Original Article

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Is Schistosomiasis a Red Herring in Carcinoma of the Bladder?

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ABSTRACT

Objective: The specific role Schistosoma ova play in bladder carcinogenesis as well as its association with a specific morphologic subtype has remained inconclusive. This study aims to re-evaluate this relationship morphologically and review the literature.

Materials: A 19-year (1999-2017) review of all cases of carcinoma of the bladder with or without schistosomiasis was conducted. This was supplemented with a review of the literature.

Results: 278 cases of carcinoma of the bladder were diagnosed. These comprised 251 males and 27 females in ratio 9:1 and mean ages 56±15 years and 54±16 years respectively (p=0.6). While none of the 27 carcinomas among females had Schistosoma ova 28 of the 251 carcinomas in males were co-morbid with schistosomiasis. These comprised 13 of the 174 TCC, 14 of the 94 SCC, and 1 of the 10 adenocarcinomas. There were no statistically significant differences in gender (p=0.6), age (p=0.6), or co-morbidity with the parasite (p=0.2) among the various histologic subtypes. A review of the literature shows an association of Schistosoma ova not only with SCC but also with TCC and, but for isolated case reports, there is a paucity of definitive association with cancers outside the bladder.

Conclusion: There were no statistically significant differences in gender, age, or co-morbidity with the parasite among the various histologic subtypes. In addition to this, the literature review suggests there must be other co-factors present only in the bladder, rather than just the ova by itself, responsible for Schistosoma-associated carcinoma in this organ.

Keywords: *Schistosomiasis, Bladder, Carcinoma, Transitional, Squamous*

Introduction

Schistosomiasis is endemic in large parts of the world and 85% of the infected reside in Africa.[1] The pooled prevalence of the infection in Nigeria is 34.7% with a higher prevalence among males, adolescents, and rural dwellers.[2]

Fergusson in 1911 was the first to associate schistosomiasis with bladder cancer while others have reported its association with squamous cell carcinoma [3, 4] In many endemic countries control of the parasite has not resulted in a significant drop in the incidence of bladder cancer. [5] Thus bringing the role of schistosomiasis in bladder carcinogenesis under scrutiny. This study aims to re-evaluate this relationship morphologically and review the literature.

Materials and Methods

A retrospective review of all cases of carcinomas of the bladder diagnosed in a tertiary hospital in northwestern Nigeria between 1999 and 2017 was conducted. Co-morbidity of cases with Schistosoma infestation was then correlated with patient ages, gender, and histologic subtypes. This was supplemented by an extensive review of the literature on the role of the parasite in bladder cancer.

Results

In the 19 years reviewed a total of 364 cases of Schistosoma-related lesions were diagnosed. Three (0.8%) of the cases were dermatological, 38(10.4%) were genital, 55(15.1%) were from the gastrointestinal tract and the remaining 268 (73.7%) were from the urinary system (Table 1). Four (1.5%) of the 268 urinary tract schistosomiasis cases were from the urethra, 36 (13.4%) from the ureter, and 228 (85.1%) from the bladder. Of the 268 urinary tract schistosomiasis cases 255 were males and 13 were females, giving M: F ratio of approximately 20:1. The mean ages of male and female patients were 35.7 years and 36.5 years respectively.

In the study period, 278 cases of carcinoma of the bladder were diagnosed. These comprised 251 males and 27 females in ratio 9:1 and mean ages 56±2 years and 54±2 years respectively. One hundred and seventy-four (63%) of the cases were transitional cell carcinomas (TCC), 166 (34%) were squamous cell carcinomas (SCC) and the remaining 10 (3%) were adenocarcinomas. While none of the 27 carcinomas among females had Schistosoma ova 28 of the 251 carcinomas in males were co-morbid with ova of the parasite. These comprised 13 of the 174 TCC, 14

of the 94 SCC, and 1 of the 10 adenocarcinomas (Table 2 and 3). Even though there were 59 ureteric and 4 urethral carcinomas, schistosomiasis was not co-morbid with any of them.

Discussion

Frequency

The 364 schistosomiasis cases morphologically diagnosed in our study are a testament to the poor coverage of

Table 1: organ distribution of cases of schistosomiasis diagnosed.

System/organ involved		Number	%
Dermatological		3	0.8
Genital		38	10.4
Gastrointestinal		55	15.1
Urinary	Ureteric Vesical Urethral	36 228 4	10.0 62.6 1.1
Total		**364**	**100**

Table 2: gender-related characteristics of diagnosed bladder schistosomiasis and bladder cancer.

Characteristic		Female	Male	p-value
Mean age	for bladder schistosomiasis	36.5	35.7	-
	for carcinoma of the bladder	54.1	56.0	
Age distribution	<56 ears	12	96	= 0.8
	>56 years	14	128	
	unspecified	1	27	
Pattern of co-morbidity	Carcinoma + schistosomiasis	0	28	0.07
	Carcinoma - schistosomiasis	27	223	
Histologic type	Transitional cell carcinoma	17	157	= 0.6
	Squamous cell carcinoma	10	84	
	Adenocarcinoma	0	10	

Table 3: histologic subtype-related characteristics of diagnosed bladder carcinoma cases.

		TCC	SCC	Adenocarcinoma	p-value
Gender	Male	157	84	10	0.6*
	Female	17	10	0	
Age	Mean age male	57.2	52.3	52.7 18	0.6
	Mean age female	52.8	56.2	-	
Co-morbidity	with schistosomiasis	13	14	1	0.2
	without schistosomiasis	161	80	9	

*calculated p-value may not be very accurate due to a cell value of 0.

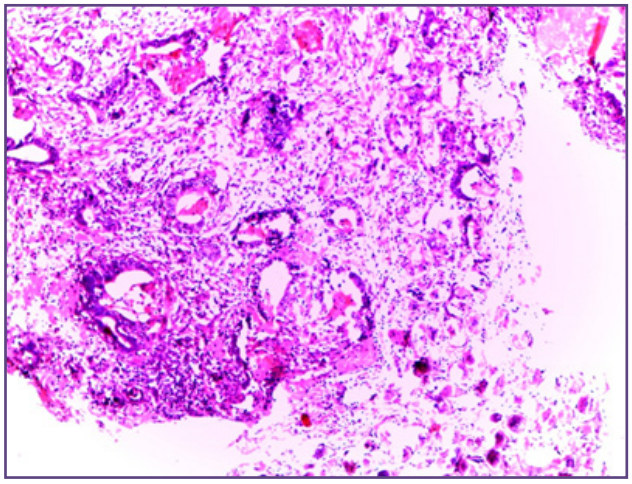

Fig. 1: Well differentiated adenocarcinoma of Urinary bladder with Schistosomiasis Ova H and E X40.

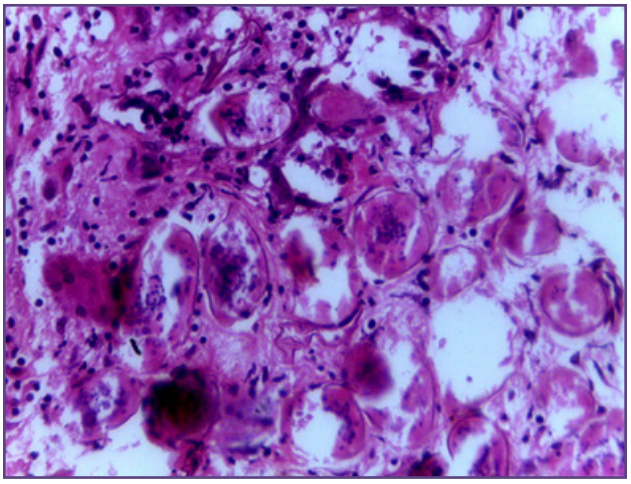

Fig. 2: Viable Ova of Schistosoma H and E X 100.

Praziquantel-based mass therapy embarked upon by the Government. This is further corroborated by the minimal change in prevalence from the 38.6% reported 31 years ago by Betterton et al [6] in 1988 and the 34.7% reported by Abdulkadir et al2 in the year 2017. In some localities, even higher prevalence rates of up to 54% have been reported. [7]

The high prevalence of the parasite is also reflected in the high frequency of urinary tract schistosomiasis in the index study. Even though 85% of the urinary tract cases were from the bladder, yet schistosomiasis was found in only 10% of carcinomas of the bladder. This contrasts with 54% reported by Eni and colleagues, [8] though from a smaller sample size of 65 cases, and the 45% reported by Rambau et al [4] in Tanzania. Incidentally, the prevalence of schistosomiasis in Tanzania is also reported to be as high as 53.3%.[9] It is, however, similar to the 7% reported by Sule et al [10] in an earlier study. Our lower frequency may also have resulted from sampling bias during the incisional biopsy.

Gender

The male to female ratio for bladder schistosomiasis in this hospital-based study was 20:1, while in the community it has been estimated as 5:1.1 [1] The m: f ratio for carcinoma of the bladder was far wider at ratio 9:1 and also wider than the up to 6:1 reported in Egypt. [12] This suggests other factors may be at play causing more females in our geographical location to develop bladder cancer. The narrower m:f ratios of approximately 2:1 for bladder cancer reported from other parts of the world including Europe and Asia have been attributed to the high rate of smoking among women. [13, 14] Interestingly, none of the bladder cancer among females was co-morbid with the parasite. There was also no statistically significant difference in their histologic subtypes compared to males (p=0.6). A similar observation was made in the studies from Tanzania and Egypt. [4, 12]

Age

The age range (10 – 83 years) at diagnosis of bladder schistosomiasis observed in this study is similar to that reported by Eni et al [8] in Maiduguri, also in northern Nigeria, and Botelho and colleagues in Angola. [15] The peak ages in the 6th decade found in this study for patients with bladder cancer, with or without schistosomiasis, and for the various histologic subtypes are similar to or slightly higher than that reported by others in parts Africa [4, 16, 17] but lower than the 7th - 8th decades for those in Western countries. [18, 19] While the lower reported mean ages for bladder cancer in schistosomiasis endemic areas have always been attributed to schistosomiasis-related pathogenesis, patients in countries with controlled parasite prevalence are still about a decade younger than their Western bladder cancer counterparts. Similar earlier age at presentation has also been noted for other cancers among Africans, including those residing in Western nations. [20, 21]

In the index study, there were no statistically significant differences in the mean ages of males and females who had bladder schistosomiasis or the mean ages of males and females who developed bladder cancer or mean ages of those who had bladder cancer co-morbid with schistosomiasis and those not co-morbid with schistosomiasis.

Histologic Subtype

Our study found a preponderance of TCC (60%) over SCC (36%). Such high frequency of SCC has also been described among blacks in the US who are less likely exposed to the parasite compared to those on the African continent.[22] In a study based on SEER's data spanning 41 years, blacks

presented with a higher frequency of non-TCC cancers than other races. [22] A similar SEER-based study also found SCC of the bladder to be twice as common in blacks in all age groups between 35 and 85 years compared to whites in the United States.[23]

Association of Bladder Cancer with Schistosomiasis

Though traditionally, several authors have described an association between carcinoma of the bladder and bladder schistosomiasis, in contrast, our study found no statistically significant difference in co-morbidity of the parasite with either SCC or TCC. Zheng et al [12] in a multicentered study from Egypt involving 1,886 bladder cancer patients also found, not only a statistically significant association between schistosomiasis and SCC but also between the parasite and TCC.

Anatomically, and to a great extent, functionally, the ureter and urinary bladder share common features. Both are lined by transitional epithelium, exposed to urine of similar constitution, and are drained in part by the same vesical plexus which is central to the pathogenesis of urinary schistosomiasis. The ratio of ureteral to bladder schistosomiasis in the index study was approximately 1:6, yet none of the 59 carcinomas involving the ureter in the study period were co-morbid with schistosomiasis.

Similarly, even though 10% and 15% of all schistosomiasis infestations diagnosed in our study period were from the genital and gastrointestinal systems respectively, none of the malignancies documented in these organs exhibited co-morbidity with schistosomiasis. Comparatively, in a review of 216 cases of colonic schistosomiasis, Mohamed et al [24] at the Armed Forces Hospital, Riyadh, also found no association between the few cases with colonic malignancy and schistosomiasis. Peterson and Weidner [25] further described this lack of definitive association in a review of gastrointestinal parasitosis and neoplasia. However, in a recent (2019) study, Nacif-Pimenta and colleagues [26] showed that the effect of Schistosoma ova on cell proliferation may depend solely on the cell type, rather than on the Schistosoma species. These shreds of evidence suggest the presence of a factor, present only in the bladder, which potentiates the carcinogenic effect of the ova, if at all, and not the ova by itself.

Literature Review

The cause-effect relationship between schistosomiasis and carcinoma of the bladder has remained inconclusive despite the parasite being classified as a category 1 carcinogen by the International Agency for Research on Cancer (IARC). [27] The erstwhile widely accepted conclusion that the infestation is mainly associated with the SCC subtype has been laid to rest based on significant association of the parasite with other subtypes. [12]

On a molecular level, Armengolet al 28 using the comparative genomic hybridization technique also demonstrated that there are no major cytogenetic differences among different epithelial tumors of the urinary bladder regardless of the Schistosoma status. In addition to this, El-Rifai et al [29] in reporting their study stated that “Changes that were observed at similar frequencies in SCC and TCC, irrespective of the schistosomal status, included gains and high-level amplifications at 1q, 8q, and 20q and losses in 9p and 13q”. Incidentally, these are some of the most important mutations that have been described in bladder carcinogenesis. Thirdly, Nacif-Pimenta et al [26] found no significant dysregulation of p53 or E2F genes when a urothelial cell line was co-cultured with Schistosoma hematobium.

Ishida et al, [30] among others, have suggested that carcinogenesis may arise from reparative cellular proliferation in response to egg traversal-associated urothelial damage and inflammation. However, in chronic schistosomiasis, as noted by Barsoum et al, [31] there is a switching of the immune response from a predominantly TH1 pro-inflammatory response to a TH2 modulatory profile. Inflammatory cells are gradually abolished and are replaced by fibroblasts. A similar paucity of inflammation in chronic cases was observed by Mohamed et al. [24] The cell culture-based study by Nacif-Pimenta et al further concluded that cellular proliferation in affected organs was secondary to excretory-secretory products of the ova rather than secondary to a foreign body-induced chronic inflammatory effect.

Scientific inquiry has recently focused on the role estrogen and estrogen receptors play in the pathogenesis of bladder cancer. In this regard, Vale et al [32] reviewed the literature and highlighted the possibility that estradiol-like metabolites, assumed to be secreted by the parasite, may play a role in the pathogenesis of this cancer. However, they raised pertinent questions regarding yet to be proven genomic ability of the parasite to code for necessary pathways to synthesize estradiol or to prove that the parasite is simply not metabolizing host estradiol. Perhaps answering this question, Nacif-Pimentaet al26found that estradiol receptor (ER1) expression by urothelial cells was not significantly altered by co-culture with S. haematobium eggs.

The latter observation is important because of the presence of estrogen receptors in normal as well as malignant urothelium. Furthermore, the expression of ER by tumor cells was not specific for SCC but also for TCC of both upper and lower urinary tracts.33, 34 In fact, the study by

Wolpert et al [35] in Egypt even found a greater association of estrogen-related risk with TCC than with SCC.

While it may be argued that even though research linking schistosomiasis to bladder cancer, especially the SCC variant, is inconclusive and sometimes contradictory, circumstantial pieces of evidence may support this notion. With control of schistosomiasis, not only has the histologic pattern in endemic countries changed from predominantly SCC to predominantly TCC, the peak age incidence has changed from the 5th decade to the 6th decade. [36] Yet, the incidence of bladder cancer is still increasing. [37] This suggests there may be more important risk factors at play other than Schistosomiasis even in countries endemic for the parasite. Persistence of/and increase in smoking among others have been identified as being responsible for this.[37]

In the projected 2018 ranking for bladder cancer according to IARC, [38] Lebanon with an incidence of 25 per 100,000 ranked 1st while Egypt, which used to have the highest incidence of schistosomiasis ranked 21st with an incidence of 11.9 per 100,000. This suggests other factors, especially smoking, may play a greater role in the etiopathogenesis of bladder cancer. Prevalence of smoking in Lebanon is 42.1% compared to 22% in Egypt. [39, 40] Attempts at curbing the practice in Egypt date back to 1981 with the passage of Law no.52, a period coinciding with periods of high Schistosoma prevalence in the country. In sub-Saharan Africa, Nigeria carries the greatest burden of schistosomiasis infestation, [41] yet, based on data from population-based registries, the age-standardized incidence rate for Schistosoma-associated bladder cancer is 0.7 per 100,000. [42] This may be because of the low (5.6%) prevalence of smoking in the country. [43]

Several of the earlier studies in Africa on the role of schistosomiasis in bladder carcinogenesis did not control for smoking in the populations studied. In a study of risk factors associated with primary SCC of the bladder Manley et al [44] found that smoking was the singular most important risk factor in 27.8% of cases. A similar finding regarding a statistically significant association between smoking and SCC of the bladder was also reported by Kantor et al [45] and Zheng et al. [12] However, these studies also revealed a significant association between primary SCC of the bladder and infection-induced or irritation-induced chronic cystitis especially from urolithiasis.

The role of infections, especially with nitrate-reducing bacteria, and the formation of carcinogenic N-nitroso compounds in the pathogenesis of SCC of the bladder is well established. [46] Association of bacteriuria in individuals with bladder schistosomiasis has also long been established.46Several observations have stood out viz a viz infection and bladder cancer.

Martin et al, [47] conducted a systematic review focusing on clinical features of Schistosoma-associated and non-Schistosoma-associated SCC of the bladder and highlighted the role of urinary tract infection (UTI) as a common aetiologic risk factor in both.

Significant bacteriuria in Schistosoma-infected individuals compared to controls has been documented in as high as 53.7% to 80.3%, with the latter study describing a near-linear association between egg load and bacterial colony counts. [48, 49]

Urinary pathogens, especially Escherichia coli which is common in bladders with Schistosoma ova,49can establish reservoirs within urothelial cells and serve as seeds for re-infection and recurrent UTI. [50] Could Schistosoma ova, especially when calcified, just like bladder stones or in-dwelling catheter tips, simply serving as reservoirs for recurrent UTI? Such relationship as a reservoir of chronic infection has been well established for the interaction of the ova and Salmonella spp. [51]

Reports from one of the largest bladder cancer case-control studies worldwide have shown the association between UTI, smoking, and bladder cancer. [52]

Experimental models have shown that mice exposed to the bladder-specific carcinogen n-butyl-n-(4-hydroxybutyl) nitrosamine, developed not only distinct urine microbial profiles but also urothelial dysplasia, hyperplasia, or carcinoma in situ. Two of the mice used for the study developed invasive urothelial carcinoma, one of which had features of a squamous cell carcinoma. [53]

Bacteria microbiota has also been shown as not only metabolizers of hormones but also as secretors of them. Such hormones secreted by microbiota include estriol and estradiol. [54] Could the estradiol-like substances associated with Schistosoma-induced bladder carcinogenesis have been synthesized by co-infecting bacteria?

Following from the foregoing, perhaps, there is a need to rethink the role of Schistosoma ova in the pathogenesis of bladder cancer. Could the diagram below encapsulate this suggested role?

In conclusion, with the current inability to establish a direct pathogenetic linkage between schistosomiasis and bladder cancer, perhaps it may be more apt, especially with emerging pieces of evidence, to consider the ova, especially when calcified, as no different from other irritants such as bladder stones and in-dwelling catheters; and that (1) supervening UTI by itself, or (2) UTI potentiated by ova-

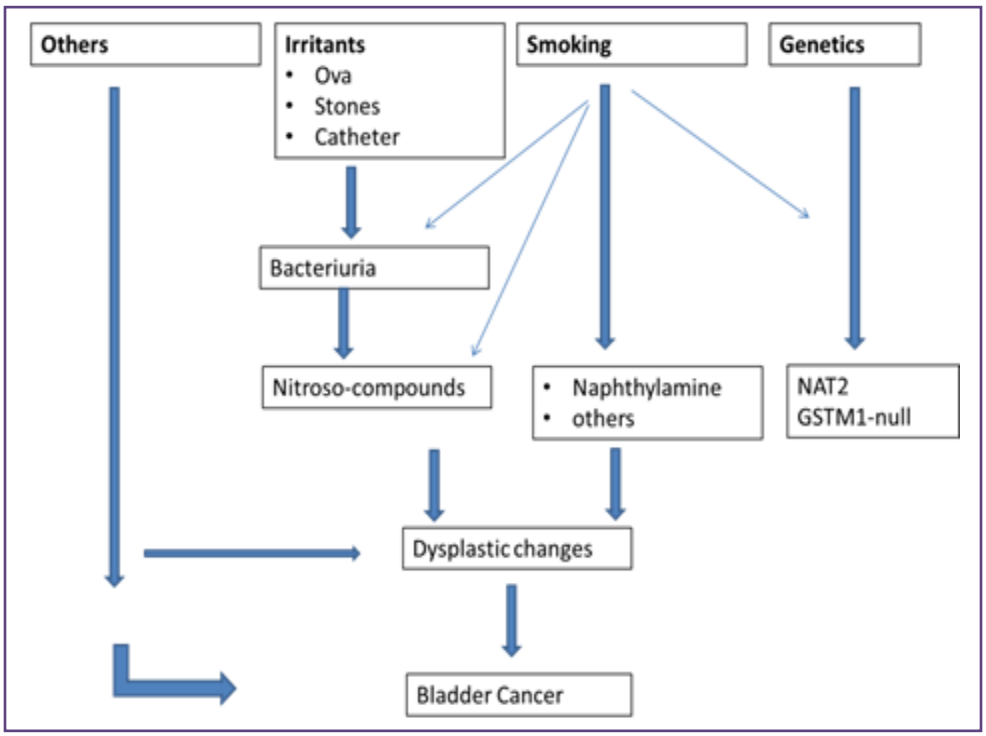

Fig. 3: proposed role for Schistosoma ova in the pathogenesis of bladder carcinoma.

related secretory-excretory products or (3) UTI, ova-related products and other environmental promoters, especially smoking, as co-culprits, rather than the ova by itself as being responsible for the pathogenesis of bladder cancer in Schistosoma endemic areas.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for Publication

Not applicable

Availability of data and material: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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