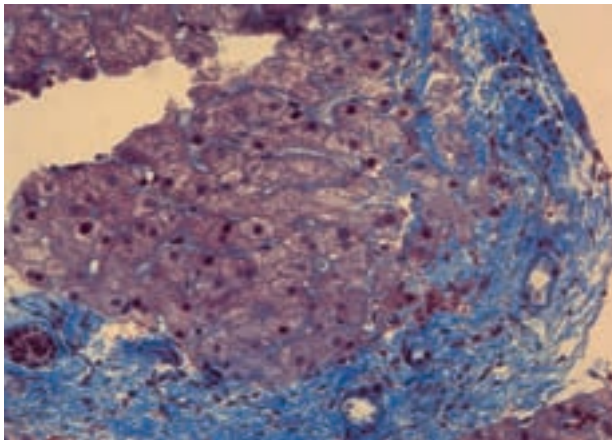

Figure 4 - CABX100: "Pipe-stem" fibrosis of the liver.

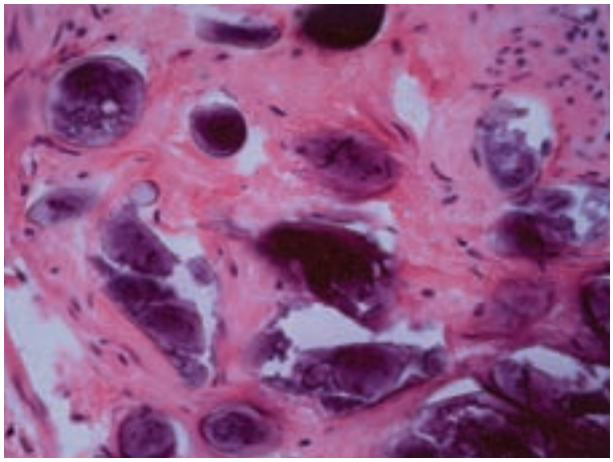

Figure 5 - HEX100: Rectal biopsy - Calcified *S. guineensis* eggs near a lymphoid folicule.

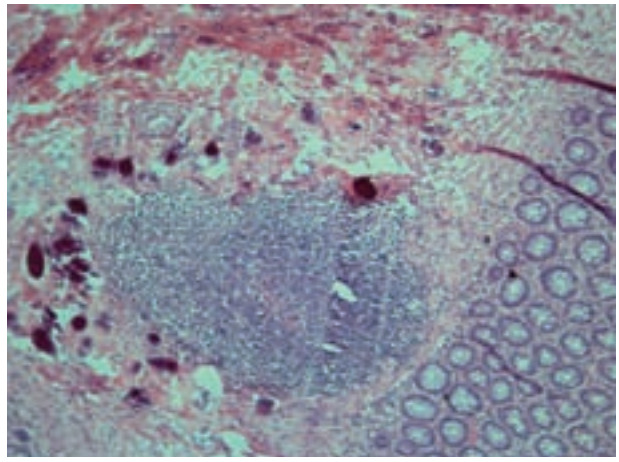

Figure 6 - Rectal biopsy - Calcified and degenerated *S. guineensis* eggs.

preted as meaning hypersplenism related to portal hypertension. Borderline abnormalities of liver function tests were attributed to liver toxicity due to lamivudine, but despite undetectable serum HBV loads and negative histological aspects characteristic of HBV hepatitis, we must continue to monitor later worsening of liver functioning in this patient with HBV carrier state.

DISCUSSION

***S. guineensis* infection is related to water conditions**. The foci of infection are often urban and of a size limited to a town district. *S. guineensis* is expanding at the present time because of the development of buit-up areas which are characterized by a disorganized town or village-planning. The disease is due to a high level of faecal pollution in the environment, causing contamination of the urban hydrographic network, which is the setting of schistosomiasis transmission. Although primarily linked to forest area, *S. guineensis* is spreading with deforestation (29). Recent studies have also shown that the epidemiology of this *Schistosoma* species is very dynamic, including invasions and extinctions (30).

Symptomatic active infection due to *S. guineensis* is usually seen in children and adolescents, and pathologic lesions are generally detected in those with egg excretion in excess of 400 eggs per gram of faeces (28). In tissues the eggs survives in the midst of an aggressive inflammatory attack. Indeed, the granulomatous response may be required by the parasite. Eggs do not appear to transverse the intestinal wall without granuloma formation. The *Schistosoma* parasites may depend on the host inflammatory response to help to move the eggs from the vascular space to the lumen of the intestine (31). It is interesting that in our patient no granulomas were found in biopsies samples of the liver and or the rectum, although one egg was found in the liver and many calcified *S. guineensis* eggs were present in the submucosa of the rectum. This was probably the reason why no eggs were found in parasitologic examination of the stools.

The **established infection** is frequently asymptomatic and when symptomatic shows predominantly with rectal manifestations: diarrhoea often times mucohaemorrhagic, rectal and abdominal pain, straining, tenesmus, prolapse of the rectum. Genital involvement is not rare, mainly taking the form of adnexal "masses"(32). A moderately enlarged and smooth and hard liver can frequently detected (33).

In certain areas it has been shown that *S. guineensis*/*S. intercalatum* and *S. haematobium* hybridise in nature and hybrid eggs are excreted in urine in these cases (34,35). The male worm determines the localization in the bladder venous plexus and the site of egg deposition, but the egg morphology is determined by the female worm(36). The existence of natural hybridisation can produce atypical clinical pictures (37). Rarely some patients may present with haematuria and dysuria and, in a recent report from Nigeria, *S. guineensis* eggs were found in the urine, but not in the faeces, in 60% of 1709 people surveyed (38). Ectopic localization of worms was thought to cause perianal discomfort and haemoespermia in some patients (39).

As in other types of schistosomiasis there is an **association with *Salmonella* or *Klebsiella* infections** (40). Individuals commonly present with recurrent *Salmonella* septicaemia or atypical typhoid fever with prolonged evolution. In the absence of treatment of *S. guineensis* infection it is commom to find early septicaemic recurrences of typhoid fever (41).

In the case of infection by *Schistosoma japonicum*

(42,43) or by *Schistosoma mansoni (*44,45,46), hepatosplenic involvement was found to be more frequent and serious in **carriers of hepatitis B surface antigen** than in patients with other forms of schistosomiasis. It is ge-nerally assumed that schistosomiasis does not lead to cirrhosis, but the interaction between HBV and these types of schistosomal infections can cause a more serious form of chronic hepatitis and hepatic decompensation (47). We have no knowledge of any review about the association of a HBV carrier state and infection by *Schistosoma guineensis*.

The former Portuguese Colony of São Tomé e Príncipe located in the Gulf of Guinea in Western Africa was discovered by Portuguese sailors in the 15th century as far back as1493. The island's *Bullinus Genus of* freshwater snails, the *Bulinus forskalii* group responsible for transmission to humans of the intermediate forms of the parasite, were first reported to be infected São Tomé by Gracio A (48) in 1988. Three districts in the northeast region of the island are most affected: Lobata, Água Grande and Mezochi. These areas are situated in a small plain at the foot of mountains from which rivers of clean water flow through several villages. Different water contact patterns were observed in these areas, including swimming and playing activities and washing of clothes and dishes (49). The studies on prevalence curves showed a peak between 10 and 15 years old. Parasitic loads by *S. guineensis* are generally weak. But serological results appear to indicate more frequent contact with the parasite than what could be inferred from the data from parasitological examination of the stool.

According to some authors and as in cases of *S. mansoni*, *S. japonicum* and *S. haematobium*, **ectopic migrations of *S. guineensis*** can be responsible for serious extraintestinal disease. Brito M . (50) published a case of liver disease with portal hypertension and compromised cardiovascular function and Gracio A. (51) reported two cases of neurological schistosomiasis, one with a solid mass in the cerebellum and another with a spinal cord syndrome. Murinello A. (52) describes the case of a 17-year old boy with intestinal *S. guineensis* disease and schistosomal liver disease causing failure to thrive, demonstration a bone age of 12 years, low height/weight percentile, low serum liver IGF1 and IGF2 and low growth hormone (GH) after insuline-induced hypoglycemic stimulus. One year after praziquantel therapy the patient was 12 cm taller and had gained 11.5 kg of weight. Liver ultrasonography showed regression of previous abnormalities. All these patients were born and lived in São Tomé. In animal experiments it has been demonstrated that liver damage by *S. guineensis* / *S. intercalatum* impairs testosterone synthesis through the intermediary of synthesised tumour necrosis factor (53).

In liver disease due to *S. guineensis* the eggs lodge in the portal venules of the liver and induce granulomas, which later on heal to form a fibrotic scar. After many granulomas develop and scar, fibrous ligation of portal blood flow ensues, producing portal hypertension. The portal vein and tributaries become fibrous and appear similar to pipe stems in cross sections of the liver, a unique pattern of scarring termed Symmers' pipe stem fibrosis. This picture corresponds to the so-called hepatosplenic schistosomiasis (31).

The life span of *Schistosoma* worms averages 3 to 5 years. There are documented cases however, of schistosomiasis with adult worms of *Schistosoma* species surviving for more than 30 years after an individual left an endemic area (54). In two other reports, patients with prolonged schistosomiasis due to *Schistosoma japonicum* were described as, harbouring living adult worms for at least 47 years (55) and 31 years (56) respectively. Apparently this prolonged life span results from the ability of the parasite to evade the immune machinery of the host. Our patient had left the endemic area of her own land seven years early, and although most of the eggs were already calcified, she clearly had active infection. *Schistosoma guineensis* is a recently described infection, and with so few reported complicated cases it is not yet possible to determine the possible life span of this parasite.

Praziquantel is currently the drug of choice for the treatment of all types of schistosomiasis, although oxamniquine is effective in *S. mansoni* and metrifonate in *S. haematobium*. Universal use of praziquantel due to its low price and few adverse effects is worrisome if we consider a potential number of 200 million people to be treated, and the possible occurrence of resistance (57), witch may already be occurring in special circumstances (58,59).

Because of the fear of resistance some authorities are recommending that in the a near future it might be good practice to give a **therapeutic combination** of praziquantel with another effective drug, such as oxamniquine, the acridanone-hydrozones (60,61) or cyclosporine analogues devoid of immunsuppressive effects and retaining anti-parasitic activity (62). Artemisin derivatives are active at almost exactly those points of the *Schistosoma* life cycle where praziquantel is inactive, but fears about the malaria parasite developing resistence to this drug act as a great obstacle to its concomitant use (63). In an experimental phase some good results were obtained by the association of HMG-CoA reductase inhibitors (statins) with an injectable contraceptive (medroxyprogesterone) (64). But up until now-most of these apparently resistant cases have been successfully treated with two courses of praziquantel therapy (65,66).

The best treatment would be to stop transmission through **individual hygiene measures, amelioration of the underlying socioeconomic deficiencies, and regular treatment of irrigation channels with anti-molluscs therapies** (64).

CONCLUSION

Schistosoma guineensis **infection is a possible and rare cause of fibrous liver disease and portal hypertension**, as well as other more rare complications of progression, such as **neurological disease and cardiovascular and pulmonary involvement**. Physicians must be aware of these possibilities in patients coming from geographically affected areas, so that they can treat them adequately and in time to prevent potentially dangerous complications.

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