CASE REPORT

Hepatosplenic schistosomiasis: playing hide-and-seek with an elusive parasite

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SUMMARY

A 27-year-old man of Eritrean origin presented with persistent left-sided abdominal pain. Initial investigation showed signs of liver fibrosis, portal hypertension and splenomegaly. A diagnosis of hepatosplenic schistosomiasis was suspected on grounds of elevated total IgE, grey area antischistosomiasis antibodies and the high endemic status of his native country. However, repeated microscopy of faecal and urine samples, as well as rectal biopsies, failed to demonstrate schistosomal eggs. Finally, the diagnosis of hepatosplenic schistosomiasis was established through demonstration of a *Schistosoma mansoni* egg in a liver biopsy taken in an attempt to clarify the cause of the above findings. The patient had recently been treated for uncomplicated malaria. Lowered schistosomiasis worm/egg burden and hence reduced sensitivity of classic microscopy-based schistosomiasis testing was attributed to the antischistosomal activity of the antimalarial chemotherapy.

BACKGROUND

In an even more globalised world, clinicians are being challenged by a wider pallet of differential diagnosis for common clinical presentation. This can be due to various reasons, among others, different geographical distribution of infectious micro-organisms.

Hepatosplenic schistosomiasis while relatively common in endemic parts of the world is a rare diagnosis in a non-endemic area such as Denmark.¹⁻³

This case underlines the importance of considering prevalence of infectious diseases as well as the influence of prior treatment of other infectious diseases when designing the diagnostic workup in patients of foreign origin. It also demonstrates the necessity of persistence in obtaining the suspected diagnosis even in the presence of ambiguous test results. Finally, it clearly emphasises the need for further research into sensitive and non-invasive tests for the diagnosis of low worm/egg burden schistosomiasis as well as further research into methods for the evaluation of treatment efficacy in such cases.

CASE PRESENTATION

A 27-year-old male refugee from Eritrea was referred to our outpatient clinic for evaluation of persistent left-sided abdominal pain. He left his local Eritrean environment approximately 1 year prior to arrival in Denmark. En route to Denmark he had been evaluated at an Italian hospital and

diagnosed with *Plasmodium falciparum* malaria for which he was treated with a 3 days course of dihydroartemisinin/piperaquine.

Just prior to the time of referral, investigations at another Danish hospital had revealed a markedly enlarged spleen (19×7 cm) and suspicion of liver cirrhosis on a CT scan. A gastroscopic examination had shown changes consistent with portal hypertensive gastropathy. No varices had been observed. Also, negative malaria (microscopy of thin/thick blood films), HIV 1+2 (antigen (Ag) and antibodies (Ab)), hepatitis C virus (Ab) and leishmaniasis (Ab) screen tests had been taken and were all negative. There was serological evidence of a past hepatitis B (HB) virus infection with positive anti-HBsAg but HbsAg negative. Chest X-ray was normal.

At the time of referral, the patient reported the above-mentioned left-sided abdominal pain and in addition symptoms of bloatedness and 'having lively bowels'. He denied any overuse of alcohol.

Physical examination was normal except for tenderness in the upper left quadrant of the abdomen and a palpable spleen. No cirrhotic stigmata were present.

INVESTIGATIONS

Blood tests showed pancytopenia with microcytic (mean cell volume 77 fL (reference interval 82–98 fL)) anaemia (haemoglobin 7.9 mmol/L (reference interval 8.3–10.5 mmol/L)), thrombocytes $42 \times 10^9/L$ (reference interval $145\text{--}350 \times 10^9/L$) and leucocytes $1.0 \times 10^9/L$ (reference interval $3.5\text{--}10.0 \times 10^9/L$) with neutropaenia, no eosinophilia. Furthermore iron deficiency (8 µmol/L (reference interval 9–34 µmol/L)), low ferritin (22 µg/L (reference interval 22–355 µg/L)), lack of vitamin B₁₂ (162 pmol/L (reference interval 200–600 pmol/L)) and an elevated INR (1.5 (reference interval <1.2)) and total IgE (254×10^3 IU/L (reference interval $<115 \times 10^3$ IU/L)) were found. Bilirubin, alanine aminotransferase, alkaline phosphatase, total IgA, IgM, IgG and sedimentation rate were within the normal range.

Transient elastography and an acoustic radiation force impulse imaging scan of the liver were performed. Both non-invasive procedures showed values indicative of moderate to severe fibrosis.

To investigate the possibility of autoimmune hepatitis antismooth muscle, antinuclear, antimitochondrial and antidouble stranded DNA Abs were taken. All were negative. Antitrypsin and coagulable plasmin were within the normal range.

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Figure 1 H&E stained liver specimen at 40× magnification illustrating the presence of a viable *Schistosoma mansoni* egg. The lateral spine used for species identification is clearly seen (arrow).

A bone marrow biopsy was normal. Haemoglobin electrophoresis was not indicative of thalassaemia. Anti-intrinsic factor and antiparietal cell antibodies could not be detected speaking against autoimmune gastritis as the cause for the low vitamin B₁₂.

Tests for malaria (Ag quick test, microscopy of thin/thick blood films), tuberculosis (Gold-in-tube interferon-gamma release assay) and strongyloides (antistrongyloides Ab) were negative. Cytomegalovirus and Epstein-Barr virus serology was consistent with past infection. Faecal microscopy (after concentration by formalin-ethyl acetat sedimentation method) of four separate faeces samples for worms, eggs and cysts was negative (all microscopy was handled by subspecialised parasitological medical laboratory technicians with many years of experience). PCR on stool samples was negative (for *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium hominis/parvum*). Schistosomiasis Abs (against gut associated Ag (GAA) and membrane bound Ag (MBA)) were in the grey area (on the exact cut-off between negative and grey area). The test was repeated with the same result.

On suspicion of schistosomiasis infection, microscopy of several samples of urine and two rectal snip biopsies was performed. All came out negative.

With the intention of clarifying the cause of the patients assumed liver fibrosis and splenomegaly, a diagnostic liver biopsy was performed. The needle biopsy specimen showed fibrosis. In addition, a vital schistosomiasis egg was identified (figure 1) establishing a diagnosis of hepatosplenic schistosomiasis.

A hepatic/splenic MRI was performed showing dilated splenic, superior mesenteric and portal veins as well as periportal and intrahepatic perivascular oedema all suggestive of portal venous hypertension (figure 2A,B). Also, multiple small splenic infarctions as well as smaller splenic haemorrhages were seen. The hepatic venous pressure gradient was measured by hepatic venous catheterisation technique to be mildly elevated (10 mm Hg) confirming the suspected portal hypertension. A repeated gastroscopic examination revealed three oesophageal varices (grade 1–2) without stigmata of bleeding thereby demonstrating the portosystemic anastomoses caused by the elevated portal venous pressure. To evaluate any possible reduction in metabolic capacity, a galactose elimination capacity test was performed. Results gave a value of 69.1% of the expected normal capacity.

DIFFERENTIAL DIAGNOSIS

Based on the anamnestic and objective findings, several working diagnosis were established among others chronic liver disease, haematological disease (leukaemia, vitamin B₁₂ deficiency, benign ethnic neutropaenia) and infectious disease particularly parasitic disease (among others giardia infection due to bloating and abdominal discomfort).

TREATMENT

Shortly after the diagnosis of *Schistosoma mansoni* infection, the patient received the first dose of praziquantel 40 mg/kg. Five weeks later, another dose was given. The treatment was well tolerated. Biochemically, the patient responded to treatment by a substantial increase in total IgE (262×10³ IU/L pretreatment to 729×10³ IU/L 35 days after the first dose praziquantel) probably due to increased antigen presentation following worm killing.^{4,5}

Parenteral iron (1000 mg before praziquantel treatment and again 6 months post-treatment), and vitamin B₁₂ (1 mg before praziquantel treatment) was administered to resolve the above-mentioned deficiency states in an attempt to treat the anaemia. Parenteral vitamin K₁ (10 mg before praziquantel treatment) was given with the intention to improve the elevated INR. However, this remained fairly unchanged.

OUTCOME AND FOLLOW-UP

Six weeks after the last praziquantel dose, the patient reported no improvement in left-sided abdominal pain and also complained about general abdominal discomfort feeling meteoristic most of the time. Thrombocytes (48×10⁹/L) and leucocytes (1.7×10⁹/L) remained low while the anaemia had resolved (9.1 x mmol/L). Total IgE decreased from 729×10³ IU/L to 535×10³ IU/L but remained elevated. Faecal microscopy revealed no schistosoma eggs. The previous grey area antischistosomiasis antibody test was repeated yielding a positive result for anti-MBA antibodies but negative against GAA antigen.

The patient was followed with blood test for the following months. Total IgE plateaued around 250×10³ IU/L (reference interval <115×10³ IU/L). The anaemia, which had initially resolved on combined praziquantel, iron and vitamin B₁₂ treatment recurred (haemoglobin 8.0 mmol/L (reference interval 8.3–10.5 mmol/L)) 4 months after ended treatment. Being of

Figure 2 A: MRI scan coronal T1 Dixon without intravenous contrast showing splenomegaly with haemosiderosis and peripheral infarctions(a). Atrophy of the right lobe of the liver(b) with enlargement of the venous drainage to the portal vein(c). B: MRI scan transverse T2 Haste with respiratory gating showing hypertrophied caudate lobe(a), inhomogeneous liver parenchyma with perivascular oedema(b), patent falciform vein(c) and splenomegaly(d) (and also an enlarged gallbladder fossa was found although not shown), indicating presinusoidal portal hypertension and early signs off cirrhosis.

Figure 3 Small bowel capsule endoscopy picture showing mm-sized lesions in the small intestine suspected to be caused by deposition of *Schistosoma mansoni* eggs (circle).

microcytic (mean cell volume 77 fL (reference interval 82–98 fL)), hypochromic (mean corpuscular haemoglobin 1.65 fmol (reference range 1.70–2.10 fmol)) nature, gastrointestinal bleeding was suspected. In an attempt to obtain definite proof of schistosomiasis treatment failure (and to assess differential diagnoses of gastrointestinal bleeding), a colonoscopy and small bowel capsule endoscopy (SBCE) was performed. SBCE found no source of bleeding but demonstrated numerous superficial mm-sized lesions throughout the entire small intestine (figure 3). Colonoscopy showed superficial vessels consistent with angioectasias. Also, a benign looking polyp was found in the descending colon and biopsied for pathological examination. As suspected the microscopic examination showed *Schistosoma mansoni* eggs with surrounding inflammatory cells indicative of persistent infection. No premalignant/malignant changes were found concluding the polyp was of inflammatory nature due to the observed schistosomiasis eggs.

The above-described praziquantel regimen was repeated. This led to resolution of the microcytic anaemia as well as subjective resolution of the left-sided abdominal pain. Total IgE continued falling (128×10^3 IU/L at the present time). Neutrophils remained low and was attributed to a combination of benign ethnic neutropaenia and hypersplenism. The latter was also deemed as the cause of the thrombocytopenia.

DISCUSSION

The microscopic demonstration of viable *Schistosoma mansoni* eggs in faeces samples and/or rectal biopsies remains the gold standard for diagnosing intestinal and hepatosplenic schistosomiasis.⁶ Concentration of faecal samples prior to microscopy by formalin-based sedimentation methods (as done in our case) has been described as increasing the diagnostic yield.⁷ Microscopy of rectal snips however is the most sensitive diagnostic method as demonstrated in other cases with negative stool microscopy and positive rectal biopsy microscopy.^{8,9} Diagnosis of schistosomiasis through liver biopsy is rare and has primarily been described as accidental findings in biopsies taken in the context of viral hepatitis.^{10,11} Previous studies have demonstrated a correlation between disease severity (measured by i.a. organomegaly) and quantitative faecal egg output.¹² Detection of antischistosomiasis antibodies in patients from endemic areas lacks sensitivity even when combining anti-GAA and anti-MBA antibodies and also does not allow differentiation between active or past disease or allow for species identification.¹³

Despite performing both repeated faecal microscopy as well as microscopy of rectal snips (by experienced personnel) no eggs were found during the initial diagnostic workup. This was highly

surprising to us considering the above-mentioned association between disease severity and faecal egg counts. Naturally, given the rarity of schistosomiasis infections in Denmark inexperience with this particular analysis (even among experienced laboratory technicians) could theoretically have played a confounding role.

It is well known that the sensitivity of microscopic egg detection in lightly infected individuals is lower.^{14,15} In our case, several factors may have contributed to low worm/egg burden and hence lowered sensitivity of classic microscopy based testing. The lifespan of adult schistosomes averages 3–5 years (but can be substantially longer) and so as the worms die off egg production may decrease.¹⁶ In our case, the patient had recent potential cercariae exposure through his local endemic environment but obviously decreasing egg production due to transmission many years ago could not be excluded.

More important in our case however, is probably the recent administration of antimalarial chemotherapy (dihydroartemisinin/piperaquine). In recent years, both piperaquine and dihydroartemisinin have been shown to possess antischistosomal activity (although this property has been known for other artemisinin derivatives since the 1980s).^{17,18} In our patient, a viable schistosomal egg was demonstrated. We therefore believe that the prior administration of antimalarial therapy functioned to lower the worm/egg burden to a degree where diagnosis became challenging while not providing a complete parasitological cure. Given the coendemic geographical distribution of malaria and schistosomiasis as well as changes in immigration patterns within recent years, we wish to call attention to this potential issue among fellow clinicians.¹⁹ The fact that dihydroartemisinin/piperaquine is recommended by the WHO as first-line treatment for uncomplicated malaria only highlights the importance of increased awareness about this possible situation.²⁰

Thus, our case demonstrates the necessity of persistence in obtaining the diagnosis of hepatosplenic schistosomiasis when suspected (in this case on grounds of geographical origin, signs of portal hypertension, raised total IgE and antischistosomiasis antibodies in grey area). This is especially important in cases with prior antimalarial therapy with drugs which also harbour antischistosomal activity (dihydroartemisinin/piperaquine but also mefloquine and atovaquone/proguanil).^{21,22} In addition, the case supports the need for routine implementation of direct and sensitive diagnostic methods (eg, PCR testing of blood/stool samples) to avoid invasive procedures through biopsies in cases of repeated negative stool examination.²³

With regards to the treatment failure (and hence need for repeated treatment) evidence points towards a substantial therapeutic gain with increased praziquantel doses. Systematic reviews indicate a significantly improved schistosomal cure rate when using a praziquantel dose of 60 mg/kg instead of 40 mg/kg as in our case.²⁴

This case also highlights the potential difficulties in monitoring treatment efficacy in the absence of demonstrable eggs in stool or rectum biopsies. Measurement of antischistosomiasis antibodies is of limited use since most assays have positive results for at least 2 years or longer.^{25,26} Eosinophilia has limited sensitivity as an indicator of chronic schistosomiasis and when normal (as in the current case) cannot be used as an indicator of treatment success.²⁷ Previous studies have shown a normalisation or at least a decrease in total IgE following successful treatment of *Schistosoma mansoni* and therefore in our case was used as a proxy of treatment efficacy.^{26,28} Detection of schistosomal DNA using PCR analysis exist at an experimental basis but so far has the disadvantage of remaining positive at least 1 year following successful treatment.²³ Therefore, for the time being monitoring

of treatment success in *Schistosoma mansoni* infection in cases such as ours remains clinically challenging.

Learning points

- Prior antimalarial treatment with dihydroartemisinin/piperazine may lower schistosomiasis worm/egg burden decreasing sensitivity of classic microscopy-based tests.
- In cases of suspected hepatosplenic schistosomiasis, liver biopsies may prove necessary when repeated faecal and rectal snip microscopy are negative.
- Further research into direct and sensitive diagnostic methods is needed for diagnosing active *Schistosoma mansoni* infection in cases of negative faecal and rectal snip microscopy.
- Evaluation of treatment efficacy in cases of *Schistosoma mansoni* infection with negative stool/rectal biopsy microscopy remains clinically challenging and involves the use of non-specific factors such as alleviation of symptoms, decline in total IgE, decrease/normalization of eosinophilia or biopsies from intestinal pathological elements obtained through colonoscopy.

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