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Good Schistosomiasis Control Led to Change in the Bladder Cancer Pattern in Egypt

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Abstract: Bladder cancer (BC) ranks as the tenth most prevalent cancer globally in terms of absolute cases. The prevalence of Schistosomiasis has been decreased to 1-2% due to mass treatment with the effective anthelmintic medicine praziquantel and public education, resulting in a dramatic decrease in the incidence of squamous cell carcinoma (SCC). However, BC is still the most prevalent cancer in the Egyptian population, notably among men, with changing the pattern towards transitional cell carcinoma (TCC). This study aimed to demonstrate the association between BC and clinicopathologic factors and to highlight the change that has occurred in the pattern of BC in Egypt over the last years. Our study included 97 subjects; 25 healthy controls, 20 benign cases and 52 malignant cases [bilharzial BC (n=15), nonbilharzial BC (n=37)], and was conducted at National Cancer Institute "NCI", Cairo, Egypt. Each subject provided 3 ml blood sample for anti-bilharzial antibody detection by Indirect Haemagglutination test and fresh urine sample for cytology examination. Results showed that the mean age for BC group was 62 years, 88.46% of cases were males and 11.54% were females with a male:female ratio ~ 8:1. There were highly significant differences between investigated groups regarding smoking, bilharziasis and urine cytology ($P<0.01$). The sensitivity of urine cytology was (51.9%), while specificity was (100%). Most cases (86.53%) were TCC type while 11.53% were SCC type. Such results indicate that there is a change in the pattern of BC which ensures good control of Schistosomiasis in Egypt.

Keywords: Bladder Cancer; Squamous Cell Carcinoma; Transitional Cell Carcinoma; Schistosomiasis; Urine Cytology.

1. INTRODUCTION

Bladder cancer (BC) is a widespread tumor with a higher tendency for recurrence and progression to higher grade and stage.[1] In Egypt; BC is the most prevalent tumor among males, second to breast cancer among females, and it has long been recognized as the leading cause of morbidity among young men with a mortality rate four times higher in Egyptians than Americans.[2] Squamous cell carcinoma (SCC) and transitional cell carcinoma (TCC) are the major pathologic types of BC, with different risk factors for every type, the former has a distinctive epidemiological pattern related to bladder infestation by Schistosoma.[3] The deposition of Schistosomal eggs in the bladder wall causes severe inflammatory reactions, by producing free radicals, leading to genetic mutations and generation of several carcinogenic compounds. The function of the healthy urothelial epithelium is a barrier for toxic materials frustrating them from passage through the wall. During chronic Schistosomal infestation, toxic leakage takes place causing more entry of carcinogenic compounds leading to tissue damage, hematuria, dysuria, anemia and, finally causing BC.[4]

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BC associated with bilharziasis has certain distinct clinicopathologic features that differ from that experienced in the western world (age, sex incidence, and prevailing pathologic type). Bilharzial BC is common in older age >50 years old; with higher male predominance, and SCC is the dominant pathologic type.[5] The infection control efforts exerted by the Egyptian government were intended for snail control, in addition to public awareness. Nevertheless, bilharzial incidence in rural regions had reached 50% by the middle of the twentieth century. The major advance in controlling infection was the discovery of praziquantel, highly effective anthelmintic medicine with negligible toxicity.[2]

In Egypt, the infection rate of Schistosomiasis has declined dramatically in recent decades, with predominance of TCC and reduced incidence of SCC. That implies variables other than Schistosomiasis may be engaged in the shifting pattern of BC as well as the pathogenesis of SCC and TCC in Egypt.[5] Increased smoking, increased exposure to pesticides, heavy metals like arsenic that found in drinking water, occupational toxins, and chemicals like aromatic amines, and the use of artificial sweeteners like saccharin are all established risk factors for BC. These risk factors have primarily been associated with TCC.[6] For more than 70 years, cytological examination of urine sediments has been utilized as diagnostic tool for urological cancers. Urine cytology is a non-invasive approach with great specificity; nevertheless, the claimed sensitivity has been extremely varied. Thus, urine cytology combined with cystoscopy have been recommended.[7,8] The current study aimed to demonstrate the association between BC and clinicopathologic factors as well as to highlight the change that has occurred in the pattern of BC in Egypt over the last years.

2. METHODS

This study was conducted between April 2022 and March 2023 at National Cancer Institute "NCI", Cairo, Egypt.

2.1. Patients' selection

Patients who had urinary symptoms, like hematuria, urine retention and dysuria were intended to undergo cystoscopy if BC was suspected. The present study was approved by ethics committee of Faculty of pharmacy (Girls)- Al-Azhar University, Egypt [Approval number (303)], and was in agreement with the Helsinki Declaration's Ethics. Written informed consent was obtained from all subjects for urine and blood samples. Demographic data and medical history were recorded for each subject.

2.1.1. Study groups

This study included 97 subjects, were classified as follow: a) 52 patients with malignant BC were selected based upon cystoscopy and cytology analysis; b) 20 patients with benign bladder lesions [benign prostatic hyperplasia, cystitis and urinary stones]; c) 25 healthy volunteers were included as a control group.

2.1.2. Inclusion criteria

Confirmed BC that was diagnosed via cystoscopy and cytology.

2.1.3. Exclusion criteria

Patients who had been treated with chemotherapy, or who had another type of cancer within the previous five years were excluded.

2.2. Samples collection

2.2.1. Urine sample

Fresh urine samples (30 ml) were obtained and centrifuged at 3000 xg for 10 minutes and then the urine pellets were collected. A proportion of the pellet was immediately processed for cytologic preparation (3µl of the pellets was placed on a slide, fixed with 95% ethanol, stained with Papanicolaou stain then examined by an expert pathologist).

2.2.2. Blood samples

Blood samples (3ml) were collected from all participants and left to clot, and centrifuged at 4000 xg for 15-20 minutes. The serum was then separated and kept at -20°C until its use in anti-bilharzial antibody detection by Indirect Haemagglutination test (IHA) using Schistosomiasis Fumouze kit, (Fumouze Diagnostics, France).

2.3. Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences Software (SPSS, Version 21, USA). Quantitative data were presented as means ± standard deviation. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normality of the data. Comparisons were carried out using chi-square for comparing categorical variables correlations and one-way ANOVA test to examine the relation between continuous variables. P-value < 0.05 was considered significant. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPP) and accuracy of the urine cytology was assessed based on the following equations: (Sensitivity =TP/ (TP+ FN) X 100, Specificity =TN/ (TN+FP) X100, PPV=TP/ (TP+FP) X 100, NPV=TN/ (TN+FN) X100, Accuracy= (TP+ TN)/ (TP+ TN+ FP+ FN) X100.

3. RESULTS

3.1. Study subject characteristics

The study population's demographic and clinical data are presented in **table I**. In general, there were highly significant differences between investigated groups regarding sex, smoking status, bilharziasis and urine cytology (P<0.01).

3.2. Clinicopathogenic characteristics of the malignant BC patients

Among the malignant BC group, there was male gender predominance, while there was a decrease in the incidence of bilharzial BC, **fig 1**. The pathologic BC types in our study were TCC (86.53%), SCC (11.53%) and columnar (1.92%), **fig 2**. There was no significant difference between bilharzial BC and nonbilharzial BC regarding age, sex and smoking status (p>0.05). While, there was significant difference between bilharzial BC and nonbilharzial BC regarding pathologic types and cytology (p<0.05), **table II**.

3.3. Urine cytology pattern in relation to clinicopathogenic factors

Regarding urine cytology pattern in relation to clinicopathologic factors for bladder cancer group, significant correlations were only detected for bilharziasis and smoking (p<0.05), **table III**. The resulted sensitivity of urine cytology was (51.9%), while specificity was (100%) and the accuracy was (74.2%). Also, PPV was (100%), while NPV was (64.2%).

Table I. Demographic and clinical data of the study groups (n=97).

Clinicopathologic factors	Normal N. (%)	Benign N. (%)	Malignant N. (%)	Statistics
Overall (97)	25(25.77%)	20(20.62%)	52(53.61%)	
Mean age±SD	42.60±10.587	53.60±16.074	62.23±10.013	F =24.354
(range)	(20-57)	(20-80)	(42-81)	P =0.000**
sex:	14 (56%)	16 (80%)	46 (88.46%)	X^2:10.529
Male	11 (44%)	4 (20%)	6 (11.54%)	p = 0.005**
Female				
Smoking:	0 (0%)	6 (30%)	38 (73.07%)	X^2: 38.776
+ve Smoking	25(100%)	14 (70%)	14 (26.92%)	p = 0.000**
-ve Smoking				
Bilharziasis:				
+ve bilharziasis	0 (0%)	1 (5%)	15(28.84%)	X^2: 12.616
-ve bilharziasis	25 (100%)	19 (95%)	37(71.15%)	p = 0.002**
Cytology:				
+ve cytology	0 (0%)	0 (0%)	27(51.92%)	X^2:32.378
-ve cytology	25 (100%)	20 (100%)	25(48.07%)	p: =0.000**

F: One-way ANOVA; X^2: Chi-Square; **p ≤ 0.01: highly significant.

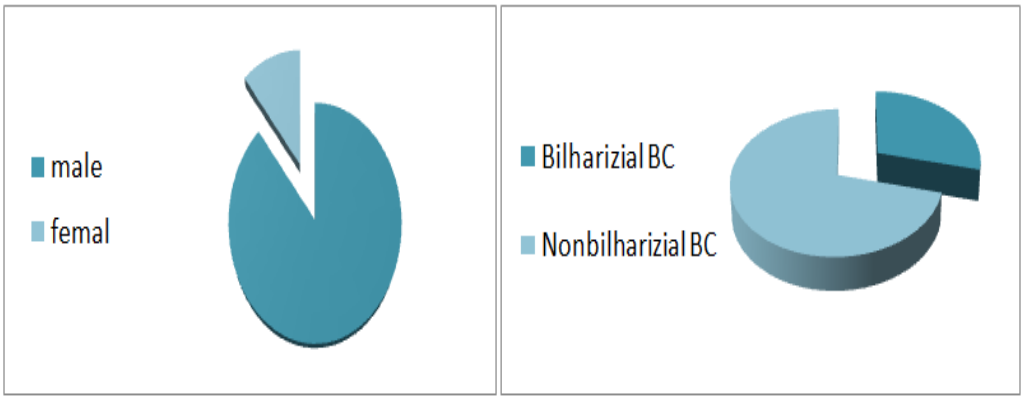

Fig. 1. Pie diagram for sex and bilharzial cases in BC group.

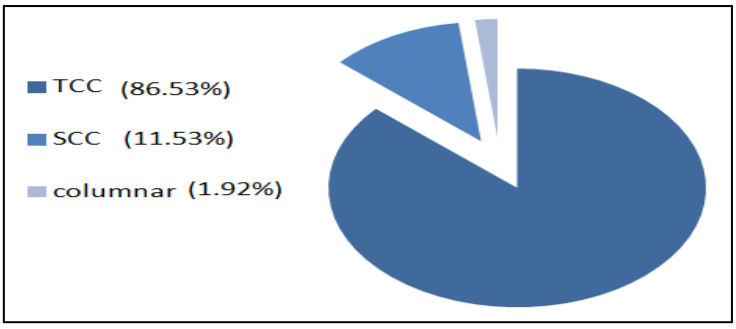

Fig. 2. Histopathologic findings of the cancer group.

Table II. Demographic and clinical characteristics of the study patients with bilharzial or nonbilharzial bladder cancer (n=52).

Clinicopathologic factors (n)	**Bilharzial BC (15)**	**Nonbilharzial BC (37)**	**Statistics χ^2 (P)**
Age: **>55 Y (N=41)** **<55 Y (N=11)**	12 (80%) 3 (20%)	29 (78.38%) 8 (21.62%)	0.017 (0.897)
sex: **Male (N=46)** **Female (N=6)**	14 (93.33%) 1 (6.67%)	32 (86.49%) 5 (13.51%)	0.490 (0.484)
Smoking: **+ve (N=38)** **-ve (N=14)**	11 (73.33%) 4 (26.67%)	27 (72.97%) 10 (27.03%)	0.001 (0.979)
Pathology: **TCC (N=45)** **SCC (N=6)** **columnar (N=1)**	10 (66.67%) 4 (26.67%) 1 (6.66%)	35 (94.59%) 2 (5.41%) 0 (0.00%)	7.610 (0.022)*
Cytology: **+ve (N=27)** **-ve (N=25)**	11 (73.33%) 4 (26.67%)	16 (43.24%) 21 (56.76%)	3.871 (0.049)*

Abbreviations: SCC "squamous cell carcinoma"; TCC, "transitional cell carcinoma".
*Significant difference was found between the study groups at P < 0.05 using "chi-square test"

Table III. Urine cytology pattern in relation to clinicopathologic factors in bladder cancer group (n =52).

Clinicopathologic factors (n)	**Urine cytology**		**Statistics**
	+ve (27)	**-ve (25)**	
Age: **>55 Yr (41)** **<55 Yr (11)**	21(77.78%) 6(22.22%)	20(80%) 5(20%)	X^2: 0.038 p = 0.845
sex: **Male** (46) **Female** (6)	26(96.30%) 1(3.70%)	20 (80%) 5(20%)	X^2: 3.377 p = 0.066
Smoking: **-ve Smoking** (14) **+ve Smoking** (38)	4(14.81%) 23(85.19%)	10(40%) 15(60%)	X^2: 4.185 p = 0.041*
Bilharziasis: **-ve bilharziasis** (37) **+ve bilharziasis** (15)	16(59.26%) 11(40.74%)	21(84%) 4(16%)	X^2: 3.871 p = 0.049*
Pathology: **TCC** (45) **SCC** (6) **Columnar** (1)	24(88.89%) 2(7.41%) 1(3.07%)	21(84%) 4(16%) 0(0%)	X^2: 1.792 p = 0.408

*p < 0.05: significant difference.

4. DISCUSSION

Based on the reported cancer incidence rates from the World Bank in 2018, the incidence of BC in Egypt was (11.9/100,000), compared to (37/100,000) in 2002, owing to reduction in the prevalence of schistosomal infestation that was accomplished as early as 2006.[9] The current study included 97 subjects, they were stratified into 3 groups; healthy group (n=25), benign group (20) and malignant BC group (52). As regards the age, the mean age of the malignant group was 62.23± 10.013 years versus 53.60 ± 16.074 years for the benign group. These findings are consistent with previously reported results in that the incidence of BC increases with age that could be attributed to chronic inflammatory process preceding the cancer.[10]

The chance of a man developing BC at any time during his life is about 9.6 in 100,000 and for a woman is 2.4 in 100,000 worldwide.[11] The majority of malignant cases in our study were males (88.5%) with a male:female ratio as high as 8:1, that confirms the predominance of BC in males. These results come in agreement with previous studies about the prevalence of BC and several molecular studies supposed a role of loss of Y-chromosome in the development of BC.[12, 13] Moreover, recent study demonstrated that transitional cell oncogenesis in bladder tissues is affected by sex hormones causing males and females metabolize a carcinogen in a different way.[14] A study demonstrates that certain androgenic hormones have the opposite effect of estrogenic hormones in bladder tissue, either stimulating or not inhibiting oncogenesis, thus, male gender is a risk for BC.[15]

As regards the pathologic types of cancer in this study, 6 cases were SCC, constituted (11.53%), while 45 cases were TCC, constituted (86.53%) of the cases. This study included (15) cases bilharzial BC and (37) cases nonbilharzial BC, and the positivity rate of bilharziasis was higher in SCC (66.67%) when compared to TCC (22.22%). This agree with previous studies that bilharzial BC is usually SCC and thus, Schistosomiasis remains a major cause of tumorogenesis; due to elevated B-cell lymphoma (BCL-2) protein expression level causing urothelium cells to divide more quickly and die less frequently.[2, 16-18] However, SCC constituted only (26.67%) of bilharzial BC cases, this is due to decreased incidence of SCC (6/52) compared to TCC (45/52). This could be attributed to the successful control of Schistosomiasis, and also confirms the shift that occurs in the pattern of BC in Egypt over the last years. [4, 16-18] Considering the relation between bilharziasis and BC, in the present study, there was a highly significant association between bilharziasis and BC group compared to non-malignant groups (benign and healthy controls), ($p<0.01$). With regard to bilharzial and nonbilharzial BC, no significant difference was found between them regarding to clinicopathologic factors except for pathologic types and cytology, ($p<0.05$).

The most well-established risk factor for BC is cigarette smoking.[19] In cope, the present study showed that the incidence of BC was 2.7 times greater in smokers (73.07%) than non-smokers (26.92%). Similarly; ***kim et al. (2023)*** reported that smokers are more susceptible for BC than non-smokers.[20] Tobacco smoking is very rich in carcinogenic compounds like aromatic amines and N-nitroso compounds, result in DNA damage.[21] Considering the relation between bilharziasis and BC, in the present study, there was a highly significant association between bilharziasis and BC group compared to non malignant groups (benign and healthy controls), ($p<0.01$). With regard to bilharzial and nonbilharzial BC, no significant difference was found between them regarding to clinicopathologic factors except for pathologic types and cytology, ($p<0.05$).

Within the bilharzial BC group, significant difference was found between males and females (93.33% vs 6.67%), smokers and non-smokers (73.33% vs 26.67%), TCC and SCC (66.67% vs 26.67%), and with regard to cytology (93.33% vs 6.67%), respectively. While, for the nonbilharzial BC group, significant difference was found between males and females (86.49% vs 13.51%), smokers and non-smokers (72.97% vs 27.03%), and with regard to TCC and SCC (94.59% vs 5.41%), respectively, ($p<0.05$).

Urine cytology is the most commonly used simple, convenient and inexpensive diagnostic method, it remains the gold standard non-invasive in vitro method for diagnosis of BC and detection of morphologic abnormalities of the cells in the voided urine long before tumour is visible by cystoscopic examination or histological techniques.[22] In this study, the sensitivity of urine cytology was (51.9%), thus, the development of laboratory techniques or searching for urinary biomarkers that could detect bladder cancer with high sensitivity is recommended.

5. CONCLUSIONS

BC is more common in males than females and in smokers than non-smokers. TCC is the commonest pathologic type in the current study, this change in the pattern of BC from SCC to TCC ensures good control of Schistosomiasis in Egypt.

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Conflicts of Interest: All authors declare no competing interests.

Ethical Statement: This research study was conducted in compliance with the ethical guidelines and policies established by the National Cancer Institute's Ethics Committee, Cairo University, Cairo "Fom El Khalig Square", (No. 2306-303-068) and approved from Ethics Committee, Faculty of Pharmacy (girls), Al-azhar University, (approval no. 303). An informed consent was obtained from all participants.

Authors Contribution: All authors contributed to all aspects of the work.

List of Abbreviations: BC; Bladder Cancer, SCC; Squamous Cell Carcinoma, TCC; Transitional Cell Carcinoma, IHA; Indirect Haemagglutination test, PPV; Positive Predictive Value, NPV; Negative Predictive Value.

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