Original Article

Changes in histopathological phenotypes of *Schistosoma*-associated urinary bladder cancer in Sohag, Egypt

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ABSTRACT

Background: Squamous cell carcinoma is the most common type in Egyptian bilharzial bladder. However, there is a proven changing pattern of *Schistosoma*-associated bladder cancer (SA-BC) that needs to be investigated.
Objective: To assess the patterns (age, incidence, and histopathological types) of SA-BC in Sohag, Egypt.
Material and Methods: This descriptive retrospective study included 152 patients histologically confirmed urinary BC diagnosed at the Pathology Department of Sohag University Hospital during 4 years, from January 2019 to December 2022. Data including age, sex, residence, and histopathological type were retrieved from the records of Pathology Department.
Results: Patients' age ranged from 35-79 years with a mean of 61.2±9.1 years, and male to female ratio was 4.6:1. Transitional cell carcinoma (TCC) was the most common histological type (80.9%), followed by squamous cell carcinoma (SCC) (12.5%), and TCC with squamous differentiation (6.6%). *Schistosoma* eggs were histologically confirmed in 39.5% of cancer cases; 76.7% were TCC, 21.7% were SCC and only 1.6% was TCC with squamous differentiation. All SA-BC were male with mean age of 59.8±7.5. At the time of diagnosis, 96.7% of SA-BC cases were bladder muscle invasive and 91.7% were of high-grade nature not significantly different from cases with non-Schistosome associated BC (NSA-BC).
Conclusion: The histopathological patterns of SA-BC have changed in Egypt over the past decade and most cases were associated with TCC.
Keywords: bladder cancer; Sohag, Egypt; SCC; TCC; urinary schistosomiasis.

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INTRODUCTION

Human schistosomiasis is one of the 21 neglected tropical disease[1]. It is endemic in 78 countries affecting ~240 million worldwide and 700 million individuals are at risk of infection[2]. In Upper Egypt, the prevalence of *S. haematobium* recorded 24%[3], 4.7%[4], and 23%[5] in Qena, Aswan, and Sohag, respectively. Chronic urinary schistosomiasis due to *S. haematobium* is commonly associated with SCC of the urinary bladder[6]. Based on data obtained from 'Global Cancer Observatory (GLOBOCAN)' in 2020, Egyptian BC was the third most prevalent cancer in both sexes with an incidence of 7.9%. Among men it was the second most prevalent cancer with an incidence of 12.6%[7].

Several factors contribute to the oncogenesis of bilharzial infection. *Schistosoma* antigens (worm extract) and soluble egg antigens cause urothelium cells to divide faster and die less frequently due to up-regulation of anti-apoptotic protein, B-cell lymphoma 2 (BcL-2) and down-regulation of tumor suppressor protein *p27* (cyclin-dependent kinase inhibitor 1B). The eggs deposited in the bladder wall produce oxygen-derived free radicals initiating intense inflammatory reactions. These free radicals are capable of producing genetic mutations and the production of numerous carcinogenic compounds (N-nitrosamines and polycyclic aromatic hydrocarbons)[8].

The SCC is a rare subset of urinary BC composing an estimated 2-5% of all BCs in Western countries[9]. However, it is still predominant in most of Africa (53-69%)[10]. This category of BC is of higher aggressiveness and worse survival outcomes compared to TCC. It is associated with a higher proportion of non-organ-confined (pT3-4: 20.6% vs. 4.4%), lymph node involvement (T1-4 N1-3: 5.3% vs. 2%) or metastatic stages (10% vs. 3%) compared to the transitional histological type[11]. The current treatment for SCC does not provide satisfactory therapeutic responses and SCC patients have relatively poor response to chemotherapy and/or immunotherapy; on the other hand, adjuvant, neoadjuvant radiotherapy, or chemotherapy show good response in the treatment of TCC[12,13].

Several studies observed that the histopathological pattern of BC is changing among Egyptians. Over the last decades, the incidence of SCC is declining, while bladder TCC is rising and schistosomiasis is associated

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with TCC[14,15]. This changing pattern of BC in Egypt explains why the incidence of BC remains high in Egypt despite the claim of controlling schistosomiasis and this change emphasizes the need for accurate reports on the actual burden of schistosomiasis in Egypt and implementation of potential national measures to control this preventable type of cancer[15,16].

The present retrospective study is designed to assess patterns (age, incidence, and histopathological types) of SA-BC in Sohag, Egypt from 2019 to 2022.

MATERIAL AND METHODS

This descriptive retrospective study was conducted at Pathology Department, Sohag University, Sohag, Egypt during the period from January 2019 to December 2022.

Study area: Sohag is located in the southern part of the country, 467 km south of Cairo. It covers an extent of the Nile Valley with a total area of 1547 Km^2, and an estimated population of 5,709,225.

Study design: All histologically confirmed cases of urinary BC were compiled from the Pathology Department of Sohag University Hospital during the study period. Patients' demographic data and tumor characteristics were retrieved from the records of the Pathology Department. Undifferentiated, adenocarcinoma, sarcoma cell types, patients with missing pathology records and failure to retrieve histology slides were excluded from the study. Histology slides were reevaluated for histological type of cancer, stage, grade, the involvement of urinary bladder muscularis propria by cancer and presence of *S. haematobium* eggs. Pathologic staging and histopathologic grading were performed according to the TNM[17], and WHO[18] classifications, respectively. *Schistosoma*-association was diagnosed if histopathologic evidence was found of *S. haematobium* eggs in the bladder wall.

Statistical analysis: Data were analyzed by IBM SPSS Statistics for Windows version 25.0. Quantitative data were expressed as mean±SD. Qualitative data were expressed as number and percentage. Chi-Square test and Fisher's Exact test were used for comparing categorical data. For all statistical tests, $P<0.05$ was considered significant.

Ethical considerations: This study was approved by Medical Research Ethics Committee of the Faculty of Medicine, Sohag University, with the IRB registration No. (Soh-Med-22-06-23). Data were collected anonymously from the lab of Pathology Department of Sohag University Hospital, so the waiver of consent was submitted to Medical Research Ethics Committee.

RESULTS

A total number of 152 patients were diagnosed with urinary BC during the study period. The patients' ages ranged from 35-79 with a mean of 61.2±9.1 years regardless of histological type of cancer. Males were 125 (82.2%) while females were 27 (17.8%) with 4.6:1 male to female ratio. Of all histologically diagnosed urinary BC, TCC was the most common constituting 123 cases (80.9%) followed by 19 (12.5%) SCC cases, and 10 (6.6%) of TCC cases were with squamous cell differentiation. Regarding total BC cases, 147 (96.7%) were muscle invasive BC (MIBC) compared to 5 cases (3.3%) with non-muscle invasive BC (NMIBC); 139 cases (91.4%) were high grade, 8 cases (5.3%) were moderate grade, and 5 cases (3.3%) were low-grade (Table 1).

Schistosomiasis was histologically confirmed in 60 cancer cases (39.5%); 46 (76.7%) were TCC, 13 (21.7%) were SCC, and only one (1.6%) was TCC with squamous differentiation. All cases of SA-BC were males.

Table 1. Demographic criteria and histopathological findings of studied patients with BC.

Patterns	No. (%) of patients
Age (years)	
Mean±SD (range)	61.2±9.1 (35-79)
Gender	
Male	125 (82.2%)
Female	27 (17.8%)
Associated schistosomiasis	
Yes	60 (39.5%)
No	92 (60.5%)
Histopathological types	
TCC	123 (80.9%)
SCC	19 (12.5%)
TCC mixed	10 (6.6%)
T stage	
T1	5 (3.3%)
T2	64 (42.1%)
T3	69 (45.4%)
T4	14 (9.2%)
Pathological grades	
High	139 (91.4%)
Moderate	8 (5.3%)
Low	5 (3.3%)

TCC: Transitional cell carcinoma; **SCC:** Squamous cell carcinoma **TCC mixed:** TCC mixed with squamous differentiation.

The mean age of patients who had *S. haematobium* eggs embedded in cancer tissue was 59.8±7.5; while the mean age of *Schistosoma* associated transitional cell carcinoma (SA-TTC) was 62.2±6.04 years compared to 50.6±4.8 years in *Schistosoma* associated squamous cell carcinoma (SA-SCC) (Fig. 1). Among SA-BC cases, 58 (96.7%) had MIBC compared to 2 (3.3%) who had NMIBC; while 55 (91.7%) were high-grade, 3 (5%) were moderate grade, and 2 cases (3.3%) were low-grade neoplasms (Fig. 2). According to histopathological type, there was significant difference between the prevalence of patients with SA-BC compared to those of non-*Schistosoma* associated BC (NSA-BC) in squamous cell type and mixed transitional cell type with squamous

differentiation (P=0.006, and 0.04, respectively), but there was no significant difference between them in transitional cell type. There was significant difference between the two groups regarding gender (P<0.001), while there was no significant difference between them regarding age, grade and muscle invasion (Table 2).

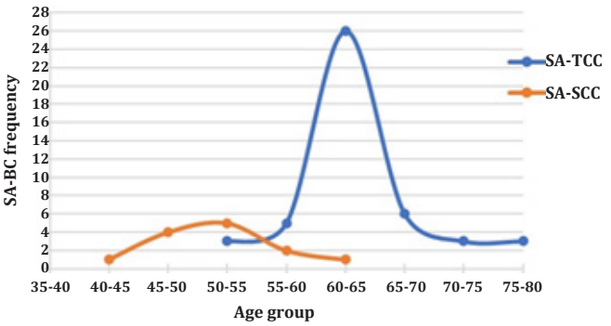

Fig. 1. Distribution of histopathological types of SA-BC according to age in Sohag.

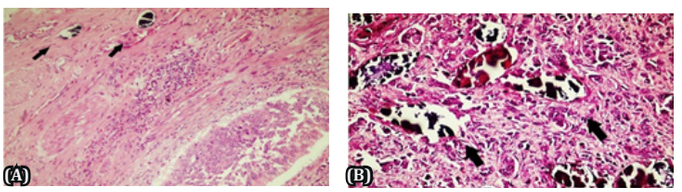

Fig. 2. Histological images of SA-TCC (H&E stain). **(A)** TCC dissecting the muscle, note two calcified destroyed eggs (arrows) X200, **(B)** Invasive high grade TCC on top of bilharzial cystitis, note dense infestation by calcified destroyed eggs (arrows) X400.

Table 2. Relation between SA-BC and demographic criteria and histopathological findings in studied patients.

Patterns	SA-BC (n=60) N (%)	NSA-BC (n=92) N (%)	Statistical analysis
Age group			
<60 years	20 (33.3%)	34 (37%)	$P = 0.6$
≥60 years	40 (66.7%)	58 (63%)	
Gender			
Male	60 (100%)	65 (70.7%)	$P < 0.001$*
Female	0	27(29.3%)	
Histopathological types			
TCC	46 (76.7%)	77 (83.7%)	$P = 0.2$
SCC	13 (21.7%)	6 (6.5%)	$P = 0.006$*
TCC mixed	1 (1.6%)	9 (9.8%)	$P = 0.04$*
Pathological grades			
High	55 (91.7%)	84 (91.3%)	$P = 0.9$
Moderate	3 (5%)	5 (5.4%)	
Low	2 (3.3%)	3 (3.3%)	
Muscle invasion (MI)			
MIBC	58 (96.7%)	89 (96.7%)	$P = 0.9$
Non-MIBC	2 (3.3%)	3 (3.3%)	

SA-BC: *Schistosoma*-associated bladder cancer; **NSA-BC:** Non-SA-BC; **TCC:** Transitional cell carcinoma; **SCC:** Squamous cell carcinoma **TCC mixed:** TCC mixed with squamous differentiation; ***:** Significant (P<0.05).

DISCUSSION

Schistosomiasis is still a public health issue in certain areas of developing countries (especially in sub-Saharan Africa). Definitely, *S. haematobium* is a proven carcinogenic agent that causes mainly bladder SCC[19]. The current study revealed that TCC was the most common comprising of 80.9% of histologically confirmed BC while SCC represented 12.5% and TCC with squamous differentiation represented 6.6%. The results of this study were in agreement with a previous study conducted by Moussa *et al*.[14] who found that the incidence of SCC among Egyptians declined over four years, from 25% in 2006-2010 to 9% in 2011-2015. Similar findings were observed by Amin *et al*.[15] from Cairo, Essa *et al*.[20] from Assiut, and Ali *et al*.[21] from Sohag who reported that the predominant type of BC was TCC (86%, 88%, 76.8% respectively). However, the results differed from those of a Tanzanian study in which SCC was the commonest histological type of BC with 57.0%, followed by TCC with 37.6%[22].

The present study reported that schistosomiasis was histologically confirmed in 60 cancer cases (39.5%); TCC cases were 76.7%, while SCC cases and

TCC with squamous differentiation were 21.7% and 1.6% respectively. Our results agreed with Amin *et al*.[15] who reported that schistosomiasis was histologically confirmed in 19 cancer cases, only 3 of whom were SCC, and other cases were associated with TCC. Previous studies interpreted the changing patterns of BC in Egypt over the past 30 years with a significant decrease in SCC and increase in TCC due to control of schistosomiasis, and genetic changes due to environmental factors such as increased smoking, exposure to pesticides and occupational exposures[23]. However, schistosomiasis was more consistently associated with TCC and this change in patterns of BC was not due to successful treatment of schistosomiasis, increased smoking as well as environmental hazards but rather due to inaccuracy of the histological evaluation of schistosomiasis which must be confirmed or excluded by using serological methods and urine tests before postulating that the increased rate of TCC was attributed to smoking[15,24]. According to (GLOBOCAN)[7], BC is the second common cancer in men representing 12.6% while the lung is the third malignancy representing only 7.2%. If smoking was a major risk factor for the increasing TCC in Egypt, a proportionate increase in lung cancer should have been expected and this did not happen in Egypt. Former studies indicated the need to analyze the underlying mechanism that favored BC formation instead of lung cancer to understand this paradox[7,15]. Besides, the extent of schistosomiasis apparently plays a significant role in the induction of different types of cancer since SCC is usually associated with moderate and/or high worm burdens, whereas TCC occurs more commonly in areas associated with lower degrees of infection[25].

The current study revealed a higher mean age at diagnosis in BC patients (61.2±9.1 y) and SA-BC patients (59.8±7.5 y). Mean age was higher in patients with SA-TTC (62.2±6.04 y) than those with SA-SCC (50.6±4.8 y). Similar findings were noticed by previous studies as Amin *et al*.[15] who recorded a higher mean age for SCC of 60.58 y and for TCC of 61.5 y in Egypt. Moreover Essa *et al*.[20] noted a higher mean age of BC patients of 61 y. Our results differed from Tanzanian studies in BC that quoted a lower mean age of 55 years in 2011-2021 in BC[22]. Our data revealed 4.6:1 male to female ratio of BC cases with male predominance in 82.2%. This is consistent with previous studies from Egypt conducted by Amin *et al*.[15] in which males represented 85.5% of reported cancer samples, and in the study by Essa *et al*.[20] in which males constituted 81% of patients and the study by Ragab, *et al*.[23] which reported 82.5% male predominance in BC cases. This gender disparity might be due to the difference in the lifestyle of both genders with men more exposed to schistosomiasis, smoking, and occupational hazards known to cause BC[26]. Additionally, studies have shown that female hormones can prevent BC or slow the disease progression and the use of antiandrogens appears to delay the development of BC in men[27,28]. In the current study, all BC patients associated with schistosomiasis were male. These results agreed with Kyritsi *et al*.[29] who found bladder tissue infection with *S. haematobium* to be significantly more prevalent in male than in female cases of BC, regardless of the type of cancer.

In our study, 91.7% of SA-BC masses were of high-grade nature in comparison to 91.3% of NSA-BC masses which were also of high grade but with no significant difference between the two groups. This result was closely similar to that recorded by Essa *et al*.[20] in Assiut who reported that 95% of masses were high-grade and by Ali *et al*.[21] in Sohag who reported a similar high-grade of 92.2%. However, Ragab *et al*.[23] in Minia recorded 62.5% high-grade.

In our study, there was no significant difference between the detection rate of patients with SA-BC either who had MIBC or those with NSA-BC (96.7%). Similar results were obtained by Essa *et al*.[20] and Ali *et al*.[21] who reported that 98% and 97% of patients had invasive BC, respectively. However, it was higher than that observed by Ragab *et al*.[23] who recorded that 75% of BC involved bladder muscle wall. The presence of SA-BC in advanced stages is usually explained by the similarity of its symptoms to those of schistosomiasis from which the patient was suffering[8]. The lack of data on individual smoking behaviors and occupation was a limitation in our study.

In conclusion, the histopathological patterns of BC in Egypt have significantly changed. An increase in TCC and a decrease in SCC were indicators of changes in exposures associated with BC induction. Although SCC is strongly associated with *S. haematobium*, schistosomiasis is more consistently related to TCC at present. Further molecular, serological, and experimental research studies in SA-TCC are required to understand the changing pattern of BC.

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REFERENCES

1. Casulli A. New global targets for NTDs in the WHO roadmap 2021-2030. PLOS Negl Trop Dis 2021;15(5):e0009373.
2. Donohue RE, Mashoto KO, Mubyazi GM, Madon S, Malecela MN, Michael E. Biosocial determinants of persistent schistosomiasis among schoolchildren in Tanzania despite repeated treatment. Trop Med Infect Dis 2017; 2(4):61.

3. El-Kady AM, Sefelnasr AM, Osman DM, Khairallah MK, Abou Faddan AH, Gaber MM. Mapping of *S. haematobium* in Qena District, Qena Governorate, Upper Egypt; Hospital-Based Study. J Egypt Soc Parasitol 2020; 50(2):358-363.
4. Dyab, AK, Abd Elmawgood, AA, Abdellah, MA., Ragab, MF. Current status of schistosomiasis and its snail hosts in Aswan Governorate, Egypt. J Egypt Soc Parasitol 2021, 51(3):553-558.
5. Abd Ellah, AK, Abdelkreem EM. Circulating cathodic antigen versus microscopy for diagnosing urinary schistosomiasis among children, in Sohag University Hospitals. J Egypt Soc Parasitol 2023; 53(2):287-292.
6. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of bladder cancer. Med Sci 2020; 8(1):15.
7. Global Cancer Observatory (GLOBOCAN), Egypt fact sheet. 2020. https://gco.iarc.fr/today/data/factsheets/populations/818-egypt-fact-sheets.pdf
8. Zaghloul MS, Zaghloul TM, Bishr MK, Baumann BC. Urinary schistosomiasis and the associated bladder cancer: Update. J Egypt Natl Canc Inst 2020; 32(1):1-10.
9. Al-Ezzi EM, Veitch ZW, Salah SH, Van der Kwast TH, Stockley TL, Selvarajah S, *et al*. Genomic characterization of non-schistosomiasis-related squamous cell carcinoma of the urinary bladder: A retrospective exploratory study. Plos one 2021; 16(12): e0259272.
10. Bowa K, Mulele C, Kachimba J, Manda E, Mapulanga V, Mukosai S. A review of bladder cancer in sub-Saharan Africa: A different disease with a distinct presentation, assessment, and treatment. Ann Afr Med 2018; 17(3):99.
11. Deuker M, Martin T, Stolzenbach F, Rosiello G, Ruvolo CC, Nocera L, *et al*. Bladder cancer: A comparison between non-urothelial variant histology and urothelial carcinoma across all stages and treatment modalities. Clin Genitourin Cancer 2021; 19(1):60-68.
12. Banek S, Hoeh B, Cano Garcia C, Koll F, Köllermann J, Chun FKH, *et al*. Metastatic squamous cell carcinoma of the urinary bladder: Urgent call for new therapies. Urol Int 2024;108(1):1-8.
13. Zaghloul MS, Christodouleas JP, Zaghloul T, Smith A, Abdallah A, William H, *et al*. Randomized trial of adjuvant chemotherapy versus adjuvant radiation therapy for locally advanced bladder cancer after radical cystectomy. J Clin Oncol 2019; 37:4507.
14. Moussa S, El-Sheshtawy W. Pathological pattern of urinary bladder cancer: Data from a single Egyptian institute. Res Oncol 2017; 13(1):14-17.
15. Amin HAA, Kobaisi MH, Samir RM. Schistosomiasis and bladder cancer in Egypt: Truths and myths. Open Access Maced J Med Sci 2019; 7(23):4023.
16. Daniel A, Bhatt A. Schistosomiasis and bladder cancer in Egypt: A historical analysis. J Glob Oncol 2016:50.
17. Magers MJ, Lopez-Beltran A, Montironi R, Williamson SR, Kaimakliotis H Z, Cheng L. Staging of bladder cancer. Histopathology 2019; 74(1):112-134.
18. Moch H, Amin MB, Berney DM, Compérat EM, Gill AJ, Hartmann A, *et al*. The 2022 World Health Organization classification of tumors of the urinary system and male genital organs—part A: renal, penile, and testicular tumors. Eur Urol 2022; 82(5):458-468.
19. Efared B, Bako ABA, Idrissa B, Alhousseini D, Boureima HS, Sodé HC, *et al*. Urinary bladder *S. haematobium*-related squamous cell carcinoma: A report of two fatal cases and literature review. Trop Dis Travel Med Vaccines 2022; 8(1):3.
20. Essa H, Abeer A, El-Morshedy S, Abd-Elmaboud, R. A Clinico-epidemiological study and clinical outcome in patients with urinary bladder cancer at Assuit University Hospital from 2015-2019 (Hospital Based Study). Med J Cairo Univ 2022; 90(12):2673-2681.
21. Ali AM, Fathy AH, Ahmed SR. Outcome of treating urinary bladder cancer in Sohag University Hospital. EJHM 2023; 92:6754-6763.
22. Yohana C, Bakuza JS, Kinung'hi SM, Nyundo BA, Rambau PF. The trend of schistosomiasis related bladder cancer in the lake zone, Tanzania: A retrospective review over 10 years period. Infect Agents Cancer 2023; 18(1):10.
23. Ragab HH, El-Badry MSM, Abdel Ghani MM, Aboelhassan, MHM. Urinary bladder carcinoma pattern at Urology Minia University Hospital. MJMP 2021; 32(1):36-43.
24. Balahbib A, Amarir F, Corstjens PL, de Dood C J, van Dam G J, Hajli A, *et al*. Selecting accurate post-elimination monitoring tools to prevent reemergence of urogenital schistosomiasis in Morocco: A pilot study. Infect Dis Poverty 2017; 6:1-9.
25. Botelho MC, Alves H, Richter J. Halting *S. haematobium*-associated bladder cancer. Int J Cancer Manag 2017; 10(9):e9430.
26. Kamal NN, Mahmoud AM, Mohammed KH, Hassan EE. Association between smoking and urinary bladder cancer (BC): Case control study in Minia, Egypt. MJMR 2023.
27. McBeth L, Grabnar M, Selman S, Hinds TD. Involvement of the androgen and glucocorticoid receptors in bladder cancer. Int J Endocrinol 2015; 2015:384860.
28. Morales EE, Grill S, Svatek RS, Kaushik D, Thompson J IM, Ankerst DP, *et al*. Finasteride reduces risk of bladder cancer in a large prospective screening study. Eur Urol 2016; 69(3):407-410.
29. Kyritsi F, Loffredo CA, Zheng YL, Philips G, Amr, S. Urinary bladder cancer in Egypt: Are there gender differences in its histopathological presentation? Adv Urol; 2018; 2018:3453808.