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The impact of Schistosoma blood fluke infection on the development of bladder cancer

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Abstract

Introduction and purpose

Schistosomiasis is a significant health problem, particularly in countries in Africa. The disease is caused by blood flukes of the genus Schistosoma. There are five main species. Most infections are asymptomatic. Schistosomiasis can contribute to the development a lot of diseases.

The aim of this article is to examine the impact of schistosomiasis on the human body, with particular focus on bladder cancer.

Brief description of the state of knowledge

Schistosoma are parasitic flatworms whose life cycle involves humans as the definitive host and freshwater snails as intermediate hosts. The cercarial larvae penetrate the human skin. Adult parasites lay eggs in the mucous membranes, causing inflammation and granulomatous reactions. Chronic schistosomiasis leads to tissue fibrosis, portal hypertension, squamous cell carcinoma of the bladder. Acute infection presents with Katayama fever. Diagnosis is based on detecting eggs in urine or stool, as well as serological tests. Treatment includes praziquantel, often supplemented with corticosteroids. Prevention involves avoiding contact with contaminated water. Untreated schistosomiasis can lead to serious complications, including bladder cancer.

Material and methods:

Literature available in the PubMed database was reviewed using the following keywords: schistosomiasis; bladder cancer; Schistosoma haematobium; bilharzia; blood fluke.

Summary

Schistosomiasis induces bladder cancer as a result of the chronic inflammatory condition in the urinary tract. The dominant histological type is SCC. Bladder cancer resulting from schistosomiasis is characterized by a younger age of onset and more advanced clinical stages. In the case of bilharzia detection, eradication of the parasite is recommended to prevent the development of cancer.

Keywords: schistosomiasis; bladder cancer; Schistosoma haematobium; bilharzia; blood fluke.

Introduction and purpose

Schistosomiasis is an infectious disease caused by blood flukes of the genus Schistosoma, also known as bilharzia. In developing countries, schistosomiasis represents a significant health problem. It primarily affects rural and partially urbanized communities, where residents frequently come into contact with freshwater bodies. After malaria and intestinal worm infections, schistosomiasis is one of the leading causes of death in countries of Africa, South America, the Caribbean, the Middle East, and Asia. More than 90% of all confirmed cases are

found in Africa. Five main species of Schistosoma can be distinguished: S. mansoni, S. haematobium, S. japonicum, S. intercalatum, and S. mekongi. Most infections are asymptomatic. Clinical disease manifests as diarrhea, weakness, hepatomegaly, splenomegaly, and cancers of the liver, colon, uterus, and bladder [1].

In this article, we will explore the consequences of infection with Schistosoma blood flukes. The aim of this article is to provide a comprehensive exploration of the impact of Schistosoma infection on the human body, with a particular focus on the induction of bladder cancer.

Description of the state of knowledge

Life Cycle of Schistosoma

Schistosoma parasites belong to the class of flatworms. Their intermediate hosts are freshwater snails. After leaving the snail's body, the larvae live for about 48 hours. During this time, the cercariae are capable of invading the human body through intact skin or mucous membranes. The next stage involves migration through the blood vessels to the lungs. After developing into the next developmental stage, they move through the circulatory system to their final habitat— the mesenteric veins and the urinary bladder. The male and female adult worms pair up. The eggs laid by the females within the tissues trigger a granulomatous reaction, leading to the excretion of eggs into the intestinal lumen and the urinary bladder. There is a possibility of re-infection of freshwater snails. Urination or defecation of an infected person into the same water source completes the life cycle [2].

The final habitat of Schistosoma haematobium is the venous plexuses surrounding the urinary bladder. The parasites lay their eggs within the mucous membrane of the bladder. In the case of Schistosoma mansoni, the final habitat is the mesenteric veins and branches of the portal vein. The parasites lay their eggs in the mucous membrane of the intestine. Schistosoma japonicum, S. intercalatum, and S. mekongi also inhabit the veins of the portal circulation [3].

Acute schistosomiasis

The clinical manifestation of the acute phase of parasitic invasion is Katayama fever. In the human body, a strong cytokine response and an increase in the level of eosinophils are

observed. This process occurs when the human body is exposed to the antigens of the parasite's eggs. The clinical symptoms are nonspecific. The most common symptoms include fever, muscle pain, headache, diarrhea, and cough. There is also a skin manifestation of schistosomiasis in the form of a urticarial rash [4,5].

There have also been reports of cases presenting with splenomegaly and involvement of the central nervous system. Symptoms include, among others, seizures, spinal pain, muscle weakness, dizziness, and nausea. If the parasite's eggs penetrate the brain, hemiparesis may occur.

The diagnosis of acute schistosomiasis is based on the clinical presentation of the disease. A characteristic feature is the history of exposure to the parasites, along with the detection of elevated levels of eosinophils in the peripheral blood [7,8].

The treatment of Katayama fever should begin with the administration of corticosteroids, followed by praziquantel at a dose of 40 mg/kg.

Chronic schistosomiasis

The accumulation of a large number of fluke eggs within tissues leads to the development of a granulomatous inflammatory response. The next stage is the process of fibrosis, which results in the development of obstructive uropathy and squamous cell carcinoma of the bladder.

S. mansoni causes liver fibrosis, which eventually leads to the development of portal hypertension. These changes occur due to the deposition of fluke eggs around the portal vessels. The severity of the disease is directly proportional to the number of eggs laid by the adult parasites in the human body [10,11].

A serious clinical problem is the presence of parasite eggs in the small intestine. This manifests as bloody diarrhea, bloating, and abdominal pain. The most significant complication is intestinal perforation with peritonitis.

Pneumonia in the course of bilharzia is characterized by hemoptysis, moderate wheezing, decreased exercise tolerance, fever, and cough [12].

Confirmation of Infection

The diagnosis of infection caused by Schistosoma flukes can be made by detecting eggs in the urine or stool samples of infected individuals. Confirmation of the presence of parasite eggs requires a 24-hour collection of urine or stool. This method has low sensitivity. In infections

caused by S. haematobium, eggs are most commonly found in the urine between 10:00 AM and 2:00 PM .

It is possible to assess the severity of the parasitic invasion. Finding more than 400 eggs per gram of stool indicates a severe infection, while confirming fewer than 100 eggs per gram of stool indicates a mild infestation.

Another method is to visualize the eggs in histopathological material obtained during a biopsy of the mucous membrane of the bladder or intestine. Serological diagnostics, which involves detecting specific antibodies against the eggs' antigens, is mainly used in countries where the disease is endemic. A thorough analysis of specific IgG antibodies plays a leading role in the diagnosis [16,17].

The detection of IgM antibodies is particularly useful for tourists returning from endemic regions. Specific antibodies can be detected as early as 6-8 weeks after infection. The highest titers are typically observed at the end of the prepatent phase.

The presence of parasite eggs in stool or urine samples can be detected for several months after treatment has been completed. A test for the viability of the eggs is used to assess the effectiveness of the treatment. The analysis focuses on the ability of the eggs to hatch and move [19].

Imaging studies play a key role in the diagnosis of schistosomiasis. Abdominal ultrasound is helpful in diagnosing liver schistosomiasis. Chest X-ray, computed tomography (CT), and echocardiography are also used to evaluate other organs.

On a plain X-ray of the abdomen, characteristic linear calcifications in the bladder can be observed, which are indicative of chronic schistosomiasis, particularly in cases caused by Schistosoma haematobium.

Management of Asymptomatic Patients

The asymptomatic form of the infection is associated with a very low number of parasites present in the body. These are most often travelers who have been accidentally infected. It is recommended to perform diagnostic tests for individuals with clinical symptoms, confirmed eosinophilia, and for those returning from endemic areas.

Parasites typically live for 5 to 10 years. Chronic infections lasting several decades have also been confirmed. There is a possibility of infection persisting for a very long time after staying in an area endemic for schistosomiasis.

Unfortunately, the typical clinical manifestation of the disease is rare, especially in non-endemic areas. Severe infections are also rarely observed. This leads to the disease being unrecognized and the lack of early treatment. Most often, the only symptom is the presence of elevated levels of eosinophils in the peripheral blood [20].

Serological tests and microscopic examination of stool and urine should be performed no earlier than 3 months after exposure to the parasites. This is due to the diagnostic window that exists between infection and the production of eggs by the adult organisms.

The antiparasitic drug praziquantel causes the formation of holes in the parasite's body covering. This leads to the exposure of antigens. The treatment process may intensify unwanted phenomena related to the parasitic invasion.

It is recommended to administer corticosteroids before starting praziquantel therapy. Unfortunately, this drug has low efficacy against immature parasites. Often, it is necessary to repeat treatment regimens in individuals with confirmed schistosomiasis [21].

Prevention of Schistosomiasis

When staying in areas where the parasite is endemic, it is important to avoid bathing in natural water bodies. It is recommended to drink only bottled or boiled water. No increased risk of infection has been observed during bathing in oceans.

There have also been cases described where the parasite larvae penetrate the skin around the mouth while drinking contaminated water. In such situations, it is recommended to thoroughly wipe the body with a towel. This will reduce the risk of larvae penetrating the skin [22,23].

In endemic areas, both biological and chemical methods are used to control freshwater snail populations. Reducing the population of intermediate hosts directly impacts the decrease in the likelihood of parasitic infections.

Complete Cure

Complete cure of schistosomiasis is possible. However, in some cases, the infection leads to severe complications such as gastrointestinal bleeding, kidney damage, bleeding from the gastrointestinal tract, bladder cancer, infertility, miscarriages, and liver cancer. In the course of schistosomiasis, there is an increased likelihood of microstrokes in the brain, paralysis, and recurrent infections caused by Salmonella bacteria.

Bladder cancer and schistosomiasis

Infection with S. haematobium increases the likelihood of developing bladder cancer. The predominant histopathological type is squamous cell carcinoma (SCC). There is substantial scientific evidence supporting the induction of bladder cancer by S. haematobium [24].

Bladder cancer of the squamous cell carcinoma (SCC) histopathological type is strongly associated with the endemicity of S. haematobium flukes. Squamous cell carcinoma is most commonly detected in Egypt, where it accounts for 10-40% of all bladder cancer cases.

The role of parasites in the induction of bladder cancer

Chronic inflammation and local irritation of the bladder by *S. haematobium* flukes trigger the development of urinary tract cancer at the site of inflammation. Neutrophils and macrophages are the predominant sources of endogenous reactive oxygen species, which contribute to the formation of carcinogenic N-nitroso compounds.

Additionally, immune system cells cause genotoxic effects. Mutations, sister chromatid exchanges, and DNA strand breaks are initiated. Inflammatory cells also activate procarcinogens such as aromatic amines and polycyclic aromatic hydrocarbons.

As a result of schistosomal infection, the urine of humans may contain bacteria that reduce nitrates, such as S. aureus, S. albus, P. mirabilis, and E. coli. These microorganisms contribute to the formation of endogenous N-nitrosoamines. Selected bacteria mediate nitration reactions between secondary amines and nitrates under the typical pH conditions found within the bladder. There is a relationship between schistosomiasis and urinary tract infections of bacterial origin that influences the endogenous formation of N-nitroso compounds. The consequence of this is the induction of precancerous conditions [26].

Bladder cancer – symptoms

The dominant symptom of bladder cancer is painless hematuria, which is often quite severe. It can be recurrent or persistent. In the case of tumors spreading intramurally, symptoms such as urgency, frequent urination, and other dysuric symptoms may occur.

In advanced stages of bladder cancer, symptoms may include lower abdominal pain, painful urination, and pain in the lumbar region.

Bladder cancer – diagnosis

For the initial assessment of the bladder and kidneys, ultrasonography is used. Intravesical ultrasound allows for a more detailed evaluation of the bladder walls. This examination is invasive and less accessible. Transrectal ultrasound in men allows for the assessment of the prostate gland, seminal vesicles, and partially the bladder. This method is used to determine the local stage of the disease.

Other imaging techniques used in the diagnosis of bladder cancer include urography and computed tomography (CT). These methods also allow for the evaluation of the upper urinary tract. In cases where the tumor is located within the bladder trigone, there is an increased risk of developing urothelial carcinoma in the upper urinary tract [28].

Urine sediment cytology is highly specific, but its sensitivity depends on the histological grade and clinical stage of the cancer. The test is more likely to detect malignant cells in more advanced or high-grade tumors. High sensitivity in urine sediment cytology is observed in patients with high-grade tumors. The test allows the detection of abnormal-shaped cells originating not only from the bladder but also from the calyceal-pelvic system, ureters, and urethra. However, in patients with coexisting urinary tract stones or urinary tract infections, the test can be difficult to interpret.

Cystoscopy is the gold standard in the diagnosis of bladder cancer. The procedure is recommended for patients with suspected abnormalities in the urinary system. This diagnostic and therapeutic procedure involves inserting a cystoscope through the urethra into the bladder. Flexible and rigid cystoscopes are used for the examination. During the procedure, tissue samples are taken, which are subsequently subjected to histopathological evaluation in the next stage of diagnosis [30].

Bladder Cancer Treatment

Treatment approach depends on the clinical stage of the disease and the histopathological grade of the bladder tumor.

Transurethral resection of bladder tumor (TURBT) is most commonly performed in patients with bladder cancer. TURBT is both a diagnostic and therapeutic procedure. Tumors smaller than 1 cm should be completely removed along with a fragment of the bladder's muscular layer. Larger tumors should be removed in fragments. The histopathological report should include information about the grade of malignancy and the depth of invasion.

In some cases of superficial bladder cancer, intravesical BCG vaccine is used for immunotherapy. BCG bacilli activate macrophages and induce an immediate inflammatory

response. In most cases of in situ bladder cancer, the vaccine leads to cystoscopic and histological remission. The vaccine complements transurethral treatment. It prolongs the disease-free interval and reduces the number of recurrences and tumor progression.

Radical cystectomy is recommended in the treatment of locally advanced bladder cancer, infiltrating the muscular layer. During the procedure in men, the bladder, prostate, and seminal vesicles are removed. In women, in addition to the bladder, the urethra, uterus, adnexa, and anterior vaginal wall are also removed. Certain cystectomy techniques aimed at preserving the prostate are described for selected individuals with cancer confined to the bladder. It is recommended to remove the bladder with as wide a margin of surrounding tissues as possible, along with the simultaneous removal of regional lymph nodes [33].

Summary

There is significant evidence indicating that urinary schistosomiasis induces bladder cancer. In the course of schistosomiasis, chronic irritation and inflammation occur.

Bladder cancer resulting from urinary schistosomiasis is characterized by a younger age of onset and advanced clinical stage. Histologically, the dominant type is SCC. Early detection of the parasite and its eradication are the main methods for preventing urinary system cancer.

Author's contribution

Conceptualization, Piotr Boszczyk, Kinga Wrzesińska; methodology, Kinga Wrzesińska; software, Piotr Boszczyk; check, Piotr Boszczyk, Kinga Wrzesińska; formal analysis, Kinga Wrzesińska; investigation, Piotr Boszczyk; resources, Kinga Wrzesińska; data curation, Piotr Boszczyk; writing - rough preparation, Piotr Boszczyk; writing - review and editing, Kinga Wrzesińska; visualization, Piotr Boszczyk; supervision, Piotr Boszczyk. All authors have read and agreed with the published version of the manuscript.

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References

1. Berry A, Iriart X, Fillaux J, Magnaval J-F. Urinary schistosomiasis and cancer. Bull Soc Pathol Exot. 2017;110(1):68–75, doi: 10.1007/s13149-017-0547-4.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49, doi: 10.3322/caac.21660.
3. Lai Y-S, Biedermann P, Ekpo UF, Garba A, Mathieu E, Midzi N, et al. Spatial distribution of schistosomiasis and treatment needs in sub-Saharan Africa: a systematic review and geostatistical analysis. Lancet Infect Dis. 2015;15(8):927–40, doi : 10.1016/S1473-3099(15)00066-3.
4. Marbjerg LH, Øvrehus ALH, Johansen IS. Schistosomiasis-induced squamous cell bladder carcinoma in an HIV-infected patient. Int J Infect Dis. 2015;40:113–5, doi: org/10.1016/j.ijid.2015.10.004.
5. Salem S, Mitchell RE, El-Alim El-Dorey A, Smith JA, Barocas DA. Successful control of schistosomiasis and the changing epidemiology of bladder cancer in Egypt. BJU Int. 2011;107(2):206–1, doi: org/10.1111/j.1464-410X.2010.09622.x.
6. Santos LL, Santos J, Gouveia MJ, Bernardo C, Lopes C, Rinaldi G, et al. Urogenital schistosomiasis-history, pathogenesis, and bladder cancer. J Clin Med. 2021;10(2):E205, doi: org/10.3390/jcm10020205.
7. Mantica G, Terrone C, Der Merwe AV. Bladder cancer and associated risk factors: the African panorama. Eur Urol. 2021;79(5):568–70, doi: org/10.1016/j.eururo.2020.11.041.

8. Yegorov S, Joag V, Galiwango RM, Good SV, Okech B, Kaul R. Impact of endemic infections on HIV susceptibility in sub-Saharan Africa. Trop Dis Travel Med Vaccines. 2019;5(1):22, doi: org/10.1186/s40794-019-0097-5.
9. Phillips AE, Tohon Z, Dhanani NA, Sofo B, Gnandou I, Sidikou B, et al. Evaluating the impact of biannual school-based and community-wide treatment on urogenital schistosomiasis in Niger. Parasit Vectors. 2020;13(1):557, doi: org/10.1186/s13071-020-04411-9.
10. Labbo R, Ernould J-C, Djibrilla A, Garba A, Chippaux J-P. Focusing of Schistosoma haematobium transmission in irrigated perimeters of the Niger valley (Niger): importance of malacological factors. Rev Epidemiol Sante Publique. 2008;56(1):3–9, doi: org/10.1016/j.respe.2007.10.011.
11. Guo CC, Gomez E, Tamboli P, Bondaruk JE, Kamat A, Bassett R, et al. Squamous cell carcinoma of the urinary bladder: a clinicopathologic and immunohistochemical study of 16 cases. Hum Pathol. 2009;40(10):1448–52, doi: org/10.1016/j.humpath.2009.03.005.
12. Maia MC, Hansen A, Alves C, Salah S. Biomarkers in non-schistosomiasis-related squamous cell carcinoma of the urinary bladder: a review. Crit Rev Oncol Hematol. 2019;135:76–84, doi: org/10.1016/j.critrevonc.2019.01.008.
13. Dotson A, May A, Davaro F, Raza SJ, Siddiqui S, Hamilton Z. Squamous cell carcinoma of the bladder: poor response to neoadjuvant chemotherapy. Int J Clin Oncol. 2019;24(6):706–11, doi: org/10.1007/s10147-019-01409-x.
14. Bartsch H, Montesano R. Relevance of nitrosamines to human cancer. Carcinogenesis. 1984;5:1381–1393, doi: 10.1093/carcin/5.11.1381.
15. Manley KV, Hubbard R, Swallow D, Finch W, Wood SJ, Biers SM. Risk factors for development of primary bladder squamous cell carcinoma. Ann R Coll Surg Engl. 2017;99(2):155–60, doi: org/10.1308/rcsann.2016.0343.
16. El-Awady MK, Gad YZ, Wen Y, et al (2001) Schistosoma hematobium soluble egg antigens induce proliferation of urothelial and endothelial cells. World J Urol 19(4):263–6.
17. El-Sebaie M, Zaghloul MS, Howard G, Mokhtar A. Squamous cell carcinoma of the bilharzial and non-bilharzial urinary bladder: a review of etiological features, natural history, and management. Int J Clin Oncol. 2005;10(1):20–25, doi: 10.1007/s10147-004-0457-6.

18. Hatta MNA, Mohamad Hanif EA, Chin S-F, Neoh H-M. Pathogens and Carcinogenesis: A Review. Biology (Basel) 2021;10:533.
19. Lagwinski N, Thomas A, Stephenson AJ, Campbell S, Hoschar AP, El-Gabry E, et al. Squamous cell carcinoma of the bladder: a clinicopathologic analysis of 45 cases. Am J Surg Pathol. 2007;31(12):1777–1787, doi: 10.1097/PAS.0b013e31805c9cd9.
20. Kitinya JN, Laurèn PA, Eshleman LJ, Paljärvi L, Tanaka K. The incidence of squamous and transitional cell carcinomas of the urinary bladder in northern Tanzania in areas of high and low levels of endemic Schistosoma haematobium infection. Trans R Soc Trop Med Hyg. 1986;80(6):935–939, doi: 10.1016/0035-9203(86)90264-6.
21. Hussain SP, Harris CC. Inflammation and cancer: an ancient link with novel potentials. Int J Cancer. 2007;121:2373–2380, doi: 10.1002/ijc.23173.
22. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. Eur Urol. 2017 Jan;71(1):96-108.
23. Hotez PJ, Kamath A. Neglected tropical diseases in Sub-Saharan Africa: Review of their prevalence, distribution, and disease burden. Plos Negl Trop Dis. 2009;3(8):412, doi: 10.1371/journal.pntd.0000412.
24. Robinson E, Picon D, Sturrock HJ, Sabasio A, Lado M, Kolaczineki J, Brooker S. The performance of haematuria reagent strips for the rapid mapping of urinary schistosomiais: field experience from Sudan. Trop Med Inter Health. 2009;14(2):1484–1487, doi: 10.1111/j.1365-3156.2009.02407.x.
25. Houmsou RS, Kela SL, Suleiman MM. Performance of micro-haematuria and proteinuria as measured by reagent strip in estimating intensity and prevalence of S. haematobium infections in Nigeria. Asian Pac J Trop Med. 2001;4(12):997–1000, doi: 10.1016/S1995-7645(11)60233-2.
26. Ugbomoiko US, Obiezue RNN, Ogunniyi TAB, Ofoezie IE. Diagnostic accuracy of different urine dipsticks to detect urinary schistosomiasis: a comparative study in five endemic communities in Osun and Ogun States, Nigeria. J Helminthol. 2009;83:203–209, doi: 10.1017/S0022149X08133570.
27. Rudge JW, Stothard JR, Basanez M, Mgeni AF, Khamis IS, Khamis AN, Rollinson D. Micro-epidemiology of urinary schistosomiasis in Zanzibar: local risk factor associated with distribution of infections among school children and relevance for control. Acta Trop. 2008;105:45–54, doi: 10.1016/j.actatropica.2007.09.006.

28. Okoli EI, Odaibo AB. Urinary schistosomiasis among school children in Ibadan, an urban community in South-western Nigeria. Trop Med Inter Health. 1999;4(4):308–315, doi: 10.1046/j.1365-3156.1999.00388.x.
29. Ogbonna CC, Dori GU, Nweze EI, Muoneke G, Nwankwo IE, Aputa N. Comparative analysis of urinary schistosomiasis among primary school children and rural farmers in Obollo-Eke, Enugu State, Nigeria: implications for control. Asian Pac J Trop Med. 2012;5(10):796–802, doi: 10.1016/S1995-7645(12)60146-1.
30. Ozumba NA, Christensen NO, Nwosu ABC, Nwaorgu OC. Endemicity, Focalitu and Seasonality of transmission of human schistosomiasis in Amagunze village, Eastern Nigeria. J Hel-minthol. 1989;63:206–212, doi: 10.1017/s0022149x00008993.
31. Zang Y, MacArthur C, Mubila L, Baker S. Control of neglected tropical diseases needs a long-term commitment. BMC Medicine. 2010;8(67):2–9, doi: 10.1186/1741-7015-8-67.
32. Southgate VR, Rollinson D, Tchuente TLA, Hagan P. Towards control of schistosomiasis in sub-Saharan Africa. J Helminthol. 2005;79:181–185, doi: 10.1079/joh2005307.
33. Doenhoff MJ, Chiodini PL, Hamilton JV: Specific and sensitive diagnosis of schistosome infection: can it be done with antibodies?. Trends Parasitol. 2004, 20: 35-39. 10.1016/j.pt.2003.10.019.
34. Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. Lancet. 2014;383:2253–2264, doi: 10.1016/S0140-6736(13)61949-2.
35. Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. Lancet Infect. Dis. 2006;6:411–425, doi: 10.1016/S1473-3099(06)70521-7.
36. Bustinduy AL, et al. An update on female and male genital schistosomiasis and a call to integrate efforts to escalate diagnosis, treatment and awareness in endemic and non-endemic settings: the time is now. Adv. Parasitol. 2022;115:1–44, doi: 10.1016/bs.apar.2021.12.003.
37. Liu R, Dong H-F, Guo Y, Zhao Q-P, Jiang M-S. Efficacy of praziquantel and artemisinin derivatives for the treatment and prevention of human schistosomiasis: a systematic review and meta-analysis. Parasit. Vectors. 2011;4:201, doi: 10.1186/1756-3305-4-201.

38. Frickmann H, et al. Evaluation of a duplex real-time PCR in human serum for simultaneous detection and differentiation of Schistosoma mansoni and Schistosoma haematobium infections – cross-sectional study. Travel Med. Infect. Dis. 2021;41:102035, doi: 10.1016/j.tmaid.2021.102035.
39. Abbasi, I., King, C. H., Muchiri, E. M. & Hamburger, J. Detection of Schistosoma mansoni and Schistosoma haematobium DNA by loop-mediated isothermal amplification: identification of infected snails from early prepatency. Am. J. Trop. Med. Hyg. (2010).
40. Archer J, et al. Analytical and clinical assessment of a portable, isothermal recombinase polymerase amplification (RPA) assay for the molecular diagnosis of urogenital schistosomiasis. Molecules. 2020;25:4175, doi: 10.3390/molecules25184175.
41. Da'dara AA et al. (2014) Schistosome tegumental ecto-apyrase (SmATPDase1) degrades exogenous pro-inflammatory and pro-thrombotic nucleotides. PeerJ 2, e316. 10.7717/peerj.316.