



A Rare Disease But Not Too Much in Times of Globalization

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Abstract

Urogenital schistosomiasis is a parasitic disease, endemic in sub-Saharan Africa and in the Middle East. We report two cases of African young men, immigrant in our country, came to our attention for hematuria. *Schistosoma haematobium* eggs were found in their urine sediment and the histological examination of the tissue obtained from transurethral resection for both patients confirmed the bladder schistosomiasis. We discussed clinical and pathological features, and the complications that may develop as a result of this parasitism, mainly the bladder neoplasia.

Keywords: Urogenital schistosomiasis; *Schistosoma haematobium*; Bladder; Bladder neoplasia; Squamous cell carcinoma

Introduction

Urogenital schistosomiasis (UGS) is a parasitic flatworm infection, caused by *Schistosoma haematobium*, which is the most prevalent form of schistosomiasis that affects humans. More than 110,000,000 people globally, most in sub-Saharan Africa and in the Middle East are affected by this trematode [1-3].

The larvae of *S. haematobium* has as his main host the humans, the prolonged contact with the infested fresh water favors the human infestation. The life cycle of *S. haematobium* begins with the excretion of the fertilized eggs from the body of the human (definitive host) through urine and faeces into ponds, river and lakes, in these environment the eggs open up and the resulting miracidia penetrate into a specific snail *Bulinus* (intermediate host). Inside the snail, the miracidia transform itself in cercariae, which are released from snail into the fresh water. When the human is exposed to the infested water, the larvae enter in the unbroken skin, and circulate in the body through the blood vessel and complete their sexual maturation. At this stage, the worms migrate and live for several years into the venous plexuses around the pelvic organs and, then the adult worms mate and the female worms deposit their eggs in the small vessels in the genitourinary system. The eggs penetrate in the wall of urogenital organ causing acute and chronic lesions [4-6].

The urinary bladder, the lower ends of the ureters, and the seminal vesicles are the most commonly affected organs [4,7].

Although the mortality correlated with schistosomiasis has generally considered low, the infestation by this parasite can result in considerable morbidity and life-threatening complications, and the chronic infection of the *S. haematobium* may be responsible for the onset of bladder cancer [8].

UGS in countries, where this parasitic is not endemic, can be imported through infected migrants or refugees, or tourists and development aid workers returning home from endemic zones [4,5,9,10].

Here in after, we report two cases of bladder schistosomiasis that are came to our attention within a few months, with emphasis on the clinical and pathological features, and the complications that may develop as a result of this parasitism, mainly the bladder neoplasia.

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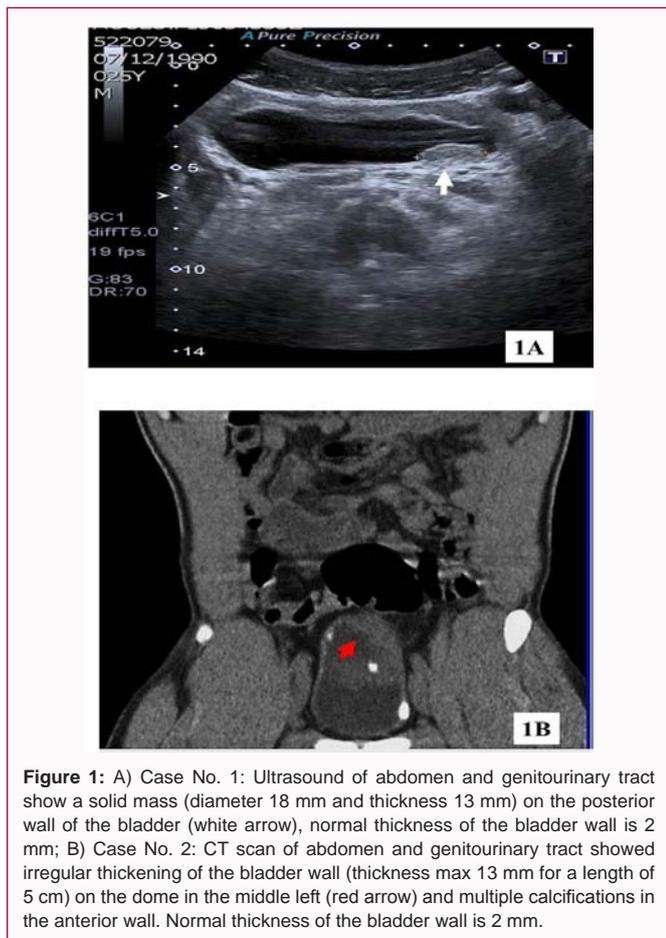


Figure 1: A) Case No. 1: Ultrasound of abdomen and genitourinary tract show a solid mass (diameter 18 mm and thickness 13 mm) on the posterior wall of the bladder (white arrow), normal thickness of the bladder wall is 2 mm; B) Case No. 2: CT scan of abdomen and genitourinary tract showed irregular thickening of the bladder wall (thickness max 13 mm for a length of 5 cm) on the dome in the middle left (red arrow) and multiple calcifications in the anterior wall. Normal thickness of the bladder wall is 2 mm.

Cases Presentation

Case 1

A 27-year-old male from Ghana, residing in Italy for two years presented with hematuria and dysuria; these symptoms are started about five months earlier. His medical history was unremarkable and the physical examination did not show significant findings.

The result of hematological exam was normal except for a blood peripheral eosinophilia with an eosinophil count of 9.4%, the renal function was normal.

The ultrasound of abdomen and genitourinary tract detected a solid mass 18 mm in diameter, bulging and vascularized, on the posterior wall of the bladder (Figure 1A).

The urine sediment showed a sheet of leucocytes and a moderate number of erythrocytes and the parasitological urine examination revealed the presence of *S. haematobium* eggs (Figure 2A).

Then the patient began the therapy with Praziquantel (40 mg/kg) two administration in a day (three plus two pills each one 600 mg for a total of 3 grams overall).

One month after the treatment, the genitourinary tract ultrasound and the CT scan showed the persistence of the lesion on the left posterior-lateral wall of the bladder with a smaller diameter than the previous observation.

Therefore the patient underwent to cystoscopy that confirmed the presence of the lesion, and was performed transurethral resection of the bladder lesion.

The microscopic examination of the biopsy specimen of the lesion has showed in the mucosae *Schistosoma* eggs associated with an intense chronic inflammation mainly consisting of eosinophils. The urothelium was devoid of atypia.

Therefore, the patient starts again the medical treatment with Praziquantel. Three months later the therapy, the examination of the urine sediment was negative for *Schistosoma* eggs and bladder ultrasound showed that the bladder lesions were no longer present.

Case 2

A 20-year-old man from Sudan, residing in Italy for eight months has reported hematuria for about six months. His medical history was unremarkable and the physical examination did not show significant findings.

The hematological exam was normal except for eosinophilia (16.5%) and the renal function was normal. The parasitological urine examination revealed the presence of rare *S. haematobium* eggs.

The CT scan of abdomen and genitourinary tract showed irregular thickening of the bladder wall, 13 mm in diameter, on the dome in the middle left and multiple calcifications in the anterior wall (Figure 1B).

The cystoscopic exam revealed small protruding lesions in the anterior wall and in the bladder dome, thus the patient was undergone to transurethral resection of the bladder lesions. The histologic examination of the resected tissue showed bladder mucosae with aspect of cystitis glandularis and focal feature of squamous metaplasia of urothelium, numerous *S. haematobium* eggs, many of which calcified, surrounded by a non-caseating granulomatous reaction with foreign-body giant cells, and an intense inflammatory infiltrate, rich in eosinophilic granulocytes with abscess formation (Figure 2B, 2C and 2D).

The therapy with Praziquantel was prescribed to the patient, but the patient was lost in the follow-up.

Discussion

S. haematobium is one of the ten species of trematode cause of

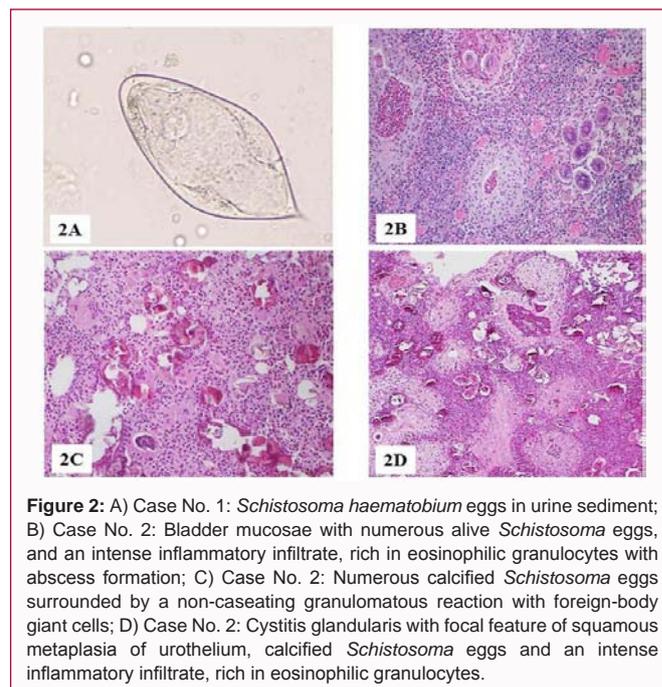


Figure 2: A) Case No. 1: *Schistosoma haematobium* eggs in urine sediment; B) Case No. 2: Bladder mucosae with numerous alive *Schistosoma* eggs, and an intense inflammatory infiltrate, rich in eosinophilic granulocytes with abscess formation; C) Case No. 2: Numerous calcified *Schistosoma* eggs surrounded by a non-caseating granulomatous reaction with foreign-body giant cells; D) Case No. 2: Cystitis glandularis with focal feature of squamous metaplasia of urothelium, calcified *Schistosoma* eggs and an intense inflammatory infiltrate, rich in eosinophilic granulocytes.

infection in the humans [11]. In the endemic areas, sub-Saharan Africa and in the Middle East, the affect patients are young with a mean of 46.7 years and a male: female ratio of 5:6 [8,12]. Patients with similar characteristics are present in both cases: two young men emigrated from poor areas of sub-Saharan Africa.

The urinary bladder is the most affected organ of the urogenital tract. The bladder schistosomiasis is relatively harmless and the most common clinical manifestation is the hematuria, which represents the epiphenomenon of the infestation, while the other clinical features are caused by the host's immune response to different stage of the parasite life [13,14]. Consequently, the pathological manifestations may be due to cellular or humoral immune response to the infection.

In the bladder, the early phase (acute phase) of infestation is characterized by coalescent granulomas around deposited eggs that form nodules or mass in the bladder wall, resulting in ulceration of the mucosae, such lesion predominantly is a T cell-mediated reaction, where the TH1 pro-inflammatory immune reaction is associated with an increased TH2 response.

In this phase the *S. haematobium* eggs can be found in the urine as in the patients of the two cases described, in fact the diagnosis of schistosomiasis is based on the presence of viable eggs in the urine sediment and is confirmed by finding the eggs surrounded by granuloma to the histological examination [4].

The chronic phase occurred after several weeks, and it involves predominantly TH2 response and the humoral mediators both of the host and the parasite. In this phase the inflammatory cells gradually disappear and are replaced by fibroblast, this is associated with collagen deposition, destruction and calcification of the eggs, and degeneration of the muscle fibers with dense interstitial fibrosis [13-15].

The natural history of bladder schistosomiasis depends on three main factors: the severity of the infestation, frequency of re-infestation and the adequacy of the therapy.

Therefore, young patients with occasional infestation and treated during the active phase of the disease have a favorable healing, that includes also a mild amount of mural fibrosis and dystrophic calcifications [7].

In both reported cases, the disease was in active phase at the time of diagnosis, but for the second case, the CT scan showed calcified areas as healing result from previous infestation.

The patient of the second case was lost on follow-up without a safe eradication of the infestation, this exposes him to the risks associated with the re-infestation and prolongation of the infestation.

Frequent re-infestation, the quantity of the eggs released, the inadequate treatment and the onset of secondary infection (bacterial or viral) are the major responsible factors of the development of bladder complications. These include: bladder contraction, impairment of ureterovesical sphincter mechanisms, bladder neck obstruction and bladder carcinoma [7,15].

The association between UGS and bladder cancer, particularly Squamous Cell Carcinoma (SCC), is widely accepted in selected populations from epidemiological point of view [16,17], although cellular and molecular mechanisms underlying the association between *S. haematobium* and SCC of the bladder are not yet defined [18-25], the WHO's International Agency for Research on

Cancer (IARC) considers the *S. haematobium* infection as suspected carcinogen for the humans with the strongest evidence [26].

The cellular and molecular mechanisms underlying the association between *S. haematobium* and SCC of the bladder are not yet defined. Recent studies have documented, in animal and in vitro models, the oncogenic potential of the *S. haematobium* total antigen. Indeed *S. haematobium* antigens affect the cell-cycle with the loss of p27 (tumor suppressor) and the reduction of the expression of Bcl2 (anti-apoptotic molecule), moreover it was found increased migration and invasion of the cells, and development of urothelial dysplasia as a direct effect of *S. haematobium* antigens [18-20].

In a study, Bernardo et al. [21] have characterized the profile of urine protein in patients with *S. haematobium* infection and SCC, using LC/MS. They found 42 exclusive proteins involved in metabolic, cellular and immune system processes in these cases. It suggested that TH2 type immune response induced by *S. haematobium* is in turn modulated by tumorigenesis.

Other studies have considered estradiol-like metabolites, detected in both the parasite and in the human urine during urogenital schistosomiasis, responsible for the carcinogenesis through the formation of DNA adducts and the mutations in the tumor suppressor p53 during UGS [22-24].

In addition *S. haematobium* infection and bacterial and viral urinary tract co-infection can play a role in carcinogenesis [17,25].

Conclusions

The diagnosis depends on physician awareness of the infection and on accurate history of the patient, especially in a country where schistosomiasis is not endemic.

As in the first case the reversibility of the bladder lesions can be obtained after adequate therapy and it depends on the duration of infection and the degree of the damage present at time of diagnosis.

The inadequate treatment and the onset of secondary infection (bacterial or viral) are the major responsible factors of the development of bladder complications, such as fibrotic lesions and bladder neoplasia.

Ethical Approval

The procedure for this research project complies with the World Medical Association Declaration of Helsinki [27]. All procedures were performed according to relevant national regulations and institutional guidelines. Patients gave their informed consent.

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