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REVIEW: A Review of the Association of Bladder and Prostate Cancers with Schistosoma Species

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ABSTRACT

Introduction: Schistosomiasis is an infection caused by the deposition of large male and female worms (trematodes) in the bladder veins. The infection affects the kidneys, ureters, bladder and genitals. In endemic geographical areas, schistosomiasis has been implicated as an etiological factor in the pathogenesis of bladder, colon and kidney cancers, especially bladder cancer occurring in such geographical locations almost two decades earlier than in non-native areas. The urinary type of this disease can also cause prostate cancer.

Material and Methods: In this review article, data were collected using the keywords schistosomiasis, bladder cancer, prostate cancer, pathogenicity, and a combination of them from PubMed, Google Scholar and Embase databases from 1995 to 2021.

Results: In this study, the effects of host endocrine system, hormonal imbalance caused by schistosomiasis, as well as the effect of epigenetic changes in the host genome on this parasitic infection and its association with bladder cancer were investigated. The association of schistosome egg soluble antigens with prostate carcinogenesis was also noted.

Conclusion: Schistosomiasis can lead to bladder cancer. But there was not adequate evidence available for prostate cancer and this parasitic infection.

Introduction

Schistosomes are blood trematodes that have a mammalian host and an invertebrate intermediate host: freshwater snails (1). Schistosomiasis or bilharziasis is a neglected tropical disease caused by parasites of the genus Schistosoma. These multicellular parasites belong to the order of flatworms, the category of trematodes, and the genus Schistosoma, and include 5 human infecting species: Schistosoma haematobium, Schistosoma mansoni, Schistosoma japonicum, Schistosoma intercalate, Schistosoma mekongi (2).

All Schistosome infections are caused by contact with fresh water containing free-floating larval forms of parasitic called cercaria, due to daily activities, agriculture, or other recreational activities (1, 3).

cercaria penetrates the skin. The head loses its bifurcated tails, and the resulting schistose-

mula enters capillaries and lymphatic vessels and travels to the lungs. The worms migrate to the portal venous system, where they mature and unite (2). The worms then migrate to the vesicular network and the ureteral drainage vessels. Egg production begins a few weeks after infection and lasts for 3-5 years. The eggs travel from the lumen of blood vessels to adjacent tissues and then pass through the bladder mucosa and enter the urine and the bloodstream and are placed inside the venous network of the bladder; where they reproduce and the females release up to 3,000 eggs per day. The life cycle is completed by the release of eggs. Miracidia, in turn, infects freshwater snails (Bulinus species), and after two generations of primary and secondary sporocysts multiply, cercaria is produced and released inside the snail. Schistosomiasis is estimated to affect more than 200 million people worldwide and is one of the most widespread parasitic infections in the world, the second most common parasitic disease after malaria (4, 5).

Schistosoma haematobium infection, which causes urinary tract schistosomiasis (UGS), is more prevalent in Africa and the Middle East. In addition, female genital schistosomiasis increases the risk of HIV transmission. Many cases of UGS present with only mild symptoms and conditions such as hematuria, urethritis, anemia, and inflammation of the genitourinary tract. However, between 25-50% of UGS cases experience moderate to severe complications, including renal impairment, ureteral obstruction, and bladder squamous cell carcinoma (6).

Globally, approximately 20% of malignancy are caused by infection (7). Bladder cancer is a recurrent and severe complication of chronic UGS. Case reports indicate that patients with schistosomiasis may develop bladder cancer earlier than non-infected individuals (6). The two predominant types of bladder cancer histologically are squamous cell carcinoma and urothelial cell carcinoma. Smoking, occupational exposure to carcinogens, and chronic infection with Schistosoma haematobium have been identified as risk factors for bladder cancer. Chronic schistosomiasis is associated with squamous cell carcinoma (SCC), which occurs at early ages (8). 5% of worldwide bladder cancer cases arise from squamous cells, and these cases are more incident in Africa, likely due to schistosomiasis, a protozoal infection which promotes inflammation (9).

Male genital schistosomiasis (MGS) and cases of prostate cancer have been reported since the 1980s. Prostate cancer is a common genitourinary disease that occurs in both endemic and non-endemic areas of schistosomiasis. Prostate cancer is the second most common cancer after lung cancer and the fifth leading cause of cancer death in men worldwide (10).

Estrogen-like molecules and their metabolites derived from Schistosoma eggs and worms are thought to be the main carcinogens in cancer-related schistosomiasis (11). Schistosoma haematobium worm/eggs have been reported to release catechol estrogen molecules that downregulate estrogen blocking reseptors thus creating a permissive of invasive cancer development (12).

Several studies in native areas of schistosomiasis have reported an association between prostate cancer and schistosomiasis. Most reported cases occur in young adults (less than 50 years) with no family history of prostate cancer, indicating a possible role for schistosomiasis infection in the pathogenesis or early progression of prostate cancer(11) .Infection with Schistosoma haematobium or mansoni can lead to increased levels of prostate-specific antigen (PSA) (13).

In general, worms may induce cancer on host cells by directly mediated by parasitic activity and indirectly by co-infection with other potentially carcinogenic species such as viruses or bacteria, as well as genetic lesions that are exacerbated by the effects of host inflammatory processes against the parasite, such as production of reactive nitrogen and oxygen species (14).

Most pathological findings of schistosomiasis are mainly due to inflammatory and immune responses to parasite eggs. Granulomatous regions form around the eggs and induce an exudative cellular response consisting of

lymphocytes, multinucleated leukocytes, and eosinophils. Histologically, granuloma around eggs has been identified as fibrosis and muscle hypertrophy. In the bladder, large masses of inflammatory granulomatous polyps containing eggs are found in different walls. Polyps can become scaly and cause hematuria. Inflammatory and fibrotic responses to oocyte deposition can lead to bladder calcification as well as infection and and stones formation in bladder, and these changes are often associated with schisto-somiasis associated with bladder cancer (15).

Methods

In this review article, data were collected using the keywords Schistosomiasis, bladder cancer, prostate cancer, pathogenicity, and a combination of them from PubMed, Google Scholar and Embase databases. In this study, studies related to the title of the article and published from 1995 to 2021 were reviewed.

Results

Schistosoma and host endocrine system infections

Hormones regulate a variety of cellular and physiological functions of organisms such as growth, reproduction, and differentiation. The mechanisms by which host hormones act on parasites have been investigated. In the case of schistosomes, host hormonal signals appear to have a major impact on larval stage formation, survival, growth, and puberty. In addition, this is a two-way talk, meaning that worm parasites have a particular impact on host fertility (16).

Hormonal imbalance caused by schistosomiasis

In a number of patients infected with Schistosoma haematobium, the sex hormones estradiol (E2), testosterone and LH were identified in their serum. In this study, 75 individuals living in native areas as well as all sera were selected based on the presence of Schistosoma eggs. In all patients, estradiol levels of serum were significantly increased compared with non-infected controls living in the same native area. Other hormones showed normal levels. The high level of estradiol observed in patients infected with schistosomiasis suggests that the hormone is produced by the parasite itself (16).

Metabolites and compounds related to parasite-derived estrogen have been suggested in the study of hypogonadism in patients with schistosomiasis, which may play a role in the development of Schistosomal bladder cancer. Proteomic analysis of the urine of people containing Schistosoma haematobium eggs showed the presence of several products in the urine of non-infected people, including estrogen-like metabolites and oxidized products derived from guanine, both of which can cause genetic mutations and are carcinogenesis. Estrogen-like metabolites have also been found in Schistosoma egg-soluble antigen (Sch.SEA), which induce major carcinogenic phenotypes if delivered to urinary tract cells, including increased cell proliferation and decreased apoptosis (17).

Due to the interactions of estrogen-related molecules from schistosomes on the endocrine and host immune systems, estrogen metabolites can be considered as carcinogenic chemicals. Several mechanisms explain the role of estrogen in the development of Schistosomal cancer. A more popular hypothesis is that estrogen receptors induce cell proliferation and increase DNA replication errors (6).

In a study to investigate the molecular basis of bladder cancer caused by Schistosoma haematobium, 9 people were divided into 3 groups: group S (patients with UGS and without bladder cancer), group S + T (patients with UGS and bladder cancer), and group T (patients with urinary tract cancer from non-endemic geographical areas for UGS). The occurrence of CFH and C9 as markers of cancer in the S + T group and their absence in the T group can indicate the association of bladder cancer and UGS (18).

Complement factor H (CFH), is a protein inhibitor of properdin, which has the main function of regulating the alternative pathway of the complement system and is known as a

sign of cancer. C9 is a component of the membrane invader complex (MAC) that plays a key role in the innate and acquired immune response by forming pores in the plasma membrane of target cells. On the other hand, neither C9 nor CFH was found in the urine of group T patients (with bladder cancer but without UGS), suggesting that different immune responses may be chemically effective in causing UGS-induced bladder cancer (18).

Epigenetic changes in the host genome

These changes in the host genome may be involved in bladder cancer associated with schistosomiasis. Urine DNA from patients infected with schistosomiasis showed hypermethylation of various genes (19). The study conducted on 7 genes (RASSF1A, RARb2, RUNX3, TIMP3, P16 and ARF) in 57 urine samples from volunteers in endemic region including infected and non-infected people with Schistosoma haematobium. RASSF1A and TIMP3 genes are tumor suppressor genes that are hypermethylated in bladder cancer. Studies have shown that these two genes have a high frequency of methylation in the bladder tissue and urine of people with schistosomiasis when severe bladder damage is evident (3).

The association between the accumulation of the p53 gene (a gene that controls cell division and apoptosis) in the urothelium and infection with Schistosoma haematobium reinforces the notion that the parasite may contribute to profound changes in urinary tract cells and ultimately lead to Invasive forms of cancer(20) . This hypothesis is further supported by Botelho et al. (21, 22). According to these authors, exposure to Schistosoma haematobium antigens inhibits the apoptotic pathways of the cell and leads to cancer (2).

Apoptosis is a genetic mediating mechanism in which cells individually regulate their death process. The Fas_FasL pathway is known to be a major pathway for the induction of apoptosis in cells and tissues. Fas-induced apoptosis is deeply involved in the death of cancer cells due to the immune system. A study was performed to determine the expression of Fas and FasL in human bladder cancer and the effect of schistosomiasis infection. The association of schistosomiasis with malignancy increased the incidence of the Fas+ immune response to 100%. Positive malignancies for Fas decreased as the grade and stage of the tumor progressed. The percentage of FasL-positive malignancies increased with the progression of the grade and stage of the tumor. All controls were negative for FasL expression (23).

Association of prostate cancer with schistosomiasis

It has been hypothesized that inflammation of the prostate due to the deposits of the eggs of Schistosoma haematobium and Schistosoma mansoni can lead to an increase in the level of prostate-specific antigen(13). For this purpose, a cross-sectional study was performed on 366 men living in an area called Murehwa in Zimbabwe. Infection with Schistosoma haematobium and Schistosoma mansoni species as well as Schistosoma hematuria were diagnosed in these individuals. A structured questionnaire was also used to assess the history of schistosomiasis infection among participants. The risk of prostate cancer was assessed by measuring the level of prostate-specific antigen in the serum of participants using Elisa. Urinary tract schistosomiasis infection is associated with levels of prostate-specific antigen, which is an indicator of prostate cancer risk. There was also an increase in the load on Schistosoma haematobium eggs in adult males in the study area (10).

The effect of Sch.SEA on prostate cancer

A study was conducted in a native area called Galilea in Ghana as one of the endemic areas for schistosomiasis, and in this study urine samples were collected from 210 people of both sexes using the PCR technique examined cell culture, oxidative stress assay, and the effect of Sch.SEA on prostate cancer. The effect of Sch.SEA oxidative stress was

determined by assessing decreased levels of cellular glutathione (GSH). The effect of Sch.SEA on apoptosis has also been determined using flow cytometry (24).
The results showed that Sch.SEA induces carcinogenic phenotypes including oxidative stress, increased proliferation, and decreased apoptosis in normal human prostate cells (PNT2) (10). According to case reports, there is a laboratory causal link between schistosomiasis and prostate cancer and is therefore a prelude to future in-vivo studies (25).

Discussion

Schistosomal involvement of the genitals is mainly reported in infection with Schistosoma haematobium, but infection may also occur in relation to other species including Schistosoma mansoni, Schistosoma intercalactum and Schistosoma japonica. Adult Schistosoma worms reside in blood vessels for years, and while they shed hundreds of thousands of eggs per day, they must either be expelled from the host body or trapped in adjacent tissues. Trapped eggs elicit a chronic granulomatous response that causes local and systemic pathological effects in the host, including anemia, growth retardation, impaired cognition by the host immune system, with many unknown effects on endocrine hormones and receptors. They become severe for organ-specific effects .In men, involvement of the testicles and scrotum, seminal vesicles, epididymis, and glands has been reported. Involvement of the genitourinary system with this parasite in women may lead to infertility and adverse pregnancy outcomes (26). According to studies conducted so far, the parasitic infection caused by Schistosoma haematobium is classified as a group 1 carcinogen by the International Agency for Research on Cancer (IARC) (13). We have described estrogen metabolites associated with people with schistosomiasis. These metabolites are expected to provide deeper insights into the carcinogenicity of schistosomiasis in the bladder as biomarkers for the diagnosis or prognosis of this neglected cancer-related tropical disease (27-30). In addition to estrogen metabolites, the interference of this parasitic species in apoptotic pathways including Fas-FasL, epigenetic changes in the host genome, effect on the host endocrine system and also the increase of some chemical markers including CFH (which is the alternative pathway complement) as well as C9 (as a factor involved in the acquired and innate immune response) may also be involved in carcinogenesis (16, 23).

Conclusion

Despite all efforts, schistosomiasis is still a major public health concern in developing countries, and bladder cancer is one of its most serious complications, affecting young people. Further studies in vitro and in vivo using appropriate and adequate animal models in the future show a better horizon for this relationship. Further efforts to understand schistosomal bladder cancer are also needed to improve diagnostic and therapeutic approaches.
In relation to prostate cancer, fewer studies have been performed and the total number of reported cases reaches 17. Although this lack of reports is partly due to limited access to endemic rural areas and lack of early diagnosis of the disease to explain the possible role of Schistosoma haematobium in Prostate cancer requires further studies.

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Conflicts of interest

Authors declare that there is no conflict of interests.

Authors' contributions

All authors have intellectually committed to the study design and process. The final manuscript was revised and accepted by all authors.

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