Schistosoma – Associated Bladder Cancer in Iraq Single Center Pathologic Review

Ausama Saadi Abdul Muhsin

ABSTRACT:

OBJECTIVE:

To study 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 Iraqi patients.

METHODS:

This is a retrospective study in which 1092 pathologic records of 933 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 Surgical Specialties Hospital, Baghdad, Iraq between June 2000 and June 2007.

RESULTS:

In this study 933 patients aged 2-100 years with a mean age of 56.87±14.3 years. Pathologic review showed schistosomiasis in 81 (8.68%) patients of whom schistosoma associated bladder cancer was reported in 49 (60.5%) patients and schistosomiasis with no pathologic evidence of malignancy in 32 (39.5%) patients. The cell type of schistosoma associated bladder cancer was transitional cell carcinoma (TCC) in 26 (53%), squamous cell carcinoma (SCC) in 19 (38.7%), adenocarcinoma in 1 (2%), and undifferentiated in 3 (6.12%) patients. Out of 852 patients with no pathologic evidence of schistosomiasis, 563 were reported to have non schistosoma associated bladder cancer. The cancer cell type was TCC in 491 (87.21%), SCC in 45 (7.99%), adenocarcinoma in 15 (2.66%), undifferentiated in 11 (1.95%) and sarcoma in 1 (0.18%) patients.

CONCLUSION:

Schistosoma associated bladder cancer is still a problem in Iraq as well as other endemic countries. Although the major histological cell type of such cancer in Iraq was SCC, there is a trend for increasing frequency of TCC among patients infected with schistosomiasis.

KEYWORDS: schistosomiasis, bladder cancer, cystoscopy specimen

INTRODUCTION:

Schistosomiasis is endemic in Middle East countries including Iraq [1,2,3]. Schistosoma haematobium cystitis appears to be causally related to the development of bladder cancer often squamous cell carcinoma (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 Iraqi patients was carried out.

Department of Urology in Surgical Specialties Hospital / Baghdad – Iraq.

MATERIALS AND METHODS:

In this retrospective study 933 patients underwent 1047 procedures of urinary bladder biopsies from bladder tumors or suspicious lesions discovered incidentally during endoscopic evaluation of urinary bladder wall for other benign conditions in Surgical Specialties Hospital, Baghdad, Iraq between June 2000 and June 2007. This hospital receives patients from almost all the provinces in Iraq. The biopsies were taken either by cold – cup forceps or transurethral resection using electrocautery loop under general or spinal anesthesia using rigid cystoscopy. Forty five patients with bladder cancer out of 933 eventually underwent radical cystectomy and urinary diversion for invasive bladder cancer during the same period. The review of pathologic records included the 1047 urinary bladder biopsies and the 45 specimens of radical cystectomy giving a total of 1092 revised pathologic records. Different

surgeons in the center performed the endoscopic procedures and radical cystectomy with urinary diversion. All samples were from formalin – fixed, paraffin – embedded archival specimens. Representative 5 µm H and E – stained sections were reviewed by different pathologists in the center. The histological grade was determined according to the 1973 World Health Organization grading system [6] and tumor stage according to the tumor, node, metastases (TNM) system [7]. 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. Patients with other pathologic records as well as those with mixed tumors were excluded from the study. The choice of endoscopic bladder biopsy, transurethral resection or radical cystectomy and urinary diversion for every patient in this study followed the ethical guidelines that ensured the optimum outcome.

Statistical analysis: Data were analyzed using mean ± standard deviation (SD), frequency and percentage. The software used in this paper was the Microsoft office Excel 2003. Chi – square and Fisher's exact tests were used for statistical analysis. P value < 0.05 was considered statistically significant.

RESULTS:

In this study 933 patients aged 2-100 years with a mean age of 56.87±14.3 years. Forty five patients with bladder cancer out of 933 eventually underwent radical cystectomy and urinary diversion for invasive bladder cancer during the same period. There were 667
(71.49 %) males and 266 (28.51%) females.

Schistosomiasis. Of the total 933 patients, pathologic evaluation showed schistosomiasis in 81 (8.68%) patients. Male to female ratio was 1.79:1 (52 males and 29 females) with a mean age of 57.77± 12.53 years. Schistosoma associated bladder cancer was reported in 49 (60.5%) patients while 32 (39.5%) patients had schistosoma infection with no pathologic evidence of malignancy. The criteria of schistosoma associated bladder cancer patients are presented in table (1).

No schistosoma infection. Pathologic analysis did not show schistosomiasis in 852 (91.32%) patients, out of whom 563 were reported to have bladder cancer (non schistosoma associated bladder cancer). The criteria of such cancer are shown in table (2).

From the total number of bladder cancer in this study which is 612 patients, schistosoma associated bladder cancer was reported in 49 (8 %) patients. The statistical association between the cell type of bladder cancer and schistosomiasis in this study is significant between TCC and not having urinary schistosomiasis. Table (3) illustrates this statistical association.

DISCUSSION:

In this study pathologic evidence of urinary schistosomiasis was shown in 81 (8.68%) patients. However, the true frequency of such infection among Iraqi patients may be higher than the estimated figure depending on certain factors such as the biopsy site, number of biopsies taken, and the intensity of infection. Besides, there may be other patients in the Iraqi society with urinary schistosomiasis who did not have the opportunity for urinary bladder biopsy due to neglected lower urinary tract symptoms or inadequate referral to urology departments in major hospitals. In other neighboring endemic countries such as Saudi Arabia schistosomiasis was reported in 88 (35%) out of 254 consecutive urinary bladder biopsies [9].

In developed countries, TCC is the predominant type of bladder cancer, whereas in schistosomiasis - endemic regions, SCC is the most common type [10]. However, there is also an increased incidence of TCCs in males with schistosomiasis [4] . Indeed there is a recent trend towards a relative increase in the frequency of the transitional cell type in schistosomiasis – associated bladder cancer [11].

In Iraq carcinoma of the bladder is the third most common tumor [12]. 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 Schistosoma haematobium [1]. Later on the frequency of TCC among Iraqi patients with bladder cancer increased, TCC constituted the main histological type (56%), followed by SCC (28%), undifferentiated carcinoma (5.3%), and adenocarcinoma (3.1%) (Iraqi Cancer Registry 1996) [13].

In this study TCC was the most common bladder cancer accounting for 53% of schistosoma associated and 87.21% of non schistosoma associated bladder cancer, in comparison to SCC which contributed to 38.7% of schistosoma associated and 7.99% of non schistosoma associated bladder cancer. This may be due to less severe schistosoma infection among Iraqi patients and early treatment [14]. The extent of schistosoma

infection apparently plays a significant role in the induction of different types of carcinoma, since SCC is usually associated with moderate or high worm burdens whereas TCC occurs more commonly in areas associated with lower degrees of infection [15]. The statistical association between the cell type of bladder cancer and schistosomiasis in this study as shown in table (3) was significant, with a relative risk (RR) of 0.63 ($0.49 < RR < 0.81$) in favor that patients without schistosomiasis are more prone to have TCC. In other words there is no direct statistical relation between TCC in particular and the presence 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, smoking, immunological status, dietary habits, and other possible environmental factors.

In this study the frequency of schistosomiasis was not compared to the age, gender, smoking, history of previous medical therapy for schistosomiasis and geographical distribution of patients which is helpful to demonstrate the map of current endemic provinces in Iraq. Besides, staging of bladder cancer was not demonstrated in this study as this needs recruitment of clinical, radiological and pathologic assessment of patients. Finally there are several questions which need answers such as; is it necessary to follow up patients discovered to have schistosomiasis with no evidence of bladder cancer, trying to detect schistosoma associated bladder cancer as early as possible? If yes how frequent, and for which group of patients with schistosomiasis for example the clinically symptomatic, those who did not receive medical treatment for schistosomiasis, ..etc? Is there any duration of such follow up to be recommended? A standard strategy based on well defined guidelines and considering the local experience of endemic countries supported by double blind controlled studies recruiting large number of patients may give the answers for such questions.

CONCLUSION:

Schistosoma associated bladder cancer is still a problem in Iraq as well as other endemic countries. Although the major histological cell type of such cancer in Iraq was SCC, there is a trend for increasing frequency of TCC among patients infected with schistosomiasis.

Table 1 – Criteria of schistosoma – associated bladder cancer patients (n= 49)

Pathologic analysis	n (%)
Carcinoma cell type	
TCC	26 (53%)
SCC	19 (38.7%)
Adenocarcinoma	1 (2%)
Undifferentiated	3 (6.12%)
Tumor grade	
Grade 1 (Well differentiated)	3 (6.12%)
Grade 2 (Moderately differentiated)	17 (34.69%)
Grade 3 (Poorly differentiated)	29 (59.18%)
TCC: transitional cell carcinoma , SCC: squamous cell carcinoma	

Table 2 – Criteria of non schistosoma – associated bladder cancer patients (n = 563)

Pathologic analysis	n (%)
Carcinoma cell type	
TCC	491 (87.21%)
SCC	45 (7.99%)
Adenocarcinoma	15 (2.66%)
Undifferentiated	11 (1.95%)
Sarcoma	1 (0.18%)
Tumor grade	
Grade 1 (Well differentiated)	73 (12.97%)
Grade 2 (Moderately differentiated)	263 (46.71%)
Grade 3 (Poorly differentiated)	227 (40.32%)
TCC: transitional cell carcinoma , SCC: squamous cell carcinoma	

Table 3 - Statistical relation of schistosomiasis and cancer cell type

Bladder cancer	TCC n= 517	SCC n= 64
Schistosoma – associated	26	19
Non schistosoma – associated	491	45

TCC: transitional cell carcinoma , SCC: squamous cell carcinoma
$X^2 = 48.46$, P= 0.00001

REFERENCES:

1. Al-Fouadi A, Parkin DM. Cancer in Iraq: seven years' data from the Baghdad Tumour Registry. Int J Cancer. 1984; 34,207-13.
2. Marina I Gutiérrez, Abdul K Siraj, Hussein Khaled, Natalie Koon, Wa'el El-Rifai, Kishor Bhatia. CpG island methylation in Schistosoma- and non-Schistosoma-associated bladder cancer. Modern Pathology. 2004; 17,1268–1274.
3. Russell RCG, Williams NS, and Bulstrode CJK. Bailey and Love's Short Practice of Surgery. 24th Ed. London: Arnold Company; 2004,155
4. Edward M. Messing. Urothalial Tumors of the Bladder. In: Alan J. Wein, Louis R. Kavoussi, Andrew C. Novick, Alan W. Partin, and Craig A. Peters. Campbell – Walsh Urology. 9th Ed. Philadelphia (PA): WB Saunders and Elsevier Company; 2007,2415.
5. A.A. Shokeir. Squamous cell carcinoma of the bladder: pathology, diagnosis and treatment. **BJU Int.** 2004 ; 93,216-20.
6. Mostofi FK, Sobin LH, Torloni H. Histological typing of urinary bladder tumors. International Histological Classification of Tumors No. 10. Geneva: World Health Organization; 1973.
7. Sobin LH, Wittekind CH. Urinary bladder, editors. UICC International Union Against Cancer. In: TNM Classification of Malignant Tumors. 6th ed. New York: Wiley-Liss; 2002,196-198.
8. Nelson G. Ordóňez, Juan Rosai. Urinary tract. In: Rosai and Ackerman's Surgical Pathology. 9th Ed.Vol. 1. Philadelphia: Mosby; 2004,1340.
9. Khurana P, Morad N, Khan AR, Shetty S, Ibrahim A, Patil K. Impact of schistosomiasis on urinary bladder cancer in the southern province of Saudi Arabia: review of 60 cases. J Trop Med Hyg. 1992; 95,149- 51.
10. Michaud DS. Chronic inflammation and bladder cancer. **Urol Oncol.** 2007; 25, 260-268.
11. Thanaa El A Helal, Mona T Fadel, Naglaa K EL-Sayed. Human Papilloma Virus and p53 Expression in Bladder Cancer in Egypt: Relationship to Schistosomiasis and Clinicopathologic Factors. Pathology Oncology Research. 2006; 12, 173 – 178.
12. Al-Nasri U. S. The changing pattern of bladder tumors, is there an environmental risk factor?. Iraqi Postgraduate Medical Journal. 2005; 4, 311 – 318.
13. Results of Iraqi Cancer Registry. Iraq Cancer Board, Iraqi Cancer Registry, Institute of Radiology and Nuclear medicine, Baghdad, Iraq 1996.
14. Rifat Usama Nihad. The prognostic importance of previously treated bilharziasis stage T1 transitional cell carcinoma of the bladder. J. Fac. Med. Baghdad. 1993; 35, 521-525
15. M. H. Mostafa, S. A. Sheweita, P. J. O'Connor**.** Relationship between Schistosomiasis and Bladder Cancer. Clinical Microbiology Reviews. 1999; 12, 97-111.