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CASE REPORT

SCHISTOSOMIASIS HAEMATOBIA: HISTOPATHOLOGICAL COURSE DETERMINED BY CYSTOSCOPY IN A PATIENT IN WHOM PRAZIQUANTEL TREATMENT FAILED

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SUMMARY

Schistosomiasis haematobia or urinary schistosomiasis is one of the main public health problems in Africa and the Middle East. A single dose of 40 mg praziquantel per kg body weight continues to be the treatment of choice for this infection. The aims of this follow-up were to study the post-treatment course of a patient infected with *S. haematobium* and not submitted to re-exposure, and to identify complications of the disease and/or therapeutic failure after praziquantel treatment by histopathological analysis. Treatments were repeated under medical supervision to ensure the correct use of the drug. In view of the suspicion of lesions in cystoscopy, the patient was submitted to bladder biopsy. The histopathological characteristics observed in biopsies obtained, after each treatment, indicated viability of parasite eggs and activity of granulomas.

KEYWORDS: Schistosomiasis haematobia; Viable eggs; Histopathological; Praziquantel; Brazil

INTRODUCTION

Schistosomiasis haematobia or urinary schistosomiasis is one of the main public health problems in Africa and the Middle East. A single dose of 40 mg praziquantel per kg body weight continues to be the treatment of choice for this infection. However, cases of treatment failure with a single dose of praziquantel have been reported in the literature and divergences exist regarding the speed and magnitude of this event[2,4]. There are also reports indicating that early treatment with praziquantel is less effective in the prevention of acute schistosomiasis than treatment during later phases, with early treatment failing to prevent the progression to chronic schistosomiasis in all cases studied[3].

Although praziquantel is the first-line drug for the treatment of infection with *Schistosoma haematobium*, efficacy monitoring is recommended because of the possible development of resistance, especially in the case of mass treatment. One study has even reported therapeutic failure with two or three doses of 40 mg/kg praziquantel, despite the high rate of cure (93%) and a 96.6% reduction in the number of eggs in 354 schoolchildren aged 5-15 years. It was reported that 20 schoolchildren remained egg-positive after the second treatment and 80% (16/20) became egg-negative after the third treatment[5].

In the absence of therapeutic failure, treatment with praziquantel results in the complete reduction of the cellular reaction and fibrosis in tissues containing a known number of dead residual eggs[1].

The follow-up of treated patients is important for the identification of cases of therapeutic failure. These cases can be well documented among patients who do not return to endemic areas, and therefore are not submitted to re-exposure.

MATERIALS AND METHODS

A patient had been infected with the parasite in 1994 during a UN peace mission, when he bathed in the Licungo River, Mozambique, Africa. The patient noted hematuria in 1997, about three years after exposure, when he had already returned to Brazil. In 2000, after notification to the Army Biology Institute, the patient paid more attention to these sporadic episodes of urinary bleeding. After clinical investigation of the patient who reported episodes of macroscopic hematuria, who was negative for bacteria in urine (abnormal elements and sedimentoscopy and urine culture) and who presented no urinary lithiasis, a 24-h urine sample was obtained and submitted to parasitological analysis.

For parasitological examination, a 24-h urine sample was collected, followed by spontaneous sedimentation for 24 h. Ten milliliter of the sediment was then removed and centrifuged at 5000 rpm and a 10-µL aliquot was observed under a light microscope at 100X and 400X magnification. We observed eggs in urine with this method (Fig. 1). We did a hatching test to check the viability of eggs and we got miracidium. It was impossible to infect the snails to complete the cycle, we didn´t have *Bulinus* gender in Brazil and it was not recommended to bring them from endemic areas.

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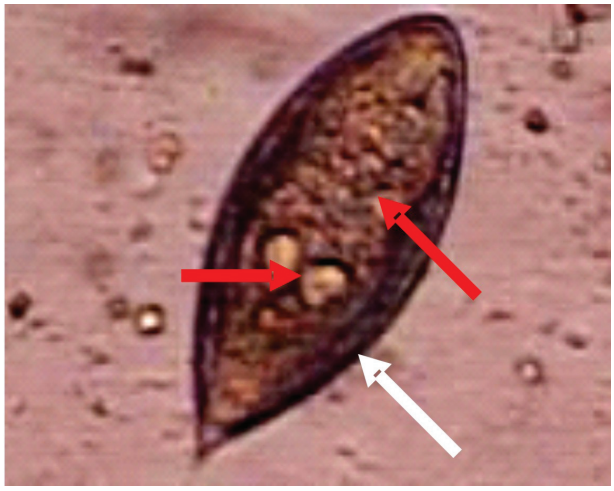

Fig. 1 - *Schistosoma haematobium* egg in urine examination (400x magnification). Viable egg (white arrow) with miracidium maintaining the internal structures (red arrows).

After the positive diagnosis, with eggs of *Schistosoma haematobium* in urine parasitological examination, the patient received a single oral dose of 40 mg praziquantel/kg body weight in 2000, July. Three 24-h urine samples collected at intervals of seven days were analyzed by the same technique as described above within a minimum period of 21 days after treatment. Treatment was repeated under medical supervision to ensure the correct use of the drug in 2000, October. In view of the suspicion of lesions, the patient was submitted to cystoscopy, followed by biopsy of observed granulomas and histopathological analysis at six month intervals under the same conditions as used during the initial diagnosis. The first histopathological exam was performed two months (2000, October) after the first treatment (2000, July). Because of a suspicion of bladder involvement, a bladder biopsy was performed and two fragments were removed, immersed in 10% formalin (one part of 40% formalin and nine parts of water) and sent to the Laboratory of Anatomopathology for the preparation of slides for diagnostic purposes. The slides were stained using the following techniques for evaluation of treatment: hematoxylin-eosin (Laboratory of Anatomopathology, Army Central Hospital, Rio de Janeiro, and Department of Pathology, Fiocruz, Rio de Janeiro), Sirius red, pH 10.2, Alcian blue, pH 1.0 and 2.5, Picrosirius, Masson's Trichrome, Gomori's Reticulin, periodic-acid Schiff, Ziehl-Neelsen, and Lennert's Giemsa (Department of Pathology, Fiocruz, Rio de Janeiro).

RESULTS

The first histopathological exam performed two months (2000, October) after the first treatment (2000, July) revealed edema and chronic inflammation of the chorion, presence of chronic granulomatous inflammatory process with macrophages and mastocytes, giant cells in vesical mucosa, eosinophils, epitheliod cells, multinucleated cell granulomas surrounding large amount of viable eggs (Fig. 2). The patient received a booster treatment (2000, October) immediately after the result of this exam, i.e., two months after the first treatment, under medical supervision. Although there was no suspicion of inadequate use of the medication, all subsequent treatments were performed under medical supervision to ensure the quality of the data. They were done due positive results in biopsy of bladder, with granulomas and viable eggs.

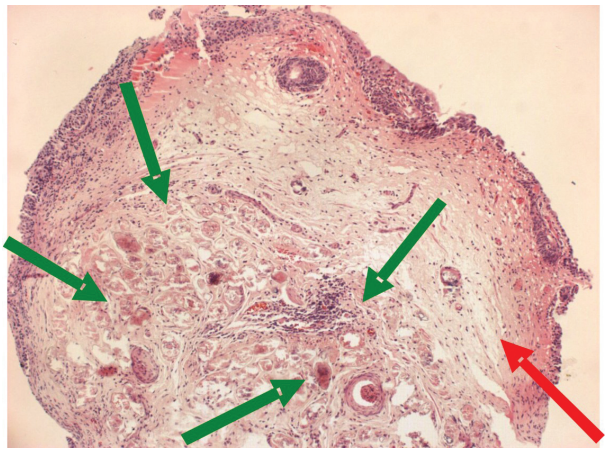

Fig. 2 - Examination after the first treatment (hematoxylin-eosin 40x magnification). Edema and chronic inflammation of the chorion (red arrow), presence of chronic granulomatous inflammatory process with macrophages and mastocytes, giant cells in vesical mucosa, eosinophils, epitheliod cells, multinucleated cell granulomas surrounding large amount of viable eggs (green arrows).

The second histopathological exam (2002, July) performed 23 months after the first treatment and 21 months after the second treatment (Fig. 3 and 4) demonstrated exudative, exudative-produtive and involutional phases in granulomas and viable eggs with internal structures (nervous system cells, germinative cells). The third treatment was administered about 23 months (2002, July) after the first treatment.

The third histopathological exam (2004, November) performed 51 months after the first treatment, 49 months after the second treatment and 21 months after the third treatment (Fig. 5 and 6) revealed granulomas, viable eggs with internal structures (nervous system cells, germinative cells, cells with pycnotic nuclei around the nervous system) and Langhans cells.

In view of the repeatedly positive exams and the repetition of

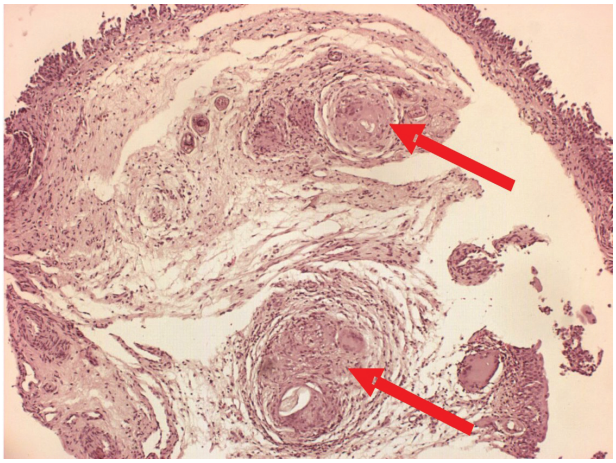

Fig. 3 - Bladder histopathological examination after the second treatment (hematoxylin-eosin 40x magnification). Exudative, exudative-productive and involutional phases in granulomas (red arrows).

conventional treatments without an adequate response, three courses of treatment with the same dose but at intervals of 15 days were administered (two treatments in 2004, April and one treatment in 2004, May). These treatments were performed about 52 months after the first treatment. In addition, another booster treatment at the same dose was applied about 60 months (2005, June) after the first treatment.

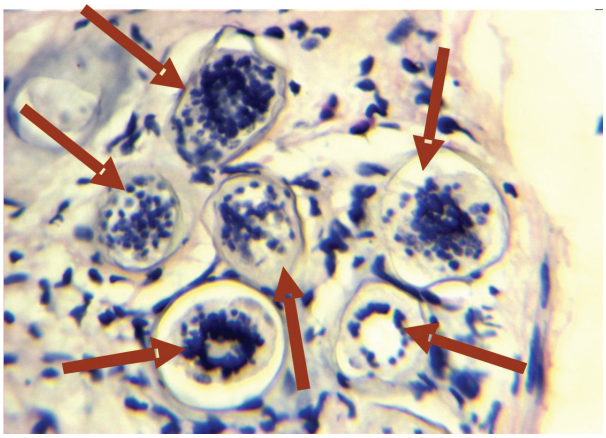

Fig. 4 - Examination after the second treatment (Sirius red ph 10 310x magnification). Viable eggs with internal structures (nervous system cells, germinative cells) - brown arrows.

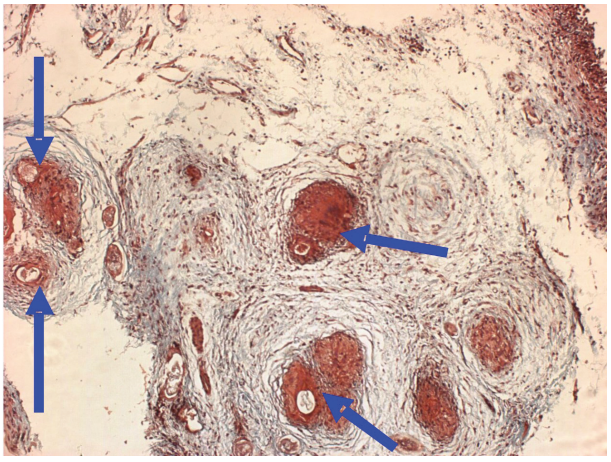

Fig. 5 - Examination after the third treatment (Masson's trichrome 40x magnification). Granulomas, viable eggs with internal structures (nervous system cells, germinative cells, cells with pycnotic nuclei around the nervous system) - blue arrows.

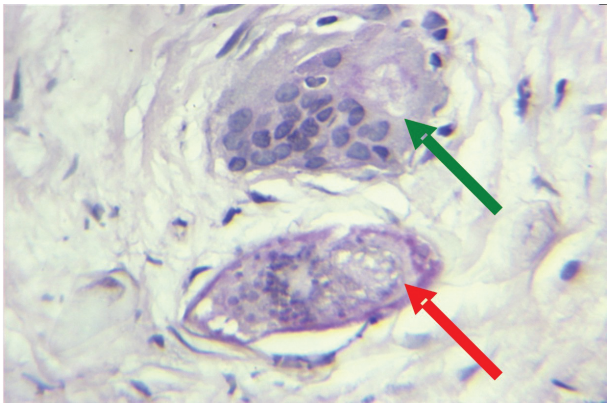

Fig. 6 - Examination after the third treatment (PAS 310x magnification). Granuloma, viable egg with internal structures (nervous system cells, germinative cells, cells with pycnotic nuclei around the nervous system - red arrow) and Langhans cells (green arrow).

The fourth histopathological exam (Fig. 7, 8 and 9) performed 62 months (2005, October) after the first treatment and after seven treatments administered over the 62 months of follow-up still demonstrated exudative-productive granuloma macrophagic-type with macrophages encircling eggs with viable miracidium maintaining the internal structures (Fig. 7), mast cells with proteoglycans and viable eggs with miracidium (Fig. 8) and exudative-productive granulomas in transitional stage to productive, concentric arrangement of reticular fibers (Fig. 9), viable eggs with miracidium maintaining the internal structures (Fig. 10).

Before each cystoscopy, three 24-h urine samples collected at intervals of seven days were analyzed by the same technique as described

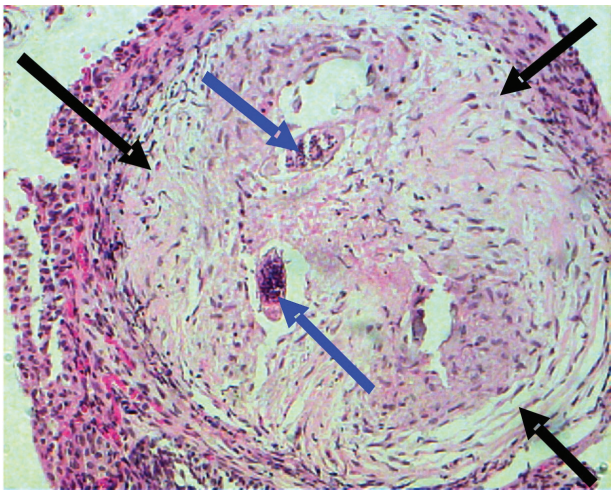

Fig. 7 - Examination after fourth treatment (Hematoxylin- Eosin - 200x Magnification). Exudative-productive granuloma macrophagic-type with macrophages encircling eggs (black arrows) with viable miracidium maintaining the internal structures (blue arrows).

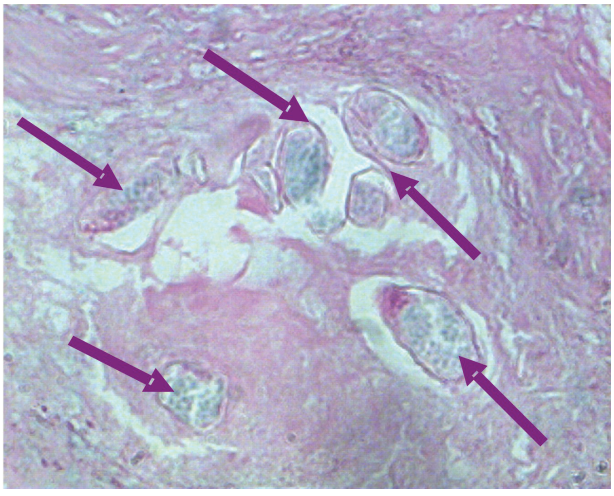

Fig. 8 - Examination after fourth treatment. (Alcian blue ph 2.5 - 310x magnification). Mast cells with proteoglycans and viable eggs with miracidium (pink arrows).

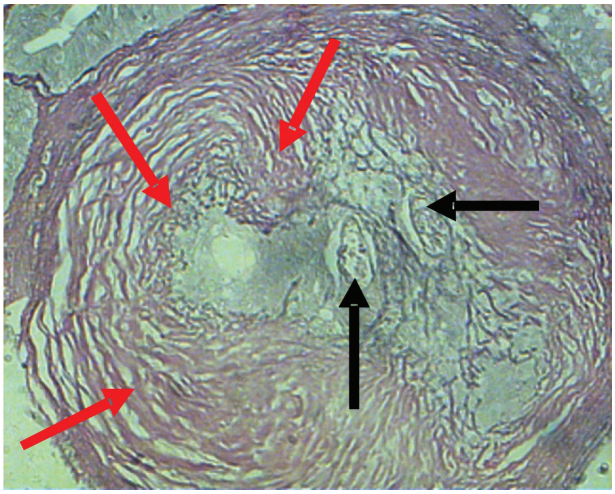

Fig. 9 - Examination after fourth treatment (Gomori's reticulin - 200x magnification). Exudative-productive granulomas in transitional stage to productive, concentric arrangement of reticular fibers (red arrows) and eggs (black arrows).

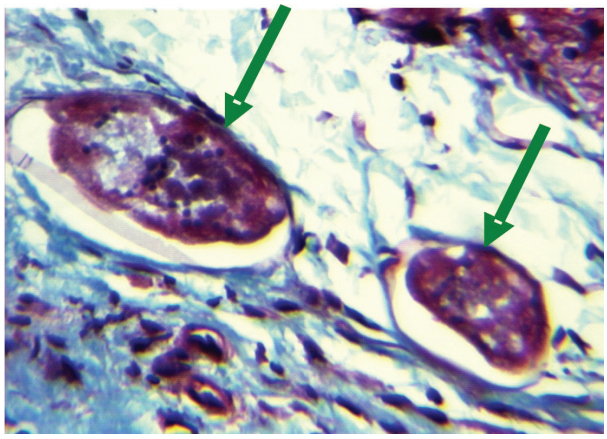

Fig. 10 - Examination after the fourth treatment (Picrosirius 400x magnification). Viable eggs with miracidium maintaining the internal structures (green arrows).

above. All of them were negative to the eggs of the parasite.

After seven treatments, we lost the contact with the patient, then it was not possible to complete the evaluation and to know the final outcome.

DISCUSSION

The histopathological characteristics observed in biopsies obtained, after each treatment, indicated viability of parasite eggs and activity of granulomas. Since this case has been well monitored, it may contribute to the elucidation of an ongoing discussion regarding the resistance to, or therapeutic failure of, praziquantel in schistosomiasis haematobia. In this respect, each report irrespective of the number of cases described but based on the evidence found should contribute to the investigation and development of new drugs for the treatment of this infection. In this study, like N'GORAN *et al.,* there were no complete signs of resistance to praziquantel[5], then we considered therapeutic failure instead of resistance, because the parasite was not studied *in vitro* in resistance test. We presented in SILVA (2005)[6], some cases with active granulomas and viable eggs after two controls, but in this presented case, these characteristics remained after seven treatments and four controls. The patient described in this study is one of the 26 cases reported in SILVA (2005)[6]. The exposition was ten years before and, the first treatment was six years after the exposition. A review of the literature shows that there is no feasible therapeutic alternative for the increasing number of cases described.

RESUMO

Esquistossomíase hematóbica: seguimento histopatológico determinado por cistoscopia em um paciente com falha terapêutica ao praziquantel

A Esquistossomíase Hematóbica ou Esquistossomíase Urinária é um dos principais problemas de Saúde Pública na África e no Oriente Médio. Uma única dose de praziquantel 40 mg/kg de peso, continua sendo o tratamento de escolha para esta infecção. Os objetivos deste seguimento foram: avaliar o período pós-tratamento de um paciente infectado com *Schistosoma haematobium* e não submetido à re-exposição e, identificar as complicações da doença e/ou falha terapêutica, após o tratamento com praziquantel, por análise histopatológica de material obtido por biópsia vesical. O tratamento foi repetido sob supervisão médica para assegurar o uso correto do medicamento. Na presença de lesões suspeitas a cistoscopia, o paciente foi submetido a biópsia vesical. As características histopatológicas observadas nos materiais obtidos por biópsia, após cada tratamento, indicaram viabilidade de ovos e atividade dos granulomas.

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