Original article

Pattern and Risk Factors of Urinary Bladder Neoplasms in Sudanese patients in Khartoum State, Sudan

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Abstract

Background: Urinary bladder neoplasm (UBN) is associated with high morbidity and mortality rate. It poses biologic and clinical challenges.

Objectives: To evaluate the pattern as regards frequency, age, sex, occupation, local geographical distribution, clinical presentations and risk factors of UBN in Sudanese patients in Khartoum State.

Patients and Methods: This study was conducted in the period from January 2004 through December 2005 at three centres in Khartoum State. One hundred and six patients with urinary bladder neoplasms were included in the study.

Results: The commonest affected age group was 60-80 years with male to female ratio 4.6:1. Urinary bladder neoplasms have some ethno-geographic variations in Sudan. The majority of these patients were from the Northern and Western regions.

Conclusion: There is significant relationship between urinary schistosomal infestation and the development of squamous cell carcinoma of the urinary bladder among Sudanese patients.

Key words: Urinary Bladder, Transitional Cell Carcinoma, Squamous Cell Carcinoma.

Neoplasms of the bladder pose biologic and clinical challenges. Although there are improvements in detection and management of urinary bladder neoplasms (UBN), the death toll remains high.

Recent research[1] indicate that carcinoma of the bladder is more common in males than females, in the industrialized than in third world, and in urban than in rural dwellers. About 80% of patients are in the age group 50-80 years[1].

A number of factors have been implicated in the aetiology of UBN such as, industrial exposure, cigarette smoking and long-term use of analgesics in cases of Transitional Cell Carcinoma (TCC) and a past history of *Schistosoma haematobium* infection in cases of Squamous Cell Carcinoma (SCC).

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The mechanisms of these influences to induce cancer is unclear, but a number of genetic alterations have been observed in TCC[2,3]. Bladder tumours produce classically painless haematuria. However, frequency, urgency, and dysuria occasionally accompany the haematuria.

In Sudan, few studies concerning bladder tumours were conducted, the latest in the period of January 1984 to December 1988 [4,5]. Updated epidemiologic and clinico-pathologic data are thus lacking.

Methodology

This is a descriptive retrospective study conducted in three medical centres: Ibn Sina Hospital, Soba University Hospital and the National Health Laboratory at Khartoum, Sudan. Ibn Sina Hospital is a specialized hospital for renal and gastrointestinal diseases. Soba University Hospital is a teaching university hospital. The National Health Laboratory (NHL) stands as a national reference laboratory. It receives samples from different parts of Sudan and host the National Cancer Research Centre.

Patients diagnosed to have urinary bladder neoplasms in the period from January 2004

through December 2005, were studied. 164 patients were reviewed, of which 106 were included in the study. During the same period 141 were diagnosed histologically to have different types of cancer.

Exclusion criteria:

Patients who were not diagnosed histopathologicaly at the three centres and those with no adequate information were excluded (n= 23).

Data were collected using patient's records, direct interviews and a pre-designed questionnaire. The questionnaire covers all the personal information, history of: industrial occupation, cigarette smoking, analgesics and other medicinal drugs, and urinary bilharziasis. Demographic data as well as the presenting symptoms and signs were also noted. The Paraffin-fixed histopathology slides were reviewed and Periodic Acid Schiff (PAS) stain was done to highlight the *S. haematobium* egg-positive sections.

Data were fed to Statistical Package of Social Sciences (SPSS), version 10. T-test (unpaired) was used for the difference of the means. Person's Correlation Coefficient was used and $P < 0.05$ was considered as statistically significant.

Results

From January 2004 through December 2005, 106 patients were included in this study. 87(82.1%) patients were males. The male to female ratio for TCC was 6.2:1 but for SCC was 2.3:1. Their mean (±SD) age was 59.49 (±13.7) range (18-90) years. When the pathology was fractionated; the mean age for TCC and SCC was 60.92 and 55.47 respectively. The peak frequency for all cases was at the age of 60-80 years.

Because of the internal immigration we reviewed both the geographical site of the residence and the tribal descent as cofactors in the environmental and genetic makeup of cancer. As regard the geographical distribution, 26(37.1%) patients were living in the North, 17(24.3%) in Central, 25(35.7) in Western, and 2(2.9%) in the Eastern region, but none from Southern Sudan. However, thirty-three (41.5%) patients were descendants of tribes of the Northern region. Among these, the Gaaleen tribe has the highest frequency of 27.3%. There were 26(38.2%) from tribes of the West, but only 5(7.4%) from Central Region tribes and 4(5.9%) from Eastern Region tribes .

Twenty-four (44.4%) patients were labourers, 10(41.7%) farmers, 16(29.6%) housewives, 6(11.1%) employees, 2(3.7%) students, and 6(11.1%) patients have other occupation. The occupation of the rest of patients was not obtained.

Table (1) shows the presenting symptoms. 18(43.9%) out of 41 patients had positive history of cigarette smoking and 16(38.1%) had positive history of urinary bilharziasis. No history of industrial occupation, use of analgesics, or medicinal drugs in the studied patients.

Table (1): Presenting symptoms of UBN among the studied patients

Symptoms	Frequency
Gross haematuria	75(84.3%)
Microscopic haematuria	03(03.4%)
Painful micturition	35(39.3%)
Urgency	14(15.7%)
Palpable pelvic mass	03(03.4%)
Others	41(46.1%)

14(53.8%) out of 26 TCC cases were smokers and three (27.3%) out of eleven SCC were ex-smokers. 11(84.6%) out of 13 patients with SCC had positive history of urinary bilharziasis with Schistosoma haematobium eggs seen in the histopathological sections (Figure1).

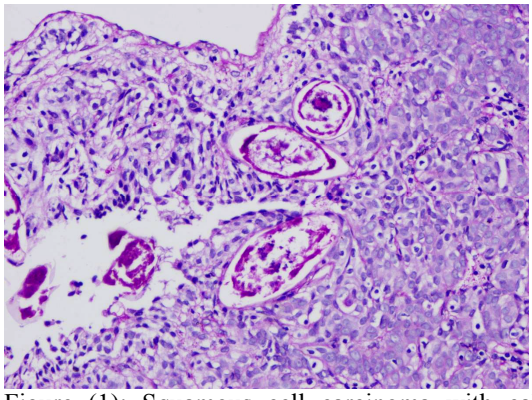

Figure (1): Squamous cell carcinoma with calcified *Shistosoma heamatobium* eggs (PASX40).

Four (16%) out of 25 patients with TCC had positive history of urinary bilharziasis (Figure 2*)*. Histopathologically, TCC with its different grades was seen in 72(67.9%) cases (Figure 3). 26(24.5%) were SCCs, three (2.8%) were TCC with squamous differentiation, and five (4.7%) other types of cancer.

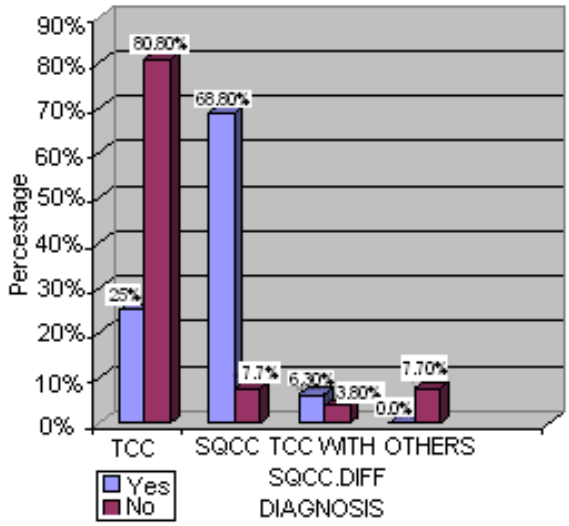

Figure (2): Relationship between diagnosis of SQCC and history of urinary schistomiasis among the studied patients (P=0.0001)

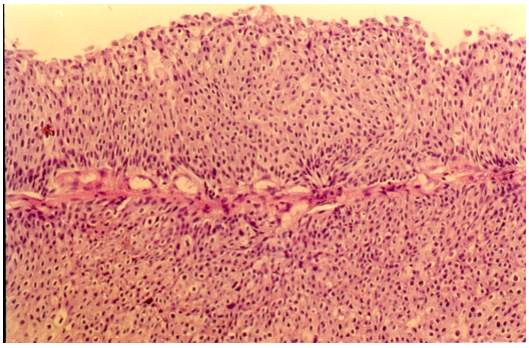

Figure (3): Non-invasive papillary urothelial carcinoma, low grade. Note variation in nuclear polarity, size, shape and chromatin pattern (H&E. X20).

Discussion

Urinary bladder tumours are heterogeneous groups of tumours with different subtypes and different behaviour. In this study, bladder cancer accounts for 0.9% of the total number of cancer cases registered in the NHL during the period of the study. It is not the exact incidence because many other cases were diagnosed in private laboratories, other hospitals, and/or private clinics, and were not registered in the National Cancer Registry at the NHL.

In this series, the highest frequency occurred in the age group 60- 80 years. This is similar to that reported by Waihenya CG and Mungai PN[6]. Also the mean age in this study is 59.5 years which is close to that reported in the United States being 57.8 years[7]. In schistosome-free countries, the peak incidence of bladder cancer occurs in the sixth to the seventh decade of life[8] with peek frequency between 65 and 75 years[9]. Only 12% of bladder cancer cases occur in people younger than 50 years[10]. In contrast, in Egypt, Iraq, Zambia, Malawi, and Zimbabwe, where there is heavy infestations of urinary bilharziasis the highest frequency of bilharzial bladder cancer is between 40 and 49 years[11-15].

In this study, the preponderance of male sex is in concordance with the literature with male to female of 5:1[16,17] but the sex ratio may vary within a range of 4:1 to 5.9:1[14]. Compared to neighboring countries, the male to female ratio (4.6:1) in this study is similar to that reported in a study from Kenyatta National Hospital, Nairobi, Kenya as 4:1 and Saudi Arabia 4.4:1[6,18]. However, the sex ratio is higher than that reported from United States (2.4:1) and Greece (3.9: 1)[7,19]. The relatively higher male gender ratio in the countries with endemic infection has been explained by the fact that in rural areas the main route for infection is through contact with infected waters during agricultural activities, which are normally performed by men[20].

Geographically, most of the patients (37.1 %) were originally from the North Region of Sudan, while Central Sudan comprised 24.3%. This is not similar to Sharfi's study where most of the patients were originally from the Central Region[5]. This could be explained by the continuous internal emigration.

The explanation to the lower frequency of UBN in the central region in this study in spite of the high infestation rate with urinary schistosomiasis could lie either in the fact that the overall prevalence was falling continually

in the province of Gezira because people in endemic areas receive anti-bilharzial treatment frequently at an earlier age or that many patients with SCC in the bladder die before having any medical advice. In addition to that Gezira Scheme has mainly *S. mansoni* and patients presenting from the central region are probably immigrants originally from Babanosa area in the west which is a focus of *S. haematobium*.

The West region of Sudan showed the 2nd high incidence (35.7%), while no one was from the South. This could be explained by the fact that the largest endemic area of S. haematobium is to be found in the middle part of Sudan, between the ninth and sixteenth latitude. South of 9° north latitude foci of transmission are sporadic. North of 16° latitude it is found only in the Nile banks[21]. Poor financial status, difficult transportation, war situations, and lack of awareness may be among the major reasons why patients do not report from Southern and Eastern Sudan.

Tribes of the North dominated, as most of the studied patients were from the North region. Galeen tribe showed the highest incidence. This is probably due to their easy transportation to Khartoum.

In this study, most of the patients were labourer (44.4%). Farmers comprise 41.7%. These results were similar to those reported from Kenya and Egypt[6,22]. It has been suggested that this could be attributed to the fact that SCC of the bladder which is common in areas endemic with urinary bilharziasis occurs mostly in farmers. This makes the male to female ratios higher in areas endemic with schistosomiasis such as Egypt (9:1) compared with non-schistomsomal countries such as United States (2.4:1) and Greece (3.9:1)[22,7,19]. That could be due to the fact that females work in the harvest when the land is dry compared to males who perform all irrigation processes that exposes them to the cercaria.

The commonest presenting symptom was haematuria in 87.7% of the patients. Patients who develop bladder neoplasm on top of bilharziasis do not appreciate development of newer symptoms and they attribute haematuria to schistosomiasis and accordingly most of them present with advanced disease. This in part explains the large number of patients presenting with other symptoms (46.1%) including suprapupic mass, obstructive uropathy and weight loss on the first visit. This reflects the poor community health education in the endemic areas.

The risk factors for UBN are both environmental and genetic. Epidemiological studies of urinary bladder cancer began in 1895 with a study of the excessive occurrence of bladder cancer among workers in the aniline dye industry; this was confirmed in 1954[23]. Case-control studies revealed that about 19 and 6% of bladder cancers in males and females, respectively, were related to occupational exposure to industrial carcinogens that are specifically implicated in the induction of bladder cancer, such as α- and β-naphthylamine, 4-aminobiphenyl, methylene dianiline, 4-chloro-*o*-toluidine and toluidine[24-27]. In the current study, there was not a single patient showed a positive history of occupational exposure.

Cigarette smoking is now recognized as a major cause of bladder cancer in developed countries, increasing the risk two- to threefold in North America and Europe and accounting for 50% of these cancers in males and 25% in females[28]. Although much less information is available from developing countries, a recent study in Egypt indicated that smoking was strongly associated with bladder cancer in males and could account, at least in part, for 75% of these cancers[29]. The aromatic amines contained in cigarette smoke are most likely responsible for this increased risk.[30]The risk increases with increasing duration and intensity of smoking[23,31]. In this study there was no significant relationship between cigarette smoking and development of UBN (P= 0.275). This could be explained by the low number of patients that were interviewed directly for cigarette smoking in the study 41 (38.7%) and the lower frequency and fewer number of cigarettes smoked per day. Several epidemiological studies indicate that chronic abuse of analgesics containing

phenacetin greatly enhances the risk of developing urothelial cancer of the renal pelvis, ureter and bladder. The relative risk has been estimated in the range of 2.4 to more than 6. Early cases have been reported from Scandinavia, Switzerland and Australia[31]. The cytotoxic agent, cyclophosphamide has long been associated with the development of leukemia and lymphoma. In addition, treatment with cyclophosphamide has been reported to be associated with an increased risk of SCC and sarcomas, especially leiomyosarcomas. Similarly chlornphazine is associated with the development of bladder cancer.[23] In the current study, there was not a single patient showed a positive history of chronic use of analgesics containing phenacetin or other drugs. Several studies showed that use of drinking water containing chlorination byproducts or contaminated by arsenic might increase risk of bladder cancer[31]. An International Agency for Research of Cancer (IARC) Monographs Working Group reviewed in 2004 the relevant epidemiological studies and concluded that arsenic in drinking water is carcinogenic to humans (group 1) and that there is sufficient evidence that it cause urinary bladder cancer. Key evidence came from ecological studies in Chile and Taiwan (China) where large populations were exposed[31].

We have to mention that environmental factors that may potentially reduce the risk of bladder cancer include the following: vitamin A; vitamin C; increased fluid intake and a low fat, high fruit and vegetable diet[30]. Oncogenes and tumour suppressor genes have been implicated in a variety of human cancers. These include the activation of H-*ras*[32], inactivation of *p53*[33], and inactivation of the retinoblastoma gene[34]. Rearrangements of chromosome 9 resulting in loss of material from 9p, 9q, or of the entire chromosome were the most frequent cytogenetic alterations, seen in 45% of the cases. Whereas loss of material from chromosome arms 1p, 8p, and 11p, and gains of chromosome 7, and chromosome arm 1q, and 8q seem to be an early, but secondary, changes appearing in superficial and well differentiated tumours, the formation of an isochromosome for 5p and loss of material from 17p are associated with more aggressive tumor phenotypes[35]. We did not study the genetic changes because of the high cost.

Schistosomiasis (also called bilharziasis after the German tropical disease specialist, Theodore M. Bilharz, 1829–1862) is second only to malaria in parasitic disease morbidity and a documented risk factor of bladder tumours. *Schistosoma* sps. infect 250 million people worldwide[36]. Bilharziasis is endemic throughout Africa, but its distribution is focal and constantly shifting as open irrigation canals spread[37,38]. Schistosomiasis is endemic in many countries, not only in sub-Saharan Africa, but the Far East, South and Central America, and the Caribbean[39].

Most epidemiologic studies regarding schistosomiasis in Sudan have been carried out in the Gezira-Managil area and in other central or northern areas of economic importance, while relatively few studies have been conducted in other parts of the country. In 1987, The World Health Organization (WHO) published The Global Atlas on schistosomiasis which describes the distribution of the infection as derived from epidemiological surveys and yet it is still an extremely useful document today (Figure 4)[21].

Figure 4: Distribution of Schistosomaiasis in Sudan[21]

Ten species of Schistosomes can infect humans, but a vast majority of infections are caused by *Schistosoma mansoni*, *S. japonicum*, and *S. haematobium*[40]. Of all people suffering from schistosomiasis, 85% live in sub-Saharan Africa where *S. mansoni, S. haematobium*, and *S. intercalatum* are endemic[41,42].

There are several well-documented relationships between infections with certain parasites and the development of cancer[43], in particular schistosomiasis and bladder cancer[44-49] and *Opisthorchis viverrini* and *Clonorchis sinensis* infections with cholangiocarcinoma[48, 49]. The evidence associating *S. haematobium* infection with the development of bladder cancer is, however, far greater than that for any other parasitic infection; it has been supported by several major studies in countries in Africa and the Middle East[44, 45,50-53,46] and more recently confirmed as definitive[54]. Various strains of bacteria that can mediate nitrosation reactions leading to the formation of N-nitrosamines have been identified in the urine of subjects with schistosomiasis at higher intensities of infection than in normal subjects. In experimental schistosomiasis, it was also found that endogenous levels of host cell DNA damage were related to the intensity of infection[55].

Chronic tissue injury could provide a promoting factor which acts to increase the rate of cell turnover via the induction of restorative hyperplasia and squamous metaplasia. At this stage, the proliferating cells are not neoplastic but are transitional and noninvasive; most of these focal hyperplasias are subsequently reversible[56]. However, in some situations, hyperplasia and dysplasia may become irreversible, particularly during concomitant exposure to low (subcarcinogenic) doses of carcinogens e.g., *N*-nitroso compounds[57].

The histopathological entities of bladder cancer associated with schistosomiasis have certain distinct features which differ from those of bladder cancer found in Western countries[58]. In the present series, 84.6% of the patients with SCC had a past history of urinary schistosomiasis. This study yielded a highly significant relationship between urinary schistosomiasis and the development of SCC (P=0.0001). This is in accordance with findings in many areas of endemic schistosomal infection. In Egypt, for example, SCC occurred in 10 of 1,000 adults infected with *S. haematobium* but only in 0 to 3 of 1,000 Schistosome-free patients[59]. In other countries also (e.g., Iraq) a strong correlation between *S. haematobium* infection and SCC is maintained[60]. The proportion of SCC varied from 54 to 81% of all bladder cancer cases in different areas of endemic infection, which contrasts to Western countries, where the frequency of SCC in bladder cancer cases is much lower (3 to 10%)[61-63]. *Groeneveld et al,* reported that ova of *Schistosoma haematobium* were seen in microscopic sections of the bladder tumour in 85% of the patients with squamous cell carcinoma, in 50% of those with undifferentiated tumours and adenocarcinoma, in 17% of those with mixed tumours or sarcoma, and in only 10% of the patients with transitional cell carcinoma[64]. Thus, in African patients, endemic schistosomiasis appears to be related to a high incidence of not only squamous cell carcinoma, but also other histological types.

Conclusion

Despite limitations of this study, it showed a significant relationship between urinary schistosomal infestation and the development of squamous cell carcinoma of the urinary bladder.

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