SCHISTOSOMIASIS-ASSOCIATED BLADDER CANCER: A SEVEN YEAR EXPERIENCE IN MAIDUGURI NORTH EASTERN NIGERIA

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ABSTRACT: BACKGROUND: Bladder cancer is one of the commonest malignancies globally. In schistosomiasis endemic areas in Africa and Middle East squamous cell carcinoma predominate. This study aimed at evaluating presentation and management outcome. **PATIENTS AND METHODS:** The study reviewed all cases of schistosomiasis- associated bladder cancer in the University of Maiduguri Teaching Hospital (UMTH) from January 2007 to December 2013. Information was extracted from the patients clinical notes and data analyzed. All bladder cancers, histologically diagnosed with co-existing schistosomiasis were included in the study. The diagnosis was based on clinical, laboratory and imaging investigations. **RESULTS:** A total of 82 patients were studied age ranged from 28 – 87 years with a male to female ratio of 3.56: 1, the peak age group was 40 – 49 years. The mean age at presentation was 46.8 years. Clinical features were Hematuria, Suprapubic mass, and anorexia /weight loss in 96.34%, 71.95%, and 85.37% respectively. The duration of symptoms ranged from 3 weeks to 3 years, all patients had childhood schistosomiasis. The histology revealed squamous cell carcinoma in 87.80% and transitional cell carcinoma in 12.20%. Muscle invasive tumours (T3, T4) were 86.59%. The procedures done were biopsy only in 25.61% and radical cystectomy and urinary diversion in 53.66%. There were 9.76% mortalities, and one year survival was 68%. **CONCLUSION:** Schistosomiasis associated bladder cancer is predominantly squamous cell carcinoma that is muscle invasive, with tendency to be locally advanced. Eradication of schistosomiasis will reduce the prevalence of the disease.

KEYWARDS: SCHISTOSOMIASIS-ASSOCIATED BLADDER CANCER, MANAGEMENT OUTCOME, NORTH EASTERN NIGERIA.

INTRODUCTION

Bladder cancer is the 5th and 7th most common malignancy among men and women respectively. In Europe and United State, transitional cell carcinoma (TCC) dominating and accounting for more than 90% of all cases[1]. In the Middle East and Sub Saharan Africa bladder cancer is the most common malignancy (25%) of all cancers in men, with a clear dominance (87%) of the squamous cell carcinoma (SCC) subtype[2]. In addition to the SCC differentiation and more pronounced male preponderance, a low mean age at diagnosis and rare involvement of the trigonal region characterized bladder cancer in Africa and Middle East[3]. The geographic and clinical differences in bladder cancer behavior appear to be due mainly to etiologic differences. Whereas chemicals including cigarette smoke and occupational exposures cause TCC of the bladder in the industrialized country, a similarly strong association with urinary bilharziasis exists in Africa and Middle East[4]. The mechanisms whereby urinary bilharziasis induced bladder cancer are not fully understood, but elevated urinary N-nitroso compounds, B-glucuronidase, and chronic mechanical irritation of the urothelium by calcified eggs deposited in the bladder wall have all been implicated[5-8]. A large and compelling body of evidence links schistosomiasis of the urinary tract to bladder cancer[9]. Schistosomiasis induces chronic irritation and inflammation in the urinary bladder and this could facilitate changes in at least two stages of the development of the disease: first, initiation of premalignant lesions, and second, action as a promoting agent to increase the likely hood of the conversion of these lesions to the malignant state. At the stage of initiation, activated macrophages induced at the site of inflammation are implicated in the generation of carcinogenic NNA and reactive oxygen radicals that lead to DNA damage and subsequently to events such as mutations DNA strand breaks, and sister chromatin exchanges. Inflammatory cells have been shown to participate in the activation of other bladder carcinogens such as aromatic amines. Various species of bacteria have been found in greater numbers in the urine of patients with schistosomiasis than in the urine of patients without schistosomiasis. Several of these bacterial species can mediate N-nitrosation of amines, thereby providing sources of carcinogenic NNA in addition to those from exogenous sours e.g. diet. All these increase and prolong the exposure of bladder to the DNA damaging agents. Mutations of bladder DNA have been observed in oncogens, tumour suppressor genes, and genes associated with cell cycle control. In particular, mutations in the tumour suppressor gene p53 have been observed more frequently in patients with schistosomiasis-associated bladder cancer than in patients with non -schistosomiasis –associated bladder cancer. Changes in these and other genes and in microsatellite DNA, presumably arising as a result of carcinogenic insult, may lead to greater genetic instability and hence to the probability in malignant conversion[10]. In general s. haematobium has been related epidemiologically and clinically to bladder carcinoma, specifically squamous cell carcinoma. This study aimed at evaluating clinical presentation, management, and outcome of schistosomiasis associated bladder cancer.

PATIENTS AND METHODS

The study reviewed all cases of bladder cancer associated schistosomiasis in the University of Maiduguri Teaching Hospital (UMTH) from January 2007 to December 2013. Permission for the study was granted by the hospital ethical committee and informed written consent was given by the patients. Information was extracted from the patients laboratory/clinical notes and data analyzed. All bladder cancers histologically diagnosed with co-existing schistosomiasis were included in the study. Emergency presentations were resuscitated with intravenous fluids, antibiotics (metronidazole and ceftriaxone) and blood transfusion where necessary. The diagnosis was based on clinical, laboratory and imaging investigations. Investigations done were full blood count, urinalysis, blood chemistry, ultrasound scan, chest x-ray, and urine cytology. Others were cystoscopy and biopsy, intravenous urography, computerized tomography and magnetic resonance imaging where applicable. Surgery was under general anesthesia with prophylactic antibiotics at induction. All patients were followed up and those that can benefit from radiotherapy and were referred to such centres.

RESULTS

A total of 82 patients were studied age ranged from 28 – 87 years with a male to female ratio of 3.56: 1, the peak age group was 40 – 49 years accounting for 21(25.61%) **table 1**. The mean age at presentation was 46.8 years (46years males and 48.5 years females), 63(76.83%) were farmer/fishermen, and 16(19.51%) were retired civil servants. The presenting clinical features were Hematuria, anemia, Suprapubic mass, and anorexia /weight loss in 79(96.34%), 76(92.68%), 59(71.95%), and 70(85.37%) respectively. Others were Necroturia in 57(69.51%), facial/pedal edema in 38(46.34%), urinary tract infection in 27(32.93%), impaired renal function in 27(32.93%), and urinary retention in 17(20.73%). The duration of symptoms ranged from 3 weeks to 4 years and the mean of 26 months, all patients had childhood schistosomiasis, with a mean of 25 years from first exposure to schistosomiasis and development of malignancy. The histology revealed squamous cell carcinoma in 72(87.80%) and transitional cell carcinoma in 10(12.20%). Muscle invasive tumour (T3, T4) in 71(86.59%), distant metastases were seen in 3, two to the lungs and one to the liver, all were TCC (30.00% of TCC). while non muscle invasive tumour (T1, T2) in 11(13.41%). The squamous cell carcinoma was well differentiated in 37(51.39%), moderately differentiated in 27(37.50%), and poorly differentiated in 8(11.11%). Transitional cell carcinoma showed well differentiated in 3(30.00%), moderately differentiated in 3(30.00%) and poorly differentiated in 4(40.00%). The overall tumour grading showed 67(81.71%) low grade while high grade was in 15(18.29%). Out of the 10 transitional cell carcinoma 4 were high grade poorly differentiated while 3 showed background squamous metaplasia. The procedures done were biopsy only in 21(25.61%) **table 2**. The post operative complications were urinary tract infection in 13(15.85%), metabolic acidosis in 23(28.05%), surgical site infection in 7(8.54%), and renal failure in 4(4.88%). There were 8(9.76%) mortalities, and one year survival rate was 68%.

DISCUSSION: Schistosomiasis associated bladder cancers are known to occur in younger age compared to non schistosomiasis associated bladder cancer. This study found the mean age at diagnosis regardless of the histological type was 46.80 for all sexes, 46years for males and 48.50years for females. This is similar to findings from Senegal that considered bladder cancer as the disease of the young age with a mean age at diagnosis being 45.50 years[11]. This study found 46.34% of the patients to be below the age of 50 years, similar to the findings from Tanzania[12] with 41.60% to be below the age of 50 years. It is known that bladder cancer in the developed countries is a disease of the elderly, this study however found a trend towards a younger age group at diagnosis. Urinary bladder cancer is generally reported to be more common in males than in females which are in keeping with findings in this study with a male to female ratio of 3.56: 1. The presenting features of Hematuria, Suprapubic mass, and weight loss characteristic of clinically advanced disease are typical of bladder cancer patients in Africa as reported by Heyns *et al*[13]. Many patients in Africa still present with advanced and inoperable bladder cancer, and many do not have access to healthcare facilities that can provide a cure and a good quality of life by means of radical cystectomy and neobladder construction. This study found such patients, procedure done were limited to biopsy only in 25.61% for histological diagnosis due to inoperability, and urinary diversion with tumour insitu in 4.32% as a result of non respectability. Bladder cancer is more common in developed than in developing countries and the majority (90-95%) are TCC [14-15]**.** In the current study however schistosomiasis associated bladder cancer was found to be predominantly SCC (87.80%), suggesting a different etiology in this setting compared to developed countries. Globally TCC has been associated with chemicals such as aniline dyes and aromatic amines from occupational exposure; others are phenacetin, cyclophospamide, and acinic all of which are commonly observed in developed countries than in developing countries[16.] In the presence study TCC constituted 12.20%, indicating that chemical carcinogens that abound in developed world are not so common in the study environment. Squamous cell carcinoma of the bladder have been linked with causes other than schistosomiasis such as bladder stones , chronic cystitis, prolonged indwelling catheters, and in patients with spinal cord injuries these particular type of SCC tend to occur in the older age groups and more aggressive[17-18] . The findings in this study of relatively young age of patients with SCC suggest that the preceding factors of causation are not important in this environment. Further evidence from this study showed that all the bladder cancer patients in this study have calcified schistosoma ova or granuloma coexisting. The present study showed that 86.59% of all cancers have already invaded bladder wall muscle at the time of diagnosis reflecting advanced stage with poor prognosis as opposed to what is obtainable in developed countries where only 25% of cancers were muscle invasive[19]. The bladder muscle wall invasion is traditionally associated with poorly differentiated tumours (high grade tumours) regardless of the histological types. It is important to note that in this study, though most tumours were well differentiated (low grade) majority of the patients had advanced disease due to late presentation as with mean duration of symptoms of 26 months. Squamous cell carcinoma whether related to schistosomiasis or not, has been reported to be o of distinct clinicopathological features, with a high tendency of bladder wall muscle invasion, and advanced stages with lower incidence of pelvic nodes and distant metastases than TCC[20]. Conversely schistosomiasis associated

TCC tend to be poorly differentiated high grade muscle invasive advanced stage with distant metastases. Major urological cancer surgeries are often associated with complications. This study had complications of surgical site infection, ascending urinary tract infection, acidosis, and acute renal failure which were managed by wound dressing, antibiotics, oral sodium bicarbonate, and hemodialysis.

CONLUSION: The study found schistosomiasis associated bladder cancer to be a major clinical challenge as patients present late with advanced disease due to poor socioeconomic status and lack of access to healthcare facilities. The burden of schistosomiasis associated bladder cancer can be reduced by eradicating schistosomiasis, public enlightenment at the primary and secondary healthcare level, and provision of state of the art facilities in tertiary health centres.

LEGEND OF TABLES AND FIGURES

TABLES 1: Age Distribution

AGE in years	No	%
20-29	03	03.66
30-39	14	17.07
40-49	21	25.61
50-59	15	18.29
60-69	13	15.85
70-79	10	12.19
80+	06	07.32
Total	82	100.00

Table2: Procedures done

Procedure	No	%
Biopsy only*	21	25.61
Partial cystectomy	11	13.41
Radical cystectomy plus Urinary diversion	44	53.66
Urinary diversion plus tumour insitu	06	07.32
Total	82	100.00

*NB Inoperable or decline surgery

Figure 1: Squamous cell carcinoma coexisting with Schistosomiasis.

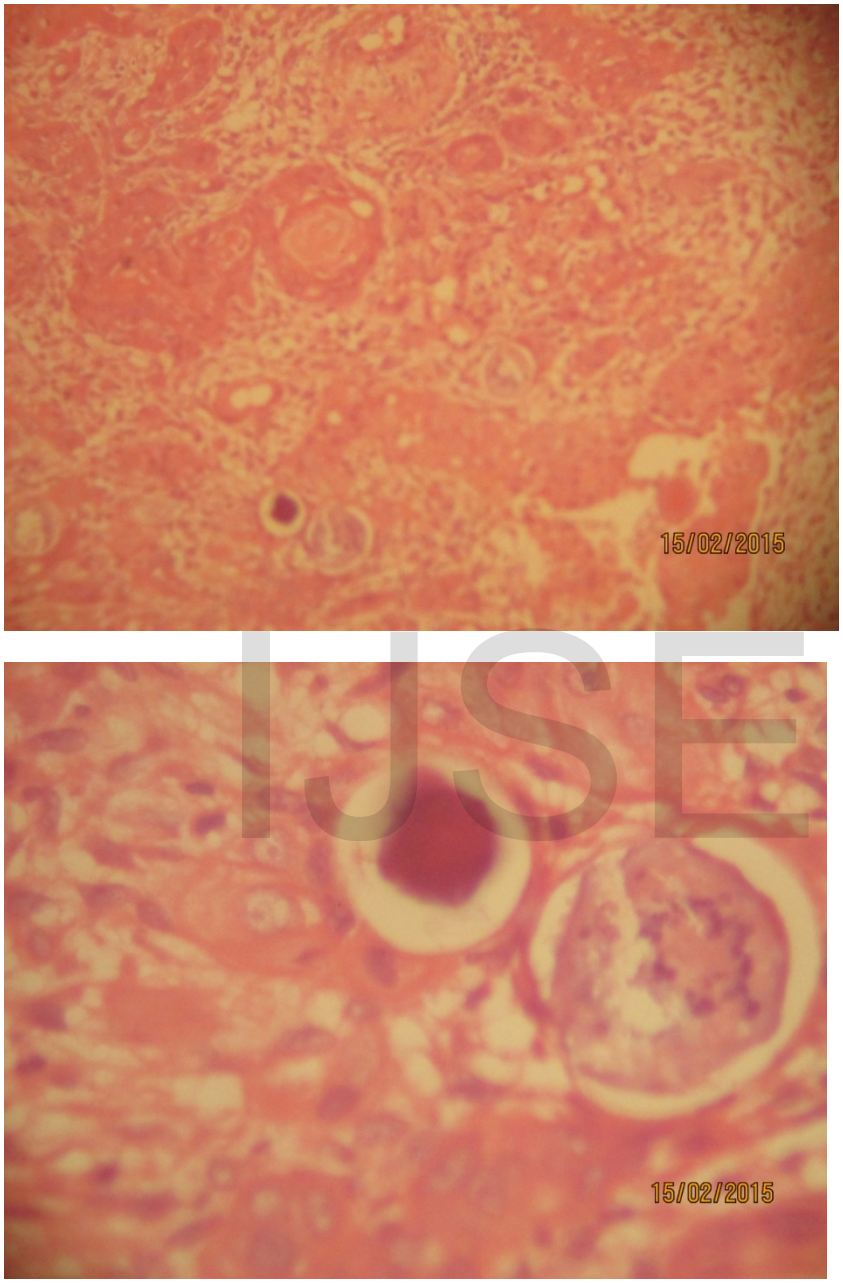
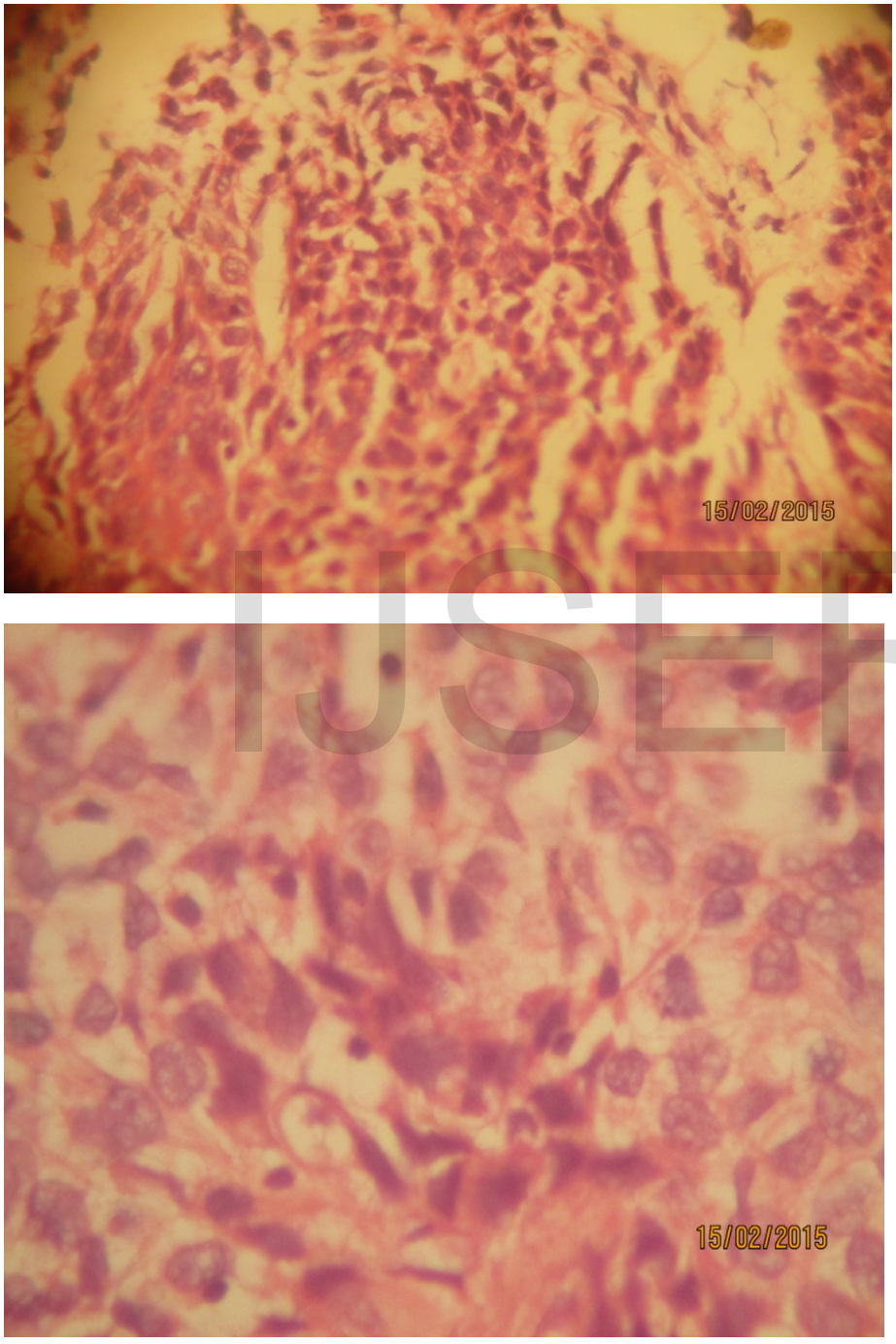


Figure 2: Transitional cell carcinoma coexisting with schistosomiasis.



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