CASE REPORT

Clinical presentations of schistosoma hematobium: three case reports and review

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Urinary schistosomiasis is a prevalent parasitic infection in certain areas of Africa and the Middle East. It could present with common as well as unusual urological symptoms, which poses a considerable diagnostic challenge in countries where there is relative low incidence of the disease. We describe three unusual cases of urinary schistosomiasis identified in patients presenting to a London hospital. One patient was found to have schistosomiasis in the seminal vesicles following surgery for prostatic adenocarcinoma. Another was found to have schistosoma-related granulomatous inflammation within a urachal cyst. Thirdly a patient was found to have simultaneous occurrence of transitional cell carcinoma and schistosomiasis of the bladder. We review the literature on the presentations of the parasite and its association with malignancy. In conclusion, awareness of the disease prevalence, clinical and histopathological features will help to avoid missing the diagnosis.

Key Words: urinary schistosoma, histopathological

Introduction

Schistosomes are a family of obligate intravascular parasites that undergo asexual reproduction in snails and sexual reproduction in man. Schistosomiasis, also known as bilharziasis, is the second most prevalent parasitic disease worldwide after malaria. It affects more than 100 million people worldwide.[1] This figure is likely to be an underestimate as schistosomiasis is not classified as a notifiable disease in most countries.

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The North Middlesex University Hospital (NMUH) in North London serves a culturally diverse population with a high proportion of immigrants from the Middle East and Africa. The urology unit at NMUH has diagnosed *schistosoma hematobium* infection in a cohort of patients, including several atypical case presentations which are described below.

Case report 1

A62-year-old male from Nigeria presented to the urology unit at NMUH with obstructive lower urinary tract symptoms (LUTS) and an elevated PSA of 9.2 ng/mL. There was no history of hematuria or abnormal storage symptoms. Comorbidities consisted of stage 2 chronic kidney disease (with estimated GFR of 45 mL/min/

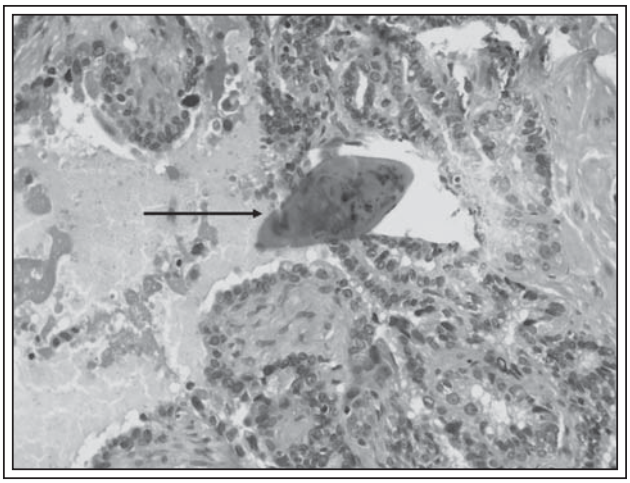

Figure 1. Photomicrograph of seminal vesicles from the radical prostatectomy specimen showing the presence of calcified schistosoma ova (arrow) (H&E, x200 magnification).

1.73 sqm) and peripheral vascular disease. Ultrasound of the kidneys and bladder demonstrated normal kidneys, complete bladder emptying and an enlarged prostate measuring 142 cc (PSA density of 0.06 ng/mL/cc).

Seventeen prostate biopsies were taken under transrectal ultrasound (TRUS) guidance. Histopathological evaluation reported 3 out of 17 cores with small foci of atypical acini. Cytokeratin antibody (34bE12) staining showed an absence of basal cell layer. The overall appearance was consistent with a Gleason pattern 3 + 3 prostatic adenocarcinoma with no evidence of perineural or lymphovascular invasion.

Staging investigations confirmed organ confined disease and the patient underwent radical prostatectomy. Histology of the prostate specimen showed adenocarcinoma of Gleason grade 3 + 3. The tumor was present in approximately 5% of the gland and involved both lobes, with no capsular invasion (stage pT2c N0 Mx). The apical and basal margins were free of tumor. No perineural invasion or lymphovascular invasion were identified. The left and right seminal vesicles were free of tumor, as were both vasa. Numerous calcified *S. hematobium* ova were present in both seminal vesicles, Figure 1. A few were also noted within the prostate. Subsequently, random bladder biopsies were taken which demonstrated schistosoma with deposition of partly calcified ova associated with moderate inflammatory reaction. There was no evidence of urothelial dysplasia or malignancy of the bladder. The patient was treated with oral praziquantel.

Case report 2

A 35-year-old gentleman of African origin presented to the urology unit at NMUH with a 2 month history of peri-umbilical pain and umbilical discharge. The patient denied any LUTS. There was no history of visible hematuria. On physical examination, the peri-umbilical skin was excoriated and a watery discharge was evident. Urine dipstick was positive for blood. Midstream urine (MSU) microscopy revealed both red cells (8×10^6/L) and white cells (6×10^6/L); urine culture was negative. Ultrasound showed normal kidneys.

Flexible cystoscopy identified a creamy orange induration at the dome of the bladder. Biopsies of the lesion showed bladder mucosa with severe inflammatory changes, edema and previous hemorrhage. There was no evidence of malignancy or dysplasia.

Abdominal and pelvic imaging with computed tomography (CT) revealed a localized wall thickening with a pouch at the anterior superior aspect of the bladder, suggestive of a urachal cyst, Figure 2. Percutaneous CT guided biopsies of the anterior wall of the bladder were performed. Histopathology of the biopsy specimens demonstrated a few loose aggregates of foamy macrophages mixed with plasma cells and occasional lymphocytes. An initial suspicion of malakoplakia was excluded as the foamy macrophages were positive for CD68 and PAS, negative for Perl and Von Kossa staining, and no Michaelis-Gutmann bodies were seen. The features were generally in keeping with xanthogranulomatous cystitis and there was no evidence of malignancy.

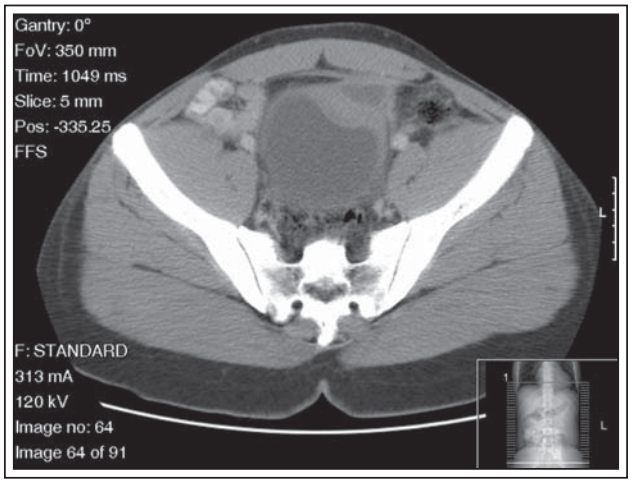

Figure 2. CT transverse image showing wall thickening with a pouch at the anterior superior aspect of the urinary bladder (arrow), suggestive of a urachal cyst.

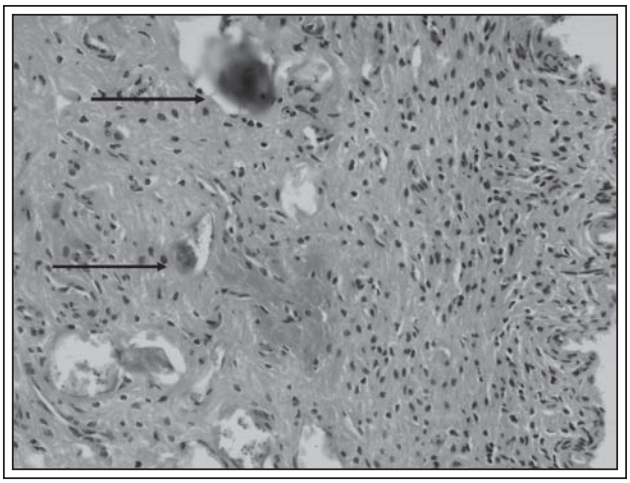

Figure 3. Photomicrograph of specimen obtained from excision of urachal cyst and adherent bladder wall mass. Calcified schistosoma haematobium eggs with terminal spines can be seen in the lamina propria of the bladder wall (arrows) (H&E, x200 magnification).

The patient underwent a laparotomy. The umbilicus was excised in continuity with the urachal cyst. As the urachal cyst was densely adherent to the dome of the bladder, a large cuff of bladder wall (84 g) was also removed. Histological examination of the resected bladder wall showed numerous calcified *S. hematobium* eggs concentrated in the lamina propria, Figure 3. The adjacent mucosa displayed hyperplasia due to the presence of granuloma, fibrosis and calcification. The urothelium was eroded but otherwise unremarkable. The central part of the mass which corresponded to the cystic space was filled with an amorphous proteinaceous material, foamy macrophages and several cholesterol clefts. The patient made an uneventful post-operative recovery and was treated with oral praziquantel.

Case report 3

A 60-year-old male from southern Ghana presented to the urology unit at NMUH with dysuria and terminal hematuria. He also described significant urgency and nocturia. Physical examination was unremarkable. Urine cytology showed neutrophils, red blood cells, bacteria but no malignant cells were seen. MSU culture was negative. Ultrasound demonstrated normal kidneys, no bladder wall mass and a prostatic volume of 48 cc. Flexible cystoscopy identified a solitary tumor measuring approximately 5 cm in diameter at the dome of the bladder which was resected under general anesthesia. A total of 9.3 g of tissue were obtained. Histological examination of the resection specimens demonstrated infection by *S. hematobium* with massive deposition of partly calcified ova associated with chronic inflammatory response and widespread infiltration by a poorly differentiated carcinoma. Foci of lymphovascular invasion were also seen. Immunohistochemically, the tumor cells were positive for cytokeratin 7 (CK7) but negative for CK20. The overall features were consistent with transitional cell carcinoma (TCC) of the bladder, grade 2-3 pT2a.

The patient subsequently underwent radiological staging with CT, showing increased bladder wall thickness anteriorly measuring 24 mm. No distant metastases were identified. Following careful counseling, the patient wished to pursue treatment with bladder conservation surgery and underwent a partial cystectomy. At surgery, localized residual tumor was identified at the dome which was resected with a minimum of 5 mm margin. Macroscopically, the resected lesion contained an ulcerated core with a rough dark tan surface protruding from the mucosa which measured 26 mm in diameter. Histopathological examination showed poorly differentiated carcinoma with extension into adjacent muscle and fat and reached the serosal surface. The tumor reached the resection margin with no intact adjacent mucosa seen. Large numbers of schistosoma were present, many of which were calcified, Figure 4. A single lymph node was identified which showed no evidence of metastatic tumor. The pathological findings were consistent with grade 3, stage pT3b N0 Mx TCC bladder. Random bladder biopsies taken intraoperatively showed

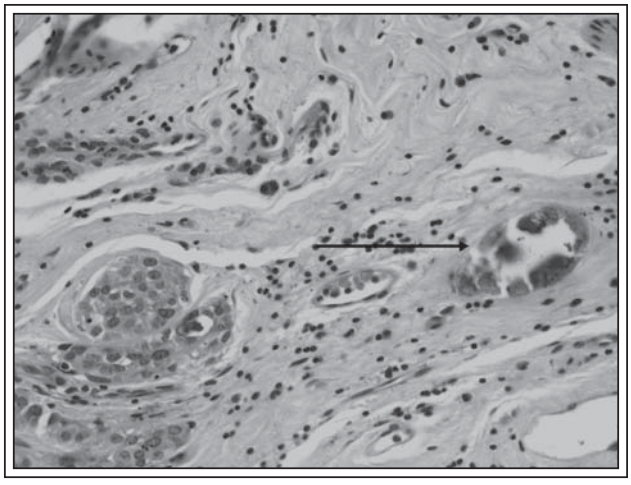

Figure 4. High power photomicrograph of cystoscopically resected bladder tumor showing pleomorphic epithelial cells with foci of lumina formation and the presence of schistosoma ova (indicated with arrows) (H&E, x 200).

moderately inflamed benign bladder mucosa with many, often calcified, schistosoma. The patient received treatment with oral praziquantel and is currently undergoing chemoradiation for his bladder tumor.

Discussion

Schistosomal infection involves contact with fresh water that is infested with snails harboring the parasite. Free-swimming schistosomal cercariae enter through the host skin into the blood stream, becoming schistosomulae in the process. The presence of parasitic components in the skin may trigger an acute localized itchy rash, but is often asymptomatic.[4] There have been reports in which cutaneous schistosomiasis has been the sole or predominant feature of the disease.[5,6] Following acute infection, the schistosomulae develop into adult worms, which form sexual couples. The pairs migrate against the flow of blood to the pelvic venous plexuses, especially around the base of the bladder. This targeted migration is aided by cell surface adhesion molecules that bind to the vascular endothelium.[7,8] Aberrant *S. hematobium* migration has been reported to the appendix, the spleen and the spinal cord, resulting in unusual disease presentations. The worm pairs mate and begin egg production after around 32 days.[9] The eggs migrate into the adjacent bladder mucosa and trigger a chronic inflammatory response with granuloma formation, eventually breeching the bladder wall to enter the urine.[10] Once in fresh water, the schistosome eggs develop into miracidia which infect fresh water snails. The infected snails release sporocysts that mature into cercariae, thus completing the parasitic life cycle.

S. hematobium, which selectively affects the urogenital tract, is endemic along the River Nile, in some Middle Eastern countries (Yemen, Saudi Arabia, Iraq and Iran) and in many parts of Africa.[1,11] In contrast, *S. mansoni* is mainly found in Africa, Middle East and South America. *S. japonicum* and *S. mekongi* are found in South-East Asia. The latter three species generally migrate to the hepatic-portal vasculature and cause intestinal symptoms, and are outside the scope of this discussion.

While the bladder is the most common site of manifestation of *S. hematobium* infection, the parasite could potentially affect any pelvic organ by virtue of the communications of the venous plexuses around the bladder, pelvic ureters, rectum and genital organs.[12] Genital lesions are generally features of prolonged *S. hematobium* infection, including epididymitis leading to reduced fertility.[13] In female patients, inflammatory lesions affecting the genitalia are well-recognized presentations of schistosomiasis, which could occur in the absence of parasitic egg excretion in the urine.[14-17] Parasitic ova have been found in the cervix, vagina, vulva and fallopian tubes.

The presence of schistosoma in the seminal vesicles as described in Case 1 is relatively uncommon but has been documented previously.[19-21] In contrast, schistosomiasis of the urachus as described in Case 2 has not been reported before. The urachus usually becomes obliterated at birth, forming the median umbilical ligament. This rare presentation may have resulted from the coexistence of bladder wall schistosomiasis and a patent urachus, which allowed infiltration by parasite ova along the urachal tract or by virtue of hematogenous spread in keeping with the venous anatomy described above.

Case 1 describes the coexistence of prostatic adenocarcinoma with schistosomiasis. The high incidence of both of these conditions in the population makes the presence of the two diseases more likely to be coincidental rather than causal. Six cases of schistosomiasis with adenocarcinoma of the prostate have been documented in the literature, some of which involved *Schistosoma mansoni* rather than *hematobium*.[22-24] There is no description in the literature of an etiological association between schistosomiasis infection and the subsequent development of prostate cancer.

Chronic and intense schistosome infection of the bladder over many years is associated with the development of squamous cell carcinoma (SCC) of the bladder.[25-28] SCC is the second most common epithelial tumor of the bladder after TCC, accounting for 45-7% of bladder malignancies in western countries. The major risk factors for the development of SCC in the West are bladder calculi and prolonged indwelling urethral catheterization.[29,30] In contrast, however, the incidence of SCC is much higher in areas where schistosomiasis is endemic to the extent that it is the most common carcinoma of the bladder in some parts of East Africa and Middle East.[31,32]

The coexistence of schistosomiasis and bladder TCC in Case 3 raises the question whether these two pathologies of the bladder might have a direct etiological association. Schistosome ova were identified in large numbers in the solid tumor and heavily dispersed in the bladder mucosa adjacent to the tumor as well as the random biopsies distant form the primary tumor. The TCC was confined to the anterior bladder wall only at the dome. This lack of precise co-localization could suggest that the existence of two diseases simultaneously may have been coincidental. However, solitary or multifocal TCCs can develop in the bladder despite whole bladder

exposure to a range of carcinogens, and urothelial "field changes" can predispose to both synchronous and metachronous bladder tumors. Several cases of TCC associated with schistosoma have been documented, notably one case involving a 5 year old child.[33-35] In the latter case, the authors proposed that the unusually early age of onset of TCC might support a causal link with the parasite.

It has long been understood that the bladder urothelium has the potential to undergo metaplastic differentiation either towards squamous metaplasia and leukoplakia, or towards mucinous and glandular epithelium.[36] Chronic irritation and infection would be the commonest causes of metaplastic change, accounting for the high incidence of bladder squamous cell cancer and to a lesser extent of adenocarcinoma in areas where schistosomiasis is endemic.[37] A number of genetic mutations have been identified which appear to be specific for schistosoma-related SCC, however, no specific mutations have been identified which are unique to schistosoma-related TCC and thus it is likely that additional carcinogenic factors may be required to induce TCC in patients with schistosomiasis infection.[34,35,38,39]

Conclusion

Three unusual presentations of *S. hematobium* infection at the urology clinic of NMUH in London from 2008 are presented here. These demonstrate that the parasite can affect almost any pelvic organ via the extensive communications of the pelvic venous plexuses and may be capable of direct extension into adjacent structures such as the urachus. While chronic schistosomiasis is well recognized to be associated with bladder SCC, it may have a general mutagenic effect and could occur concurrently with bladder TCC and prostatic adenocarcinoma. The prevalence of *S. hematobium* amongst immigrants from endemic regions should make physicians vigilant about the applications of screening tests to rule out schistosomiasis as the underlying cause for common as well as unusual urological symptoms. Diagnosis is based upon the detection of parasitic ova. In accordance with European Association of Urology (EAU) guidelines, initial investigation involves urine collection (with morning specimens on consecutive days) for urinalysis, microscopy and cytology.[40] Secondary evaluation is based on cystoscopy with biopsy of characteristic schistosomal lesions which vary according to the stage of disease from erythematous changes to granulomatous "sandy" patches. The mainstays of medical treatment for *S. hematobium* are with praziquantel or metrifonate. □

References

1. Savioli L, Renganathan E, Montresor A, Davis A, Behbehani K. Control of schistosomiasis - a global picture. *Parasitol Today* 1997; 13(11):444-448.
2. Touge H, Watanabe T, Fujinaga T, Ogawa T. Urinary schistosomiasis: report of a case. *Hinyokika Kiyo* 1997;43(12): 879-882.
3. Tsuboi T, Matsumoto K, Irie A et al. A case report: Bilharzial schistosomiasis in the urinary bladder presented with gross hematuria. *Hinyokika Kiyo* 2006;52(4):281-283.
4. Whitty CJ, Mabey DC, Armstrong M, Wright SG, Chiodini PL. Presentation and outcome of 1107 cases of schistosomiasis from Africa diagnosed in a non-endemic country. *Trans R Soc Trop Med Hyg* 2000;94(5):531-534.
5. Romero JA, Alvarez-Vijande R, Gutierrez R et al. Urinary schistosomiasis with cutaneous lesions. *Urol Int* 1991;46(1):85-86.
6. Davis-Reed L, Theis JH. Cutaneous schistosomiasis: report of a case and review of the literature. *J Am Acad Dermatol* 2000;42(4): 678-680.
7. Ngaiza JR, Doenhoff MJ, Jaffe EA. Schistosoma mansoni egg attachment to cultured human umbilical vein endothelial cells: an in vitro model of an early step of parasite egg excretion. *J Infect Dis* 1993;168(6):1576-1580.
8. Lejoly-Boisseau H, Appriou M, Seigneur M, Pruvost A, Tribouley-Duret J, Tribouley J. Schistosoma mansoni: in vitro adhesion of parasite eggs to the vascular endothelium. Subsequent inhibition by a monoclonal antibody directed to a carbohydrate epitope. *Exp Parasitol* 1999;91(1):20-29.
9. Bloch EH. In vivo microscopy of schistosomiasis - Migration of Schistosoma mansoni in the lungs, liver, and intestine. *Am J Trop Med Hyg* 1980;29(1):62-70.
10. Bloch EH. Inflammation in schistosomiasis. *Bibl Anat* 1979; (17):105-114.
11. Ross AG, Bartley PB, Sleigh AC, Schistosomiasis. *N Engl J Med* 2002;346:1212–1220.
12. Mohammed AZ, Edino ST, Samaila AA. Surgical pathology of schistosomiasis. *J Natl Med Assoc* 2007;99(5):570-574.
13. Bichler KH, Feil G, Zumbrägel A, Eipper E, Dyballa S. Schistosomiasis: a critical review. *Curr Opin Urol* 2001;11(1): 97-101.
14. Wright ED, Chiphangwi J, Hutt MS. Schistosomiasis of the female genital tract. A histopathological study of 176 cases from Malawi. *Trans R Soc Trop Med Hyg* 1982;76(6):822-829.
15. Ekoukou D, Luzolo-Lukanu A, Mulard C, Bazin C, Ng Wing Tin L. Peritoneal and tubal Schistosoma haematobium bilharziasis. *J Gynecol Obstet Biol Reprod* 1995;24(8):819-824.
16. Helling-Giese G, Sjaastad A, Poggensee G et al. Female genital schistosomiasis (FGS): relationship between gynecological and histopathological findings. *Acta Trop* 1996;62(4):257-267.
17. Poggensee G, Feldmeier H, Krantz I. Schistosomiasis of the female genital tract: public health aspects. *Parasitol Today* 1999; 15(9):378-381.
18. Kjetland EF, Kurewa EN, Ndhlovu PD et al. Female genital schistosomiasis - a differential diagnosis to sexually transmitted disease: genital itch and vaginal discharge as indicators of genital Schistosoma haematobium morbidity in a cross-sectional study in endemic rural Zimbabwe. *Trop Med Int Health* 2008; 13(12):1509-1517.
19. Patil PS, Elem B. Schistosomiasis of the prostate and the seminal vesicles: observations in Zambia. *J Trop Med Hyg* 1988;91(5): 245-248.
20. Fender D, Hamdy FC, Neal DE. Transrectal ultrasound appearances of schistosomal prostato-seminovesiculitis. *Br J Urol* 1996;77(1):166-167.
21. Ingram PJ, Allen DC, Irwin ST. Experience with schistosomiasis in Northern Ireland. *Ulster Med J* 1996;65(2):123-125.

22. Alexis R, Domingo J. Schistosomiasis and adenocarcinoma of prostate: a morphologic study. *Hum Pathol* 1986;17(7):757-760.
23. Godec CJ, Grunberger I, Carr GA. Simultaneous presence of schistosomiasis and advanced cancer in prostate. *Urology* 1992; 39(6):547-549.
24. Bacelar A, Castro LG, de Queiroz AC, Café E. Association between prostate cancer and schistosomiasis in young patients: a case report and literature review. *Braz J Infect Dis* 2007;11(5): 520-522.
25. Bhagwandeen SB. Schistosomiasis and carcinoma of the bladder in Zambia. *S Afr Med J* 1976;50(41):1616-1620.
26. Hodder SL, Mahmoud AA, Sorenson K, Predisposition to urinary tract epithelial metaplasia in Schistosoma haematobium infection. *Am J Trop Med Hyg* 2000;63:133-138.
27. Gouda I, Mokhtar N, Bilal D, El-Bolkainy T, El-Bolkainy NM. Bilharziasis and bladder cancer: a time trend analysis of 9843 patients. *J Egypt Natl Canc Inst* 2007;19(2):158-162.
28. Heyns CF, van der Merwe A. Bladder cancer in Africa. *Can J Urol* 2008;15(1):3899-3908.
29. Shokeir AA. Squamous cell carcinoma of the bladder: pathology, diagnosis and treatment. *BJU Int* 2004;93(2):216-220.
30. Riadh BS, El Atat R, Sfaxi M, Derouiche A, Kourda N, Chebil M. Clinical presentation and outcome of bladder schistosoma-unrelated squamous cell carcinoma: report on 33 consecutive cases. *Clin Genitourin Cancer* 2007;5(6):409-412.
31. El-Boulkany MN, Ghoneim MA, Mansour MA. Carcinoma of the bilharzial bladder in Egypt. Clinical and pathological features. *Br J Urol* 1972;44:561-570.
32. El-Bolkainy MN, Mokhtar NM, Ghoneim MA, Hussein MH. The impact of schistosomiasis on the pathology of bladder carcinoma. *Cancer* 1981;48:2643-2648.
33. Brumskine W, Dragan P, Sanvee L. Transitional cell carcinoma and schistosomiasis in a 5-year-old boy. *Br J Urol* 1977;49(6):540.
34. El-Rifai W, Kamel D, Larramendy ML. DNA copy number changes in Schistosoma-associated and non-Schistosoma-associated bladder cancer. *Am J Pathol* 2000;156(3):871-878.
35. Muscheck M, Abol-Enein H, Chew K et al. Comparison of genetic changes in schistosome-related transitional and squamous bladder cancers using comparative genomic hybridization. *Carcinogenesis* 2000;21(9):1721-1726.
36. Mostofi FK. Potentialities of bladder epithelium. *J Urol* 1954;71: 705-711.
37. Manunta A, Vincendeau S, Kiriakou G, Lobel B, Guillé F. Non-transitional cell bladder carcinomas. *BJU Int* 2005;95(4):497-502.
38. Vauhkonen H, Böhling T, Eissa S, Shoman S, Knuutila S. Can bladder adenocarcinomas be distinguished from schistosomiasis-associated bladder cancers by using array comparative genomic hybridization analysis? *Cancer Genet Cytogenet* 2007;177(2):153-157.
39. Armengol G, Eissa S, Lozano JJ et al. Genomic imbalances in Schistosoma-associated and non-Schistosoma-associated bladder carcinoma. An array comparative genomic hybridization analysis. *Cancer Genet Cytogenet* 2007;177(1):16-19.
40. Bichler KH, Savatovsky I Tenke P et al. EAU guidelines for the management of urogenital schistosomiasis. *Eur Urol* 2006;49(6): 998-1003.