Urinary Schistosomasis – Associated Bladder Cancer in Yemen Single Center Pathologic Review

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ABSTRACT

To study the frequency of schistosomiasis in pathologic urogenital tract specimens among Yemeni patients. This is a descriptive, retrospective study in which 24456 pathologic records of 547 patients, who underwent urinary bladder biopsies from bladder tumors or suspicious lesions discovered incidentally during endoscopic evaluation and those who ultimately had radical cystectomy and urinary diversion for invasive bladder cancer, were reviewed in Section of Histopathology, Department of Pathology, University Sana'a in Sana'a, Yemen between January 2005 and September 2009. The total number of specimens dealt with in this study was 547 patients with a mean age of 54.04±17.1 years. Pathologic review showed schistosomiasis in 99 (18%) patients of whom schistosoma associated bladder cancer was reported in 39 (39%) patients and schistosomiasis with no pathologic evidence of malignancy in 60 (61%) patients. The cell type of schistosoma associated bladder cancer was transitional cell carcinoma (TCC) in 6 (15%), squamous cell carcinoma (SCC) in 28 (72%), Verrucous carcinoma in 2 (5%), urothelial with squamous differentiated cancer in 2 (5%) and infiltrative adenocarcinoma of the prostate in 1 (3%) patients. Out of 547 patients with no pathologic evidence of schistosomiasis, 308 were reported to have non schistosoma associated bladder cancer. The cancer cell type was TCC in 243 (79%), SCC in 43 (14%), adenocarcinoma in 8 (3%), small cell cancer 1 (0.31%), rhabedmyosarcoma in 3 (1%) and suspect of cancer in 10 (3%) patients. Schistosoma associated bladder cancer is still a problem in Yemen as well as other endemic countries. Although the major histological cell type of such cancer in Yemen was SCC, while the TCC is the most common type of cancer among patients in non schistosomiasis.

Keywords: *Schistosomiasis, urinary tract, bladder cancer, cystoscopy specimen*

INTRODUCTION

Schistosomiasis is a parasitic disease caused by blood flukes (trematodes) of the genus schistosoma. It is the third most common parasitic infection of humans after malaria and intestinal helminthiasis [(1)]. More than 207 million people are infected globally in 76 countries and about 700 million people are at risk for infection in tropical and subtropical regions of Africa, Asia, South America and the Caribbean. Approximately; 85% of the infected people live in 42 African countries[(1-3)]. The international agency for research on cancer (IARC) considers S. haematobium infection a definitive cause of urinary bladder cancer with an associated 5-fold risk [(4)]. This conclusion is based on ecological studies reporting strong positive correlation, case reports and several case control studies [(6)]. Bladder cancer associated with S. haematobium is histologically and pathologically distinct from non S. haematobium associated bladder cancer occurring in North America and Europe, the former being a squamous cell carcinoma (SCC), with an earlier age of onset and generally sparing the trigone of bladder while the latter is of transitional cell type occurring in the older age group [(5,6)].

In Middle East countries schistosomiasis is endemic including Yemen [(1-3)]. S. haematobium cystitis appears to be causally related to the development of bladder cancer often SCC [(4)]. Bladder carcinogenesis is probably related to bacterial and viral infections, commonly associated with bilharzial infestation, rather than the parasite itself [(5)]. In this study evaluation of the frequency of schistosomiasis in pathologic urinary bladder specimens and the contribution of transitional cell and squamous cell types to the schistosoma associated and non schistosoma associated bladder cancer among Yemeni patients was carried out.

MATERIALS AND METHODS

This was a retrospective study confined to biopsy specimens received from different hospitals in Sana'a at one histopathology center in Sana'a the capital city of Republic Yemen between January 2005 and September 2009. Out of the total collected cases (24.456) 547 patients underwent procedures of urinary bladder biopsies from bladder tumors or suspicious lesions discovered incidentally during endoscopic evaluation of urinary bladder wall. The biopsies were taken either by cold–cup forceps or transurethral resection using electrocautery loop under spinal or general anesthesia using rigid cystoscopy. The review of pathologic records included the 545 urinary bladder biopsies and the 2 specimens of radical cystectomy giving a total of 547 revised pathologic records. Clinical notes and personal data were obtained from the histopathological reports of the patients.

All samples were from formalin – fixed, paraffin–embedded archival specimens. Representative 5 μm H and E–stained sections were reviewed by the same consultant pathologists in the center. Schistosomiasis infection was confirmed histopathologically by the presence of schistosoma – ova in every case. Since focal squamous cell changes are common in high grade transitional cell carcinoma (TCC), the term SCC in this study was reserved for those tumors that are squamous throughout [(8)]. The inclusion criteria involved patients in whom pathologic records showed bladder cancer, schistosomiasis or both.

Statistical analysis: Data were analyzed using mean ± standard deviation (SD), frequency and percentage. All data was recorded and analyzed using commercially available SPSS 16.0 software package. Fisher exact and chi square tests were used to calculate p-values for different variables. P-value equal to or less than 0.05 was considered significant.

RESULTS

In this study 547 patients with mean age of 54.04±17.1 years underwent procedures of urinary bladder biopsies.

Of the total 547 patients, pathologic evaluation showed schistosomiasis in 99 (18%) patients. Male to female ratio was 5.6:1 (84 males and 15 females) with a mean age of 45.12± 18.85 years. Schistosoma associated bladder cancer was reported in 39 (39%) patients while 60 (61%) patients had schistosoma infection with no pathologic evidence of malignancy.

The cell type of schistosoma associated bladder cancer was transitional cell carcinoma (TCC) in 6 (15%), squamous cell carcinoma (SCC) in 28 (72%), Verrucous carcinoma in 2 (5%), urothelial with squamous differentiated cancer in 2 (5%) and adenocarcinoma in 1 (3%) patients (Table 1).

Table 1: Evaluation of the Histopathological diagnoses of the 99 cases of genitourinary chistosomaisis.

	N	*Percent %*	*Male*	*Female*	*Average age(Year)*	*Clinical*
No evidence of malignancy						
BPH	3	3%	3	0	55.53	LUTS
Cystitis	51	52%	45	6	38.37	Haematuria
F. of Spermatogense	1	1%	1	0	20	Infertility
Polyp	3	3%	2	1	30.67	Haematuria
Ureteritis	2	2%	1	1	13.5	UUTS
Malignancy						
SCC	28	28%	21	7	55.1	Haematuria
Urothelial and SCC	2	2%	2	0	60	Haematuria
TCC	6	6%	6	0	63.5	Haematuria
PCa	1	1%	1		65	LUTS
Verrucous cancer	2	2%	2	0	48	Haematuria
Total	99	100%	84	15	45.12±18.85	

F.: Failure, TCC: transitional cell carcinoma , SCC: squamous cell carcinoma, PCa: prostatadenocarcinoma, BPH: benign prostate hyperplasia, LUTS: lower urinary tract obstruction UUTS: upper urinary tract obstruction

The criteria of schistosoma associated bladder cancer patients are presented in table 2. The correlation of S. hammatobium eggs and urinay bladder cancer appear to frequently coexist in the same individual, and the bladder tumors are of squamous cell origin, rather than transitional cell carcinomas.

Table 2: Criteria of schistosoma associated bladder cancer patients

Pathologic analysis	***n (%)***
Carcinoma cell type	
Squamous cell carcinoma	28 (72%)
Tumor grade	
Grade 1 (Well differentiated)	18 (64%)
Grade 2 (Moderately differentiated)	7 (25%)
Grade 3 (Poorly differentiated)	3 (11%)
Transitional cell carcinoma	6 (15%)
Tumor grade	
Grade 1 (Well differentiated)	1 (14%)
Grade 2 (Moderately differentiated)	0
Grade 3 (Poorly differentiated)	5 (86%)
Urothelial with squamous cell cancer	2 (5.5%)
Adenocarcinoma	1 (3%)
Verrucous cancer	2 (5.5%)

Bilharzial cystitis lesions included mostly bladder polyps, bladder wall thickening, and irregularities. Bladder calcification, suggested to be the most characteristic lesion of S. haematobium infection and an important risk factor for urinary bladder cancer with association to squamous cell metplasia (Figure 1).

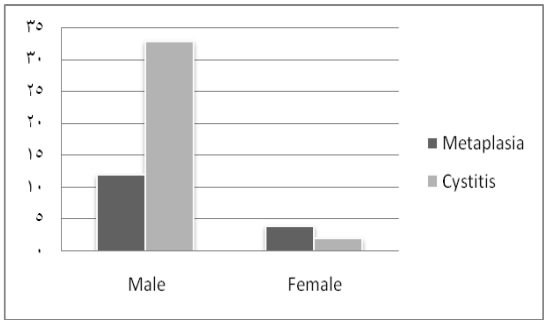

Figure 1: Gender and cases of Cystitis with and without cell metaplasia (n=51).

Of the total 51 cases of schistosoma-cystitis showed 16 cases (31%) squamous cell metplasia.

Histopathologic analysis of the urinary bladder specimens did not show schistosomiasis in 448 (82%) patients, out of which 308 were reported to have urinary bladder cancer (non schistosoma associated bladder cancer). The cancer cell type was TCC in 243 (79%), SCC in 43 (14%), adenocarcinoma in 8 (3%), small cell cancer 1 (0.31%), rhabedmyosarcoma in 3 (1%) and suspect of cancer in 10 (3%) patients. The criteria of such cancer are shown in table 3.

Table 3: Criteria of non schistosoma associated bladder cancer patients (n = 308)

Pathologic analysis	**n (%)**
Carcinoma cell type	
Transitional cell carcinoma	243 (79%)
Tumor grade	
Grade 1 (Well differentiated)	35 (14%)
Grade 2 (Moderately differentiated)	112 (46%)
Grade 3 (Poorly differentiated)	96 (40%)
Squamous cell carcinoma	43 (14%)
Tumor grade	
Grade 1 (Well differentiated)	25 (58%)
Grade 2 (Moderately differentiated)	13 (30%)
Grade 3 (Poorly differentiated)	5 (12%)
Adenocarcinoma	
	8 (2.69%)
Adenocarcinoma	1 (0.31%)
Small cell cancer	3 (1%)
Rhabedomyosarcoma	10 (3%)
Suspect cancer	

From the total number of urinary bladder cancer in this study which is 347 patients, schistosoma associated bladder cancer was reported in 39 (11 %) patients. The statistical association between the cell type of urinary bladder cancer and schistosomiasis in this study is not significant between TCC and not having urinary schistosomiasis. In other words there is no direct statistical relation between TCC in particular and the existence of schistosoma infection. There may be other factors which contribute to bladder carcinogenesis and affect the cancer cell type in patients with schistosomiasis such as intensity of infection, immunological status, smoking, dietary habits, and other possible environmental factors. Table 4 illustrates this statistical association.

Table 4: Statistical relation of schistosomiasis and cancer cell type

Squamous cell carcinoma n= 71	*Transitional cell carcinoma n= 249*	*Bladder cancer*	*P=value*
28 (9.5)	6 (26.5)	Schistosoma	➢ 0.05*
43 (63.5)	243 (222.5)	No schistosoma –	

*, this association cannot be validated

DISCUSSION

Urinary schistosomiasis is characterized by haematuria as a classical sign. It is associated with bladder and uretral fibrosis, sandy patches in the bladder mucosa and hydronephrosis that are commonly seen in chronic cases while bladder cancer is possible as late stage complication [(8)]. Among the Middle East countries, Yemen has the highest percentage of people living in poverty where more than 50% of the population of nearly 25 million people lives below the poverty line [(9)]. The country has been unstable for several years, suffering from civil wars, a deteriorated economy and severe depletion in water resources.

A higher prevalence of schistosomiasis (58.9%) was reported among children from Khamir district and Amran province [(10)]. A significant reduction in the prevalence rates of schistosomiasis have been reported after 4 campaigns were implemented during 2002–2007 using school based drug distribution and focal molluscicide [(10)]. Subsequently, the prevalence rate increased again and prevalence rates of 30%–60% have been reported from different areas in 2003–2010 [(11)]. Nowadays, both urinary and intestinal schistosomiasis are endemic in all provinces of Yemen with an estimated overall prevalence of 14%–49% [(12,13)]. The prevalence of S. haematobium was highest in Taiz and Sana'a followed by Hodiedah (36.0%, 36.0% and 33.3%, respectively). In Egypt urinary Bladder cancer was the commonest of all cancers in men and more than twice as common as lung cancer [(14)]. This substantial excess has been generally attributed to a high prevalence of Schistosoma haematobium infestation (urinary schistosomiasis). A significant decline in the relative frequency of bladder cancer (from 27.6% to 11.7%) was observed in the past 37 years and a decline in the frequency of bilharzia egg positivity in specimens and infestation severity is most probably the result of better control of bilharziasis in Egypt following the use of oral antibilharzial drugs.[(15)]. An association between bladder cancer, particularly squamous cell cancer [(16)], and infection with S. haematobium has long been suggested by clinical observations as well as by analytical and descriptive epidemiology. The relation has been explained through chronic irritation of the urothelium, altered metabolism with elevated urinary levels of carcinogenic metabolites and N-nitroso compounds and/or elevated urinary levels of glucuronidase [(17-19)].

The risk estimates of bladder cancer in studies conducted in various parts of Africa are compatible with a relative risk between 2 and 10 in patients with a history of schistosomiasis [(20)]. Bladder cancer in the setting of S. haematobium has an early onset (40 to 50 years) and a high frequency of squamous cell carcinomas (60% to 90%), with 5% to 15% adenocarcinomas[(14,16,21,22)].

In this study pathologic evidence of urinary schistosomiasis was shown in 99 (18%) patients. However, the true frequency of such infection among Yemeni patients may be higher than the estimated figure depending on specific factors such as the biopsy site, number of biopsies taken, and the intensity of infection. Besides, there may be other patients in the Yemeni society with urinary schistosomiasis who did not have the opportunity for urinary bladder biopsy due to ignored lower urinary tract symptoms or inadequate referral to urology departments in major hospitals. In other neighboring endemic countries in the middle East such as Saudi Arabia, Iraq, Iran, kuwait and Syria due to either mix or S hamatobium infestation bladder cancer was reported to be the leading cancer [(26)]. For example in Saudi Arabia the schistosomiasis comprises 35% (88) out of 254 consecutive urinary bladder biopsies [(23)]. In Iraq the major cell type according to Baghdad Cancer Registry for the period 1976-1982 was SCC and the occurrence of this type was associated with histological evidence of infection with S. haematobium [(28)]. In developed

countries, TCC is the predominant type of bladder cancer, whereas in schistosomiasis endemic regions, SCC is the most common type [(24)]. Conversely, there is also an increased incidence of TCCs in males with schistosomiasis [(25)].

The findings of this study suggest that there is a high prevalence of infection with S. haematobium among males as compared to females.

In Yemen carcinoma of the bladder is the fifth most common tumor [(27)]. In this study the frequency of TCC among Yemeni patients with bladder cancer was the most common bladder cancer accounting for (79%), followed by SCC (14%) and adenocarcinoma (3%) of non schistosoma associated bladder cancer. The extent of schistosoma infection apparently plays a significant role in the induction of different types of carcinoma, in comparison to SCC which contributed to 72% of schistosoma associated and 14% of non schistosoma associated bladder cancer, since SCC is usually associated with moderate or high worm burdens while TCC occurs more frequently in areas associated with lower degrees of infection [(29,30)].

The association between S. haematobium infection and squamous-cell carcinoma of the urinary bladder has been the subject of debate for a long time. Co-existence of squamous-cell or adenocarcinoma of the urinary bladder, prostate gland and eggs of S. haematobium has been observed in hospitalized cases [(31-33)]. The predominance of SCC in schistosoma associated bladder cancer series is probably related to squamous metaplasia and dysplasia which are relatively common in chronic schistosomal cystitis [(34)].

There is need to follow up patients discovered to have schistosomiasis with no evidence of bladder cancer trying to detect schistosoma associated urinary bladder cancer as early as possible, since 31% of the cases with schistosoma-cystitis have had a squamous cell metaplasia.

Schistosoma associated urinary bladder cancer is a preventable disease if the strategy adopted in Egypt (Education, snail control and mass therapy of the exposed population) is successfully adopted in Yemen and for non schistosoma associated bladder cancer a new strategy is needed for smoking limiting which is not available in Yemen to prevent the increased TCC prevalence.

CONCLUSION

Schistosoma associated bladder cancer is still a problem in Yemen as well as other endemic countries. Although the major histological cell type of such cancer in Yemen was SCC, while TCC is the most common type of cancer among patients in non schistosomiasis.

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